INCONTINENCE

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EDITORS
LINDA CARDOZO, ERIC ROVNER,
ADRIAN WAGG, ALAN WEIN,
PAUL ABRAMS

7th International Consultation on Incontinence

ICS ICUD

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FOREWORD

The 7th International Consultation on Incontinence was held virtually in November 2021 under the restrictions placed upon us all by the ongoing Covid-19 pandemic. Once again, the Consultation was facilitated by the generous support of the International Continence Society.

This consultation has seen the incorporation of a joint ICI and ICS advisory board which proved to be invaluable in the identification and selection of experts across the 22 committees which, for this Consultation, has included more than 200 experts from across the world. We have also welcomed Eric Rovner to the Editorial Board, as Paul Abrams stepped back from the forefront of responsibility. As Editors, we remain grateful for Paul's ongoing advice and guidance. We are also grateful for the tremendous support of the team in the ICS office who finalize the proofing and production of the chapters as they emerge from the process.

The principle of the Consultation remains the same; the production of a contemporary, evidence based, wide ranging publication which should prove invaluable to all those who commit their professional lives to men and women suffering from the conditions with which they deal. The Consultation was well received by its international audience. Considerable feedback on the committee presentations was acknowledged and responded to, resulting in improvements to the committee's work, where relevant.

We should like to thank all those who watched, participated online and sent in their comments and suggestions

We feel that the work of the ICI remains vitally important to the many millions of men, women and children who suffer from pelvic floor and allied disorders and hope that the resulting publication is equally useful to clinicians and researchers throughout the world.

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

INTRODUCTION

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

The Agency for Health Care Policy and Research (AHCPR) have used specified evidence levels to justify recommendations for the investigation and treatment of a variety of conditions. The Oxford Centre for Evidence Based Medicine have produced a widely accepted adaptation of the work of AHCPR. (June 5th 2001 http://minerva.minervation.com/cebm/docs/levels.html).

The ICUD has examined the Oxford guidelines and discussed with the Oxford group their applicability to the Consultations organised by ICUD. It is highly desirable that the recommendations made by the Consultations follow an accepted grading system supported by explicit levels of evidence. The ICUD proposes that future consultations should use a modified version of the Oxford system which can be directly 'mapped' onto the Oxford system.

1st Step: Define the specific questions or statements that the recommendations are supposed to address.

2nd Step: Analyse and rate (level of evidence) the relevant papers published in the literature.

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

2.1. What papers should be included in the analysis?

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

An exhaustive list should be obtained through:

i. **the major databases** covering the last ten years (e.g. Medline, Embase, Cochrane Library, Biosis, Science Citation Index)
ii. **the table of contents** of the major journals of urology and other relevant journals, for the last three months, to take into account the possible delay in the indexation of the published papers in the databases.

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

2.2. How papers are analysed?

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

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

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

is influenced by:

the type of study

- The hierarchy of study types are:
- Systematic reviews and metaanalysis of randomised controlled trials
- Randomised controlled trials
- Non-randomised cohort studies
- Case control studies
- Case series
- Expert opinion

how well the study was designed and carried out

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

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

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

how well the study was reported

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

http://www.consort-statement.org

2.3. How papers are rated?

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

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

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

the Oxford Center for Evidence-Based Medicine Website:

http://minerva.minervation.com/cebm/docs/levels.html

3rd Step: Synthesis of the evidence

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

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

Having completed a rigorous and objective synthesis of the evidence base, the committee must then make a judgement as to the grade of the recommendation on the basis of this evidence. This requires the exercise of judgement based on clinical experience as well as knowledge of the evidence and the methods used to generate it. Evidence based medicine requires the integration of individual clinical expertise with best available external clinical evidence from systematic research. Without the former, practice quickly becomes tyrannised by evidence, for even excellent external evidence may be inapplicable to, or inappropriate for, an individual patient: without current bestevidence, practice quickly becomes out of date. Although it is not practical to lay our “rules” for exercising judgement, guideline development groups are asked to consider theevidence in terms of quantity, quality, and consistency; applicability; generalisability; and clinical impact.

5th Step: Final Grading

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

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

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

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

6 Levels of Evidence and Grades of Recommendation Therapeutic Interventions

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

6.1. Levels of Evidence

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

- **Level 1** evidence (incorporates Oxford 1a, 1b) usually involves meta-anaylsis of trials (RCTs) or a good quality randomised controlled trial, or ‘all or none’ studies in which no treatment is not an option, for example in vesicovaginal fistula.
- **Level 2** evidence (incorporates Oxford 2a, 2b and 2c) includes “low” quality RCT (e.g. < 80% follow up) or metaanalysis (with homogeneity) of good quality prospective ‘cohort studies’. These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.
- **Level 3** evidence (incorporates Oxford 3a, 3b and 4) includes:
  - **good quality** retrospective ‘case-control studies’ where a group of patients who have a condition are matched appropriately (e.g. for age, sex etc) with control individuals who do not have the condition.
  - **good quality** ‘case series’ where a complete group of patients all, with the same condition/disease/therapeutic intervention, are described, without a comparison control group.
- **Level 4** evidence (incorporates Oxford 4) includes expert opinion were the pinion is based not on evidence but on ‘first principles’ (e.g. physiological or anatomical) or bench research. The Delphi process can be used to give ‘expert opinion’ greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of ‘options’; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made.

6.2. Grades of Recommendation

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

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

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

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

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

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

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

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

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

CONCLUSION

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

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

P. Abrams, S. Khoury

The full paper can be accessed through the ICUD website (www.icud.info)

COMMITTEE 1

EPIDEMIOLOGY OF URINARY INCONTINENCE (UI) AND OTHER LOWER URINARY TRACT SYMPTOMS (LUTS), PELVIC ORGAN PROLAPSE (POP) AND ANAL (AI) INCONTINENCE

I. MILSOM (Sweden), *Chairman*
D. ALTMAN (Sweden)
R. CARTWRIGHT (UK)
M.C. LAPITAN (The Philippines)
R. NELSON (UK)
S. SJÖSTRÖM (Sweden)
K. TIKKINEN (Finland)

Contact address:
Professor Ian Milsom, M.B.,Ch.B.(Hons), Ph.D.
Gothenburg Continence Research Centre (GCRC), Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg,Sahlgrenska University Hospital, SE-416 85 Gothenburg, Sweden
Ian.Milsom@gu.se

COMMITTEE 1

EPIDEMIOLOGY OF URINARY INCONTINENCE (UI) AND OTHER LOWER URINARY TRACT SYMPTOMS (LUTS), PELVIC ORGAN PROLAPSE (POP) AND ANAL (AI) INCONTINENCE

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorders
ADL	Activity of Daily Living
AI	Anal Incontinence
BMI	Body Mass Index
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostatic Obstruction
CAT	Childrens Apperception Test
CBCL	Childs Behaviour Check List
CI	Confidence Interval
DO	Detrusor Overactivity
DV	Dysfunctional Voiding
EEG	Electroencephalogram
FI	Faecal Incontinence
GWAS	Genome-wide association study
IBD	Irritable Bowel Disorder
IBS	Irritable Bowel Syndrome
ICCS	The International Childrens Continence Society
ICI	International Consultation on Incontinence
ICS	International Continence Society
LOE	Level of Evidence
LUTS	Lower Urinary Tract Symptoms
MDS	Mininimum Data Set
MMSE	Mini Mental Status Examination
MNE	Monosymptomatic Nocturnal Enuresis
MRI	Magnetic Resonance Imaging
MUI	Mixed Urinary Incontinence
NE	Nocturnal Enuresis
NME	Non-Monosymptomatic Nocturnal Enuresis
OAB	Overactive Bladder
OR	Odds Ratio
POP	Pelvic Organ Prolapse
POPQ	The ICS Pelvic Organ Prolapse Quantification Examination
PSA	Prostate Specific Antigen
RR	Relative Risk
SUI	Stress Urinary Incontinence
TAH	Total abdominal Hysterectomy
TURP	Trans Urethral Resection of Prostate
UI	Urinary incontinence
USI	Urodynamic Stress Incontinence
UTI	Urinary Tract Infection
UUI	Urgency Urinary Incontinence
VD	Voiding postponement
VH	Vaginal hysterectomy

I. INTRODUCTION

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

A section on overactive bladder and nocturia which are commonly occurring LUTS has been included. A worldwide estimation of the current and future number of individuals with LUTS including urinary incontinence and overactive bladder is also included at the end of this chapter.

The epidemiological population under study for this review will mainly be community dwelling non-institutionalisedpersons. The review will include discussion of the prevalence, incidence, natural history, and the presence of racial and ethnic differences. We also review correlates and potential risk factors that have been revealed in epidemiological studies. We have searched the literature for relevant new articles, thus reviewing a large number of high-quality and population based studies, as well as clinical trials that might include relevant epidemiological data. Because of an abundant number of studies, only a small fraction can be presented in a text like this. Other studies not presented here may have equally useful information, but lack of space precluded their inclusion.

Summary points:

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

II. BASIC EPIDEMIOLOGICAL CONSIDERATIONS

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

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

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

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

Prevalence is defined as the probability of experiencing a symptom or having a condition or a disease within a defined population and

at a defined time point. The concept is important for establishing the distribution of the condition in the population and for projecting the need for health and medical services.

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

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

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

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

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

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

Summary points:

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

III. EPIDEMIOLOGY OF ENURESIS AND URINARY INCONTINENCE IN CHILDREN

1. GENERAL COMMENTS AND DEFINITIONS

The International Children's Continence Society (ICCS) has issued recommendations regarding the terminology of lower urinary tract (LUT) function and dysfunction in children in 2006 [1], with a standalone updated document in 2014[2] and again in 2016 [3]. Bedwetting or nocturnal enuresis (NE) is the term for all urinary incontinence during sleep taking place in discrete episodes in children aged five years or more, regardless of the presence or absence of concomitant daytime symptoms. Monosymptomatic nocturnal enuresis (MNE) denotes bedwetting without any other LUTS, and non-monosymptomatic nocturnal enuresis (NMNE) should be used for those with any concomitant LUTS.

NE is caused by relative nocturnal polyuria [4] and/or nocturnal bladder over-activity [5], combined with the lack of arousal [6] at the time when the bladder needs to be emptied. The most important cause is, of course, the lack of arousal, otherwise the child would have had nocturia.

Any other leakage of urine in children during both the day and night is referred to as urinary incontinence (UI), just as it is in the adult population. UI can be continuous or intermittent. Continuous leakage in children is often caused by a congenital malformation, such as ectopic ureter or exstrophy epispadias complex. Other causes of continuous leakage can be neurogenic bladder in children with spina bifida, tethered cord or other spinal or sacral malformations. Daytime UI with no obvious cause, i.e. without neurological or congenital anatomic alterations, is often seen together with other urinary symptoms such as frequency, urgency and infections. Altogether these symptoms are referred to as functional LUT dysfunction, which is the term used to describe the entire spectrum of functional filling-voiding disturbances [2]. Several sub-classifications have been used for children who present with varying degrees of "functional" urinary symptoms. Some are based on urodynamic patterns, others on clinical presentation.

According to definitions by the ICCS [3], based on symptoms and flow-residual studies rather than invasive urodynamic investigations, incontinence as a result of a storage-phase dysfunction, is in most cases due to an OAB, which can also be referred to as "urge syndrome" and "urgency incontinence". Children with OAB usually have detrusor overactivity, but this label cannot be applied to them without cystometric evaluation. SI is the involuntary leakage of small amounts of urine during effort or physical exertion that increases the intra-abdominal pressure, for example, coughing or sneezing. During urodynamic investigation, this leakage is confirmed in the absence of detrusor contraction. When incontinence is the result of a voiding-phase dysfunction, the diagnosis is often dysfunctional voiding (DV), which is induced by increased activity in the sphincter and pelvic floor during voiding. It is subdivided into staccato and fractionated voiding, and the terms cannot be applied unless repeat uroflow measurements have been performed. Voiding postponement (VD) is another common LUT dysfunction causing UI in children, but differs from the other since it is induced by a habitual postponement of voiding and not a LUT dysfunction per se.

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

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

Although the ICCS standardization of terminology of LUTS in children and adolescents has allowed for clarity and a more uniform communication in scientific publications, there is still a variety of descriptions regarding frequency of symptoms in epidemiological studies. According to the ICD-10 and DSM-5 definitions and criteria the symptoms of incontinence (daytime UI and/or enuresis) requires a minimum age of 5 years, a minimum of one episode per month and a minimum of three months to be diagnosed as a condition. The ICCS standardisation terminology updated document in 2016 further proposes to qualify the significance of enuresis as frequent (>4 times a week) or infrequent (< 4 times per week)[3].

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

Author	Country	Year	Prevalence of NE (%)		
			7 years	11-12 years	16-17 years
Fergusson [12]	New Zeeland	1986	10.3		
Järvelin [40]	Finland	1988	8		
Hellström [39, 41]	Sweden	19,901,995	9.5		0.5
Swithinbank [42, 43]	UK	19,941,998		4.7	1.1
Serel [22]	Turkey	1997	15.1	4	
Chiozza [18]	Italy	1998	6.8	2	
Spee-van der Wekke [20]	The Netherlands	1998	8	4.6	
Lee [23]	Korea	2000	16.4	4.5	
Cher [21]	Taiwan	2002	9.3	1.7	
Kanaheswari [27]	Malaysia	2003	10.3	3.3	
Soderstrom [25]	Sweden	2004	7	2.6	
Kajiwara [24]	Japan	2006	10.1	3.7	
Yeung [26]	Hong Kong, China	2006	10.1	2	1.7
Butler [15]	UK	2008	14.2		
Su [28]	Hong Kong, China	2011		1.9	
Yousef [29]*	Yemen	2011	31.5	10	8.7
Aloni [30]*	Congo	2012	34.5	13.3	
Yazici [31]	Turkey	2012	13.4	4.8	
Srivastava [32]	India	2012	15.5	4.1	
Fockema [44]	South Africa	2012	12.3		
Aljenfri [33]*	Yemen	2013	45.4	28.4	
Mota [16, 17]	Brazil	20,152,020	10.6	5.4	
Sarici [34]	Turkey	2015	17.2	2.6	
Doganer [35]	Turkey	2015	14.1	3.8	
Kanata [45]	Japan	2016		10.2 (10y)	
Hamed [36]	Egypt	2017	23.15	11.07	
Wang [37]	China	2019	11.38	2.51	1.13
Huang [38]	China	2020	3.85	2.51	
Warner [46]	Denmark	2019	16.8		

Smaller study populations (Total N in study <1000) not included in meta-analyses of total prevalence.

2. PREVALENCE OF NOCTURNAL ENURESIS (NE)

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

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

2.1. Prevalence of all night wetting (MNE+ NMNE) according to age

Longitudinal cohort studies are ideal when analysing epidemiology in childhood NE, as there is a successive reduction in prevalence. Only a few studies are available [10-17] and cross-sectional studies at different ages therefore have to be used.

Most studies investigate cohorts of children in an age span of six to twelve years of age, for example, and give the prevalence for the entire group. Some of them also give the age-related prevalence [13, 18-38] which is summarised in Table 1. Cross-sectional studies of a specific age are also included [16, 17, 39-46] in Table 1.

In most studies the prevalence for seven- year-olds was between 7% and 10%. In a some studies, the prevalence was higher; 15% to 23% for children in Turkey [22,34,47], India [32], Denmark [46], Korea [23] and Egypt [36], despite the fact that the inclusion criteria were similar in all the studies of seven-year-olds (NE=night wetting once/month or more). Two cross sectional epidemiological studies from Yemen and one study from the Republic of Congo [30] have showed markedly higher frequencies with 31%-45% NE among children 6-8 years declining to 8.7% in adolescents 15 years or older [29, 33]. These studies have smaller study populations compared to other studies cited and selection bias can therefore not be ruled out, but the findings are interesting. The studies by Hellström [39] and Järvelin [40] differ in NE criteria (once/3 months or more and once/6 months or more respectively). The prevalence of more frequent wetting (once/week or more) was lower compared to the prevalence for all wetting (once/month or more) by age, which has been illustrated in Fig.1.

In 18 studies at age seven years [12, 16, 18, 21, 23-26, 31, 32, 34, 35, 37-40, 44, 46] the numbers of both non-enuretic and enuretic children were given and the definitions for enuresis were similar (MNE and NMNE, wetting once/1-3 months or more). A prevalence of 11.4% was obtained by meta-analyses of these studies (a cohort of 29 097 seven-year-old children, of whom 3320 were enuretic). Only a few studies included groups of children that were chosen at random from the population [18, 23, 26, 30, 40].

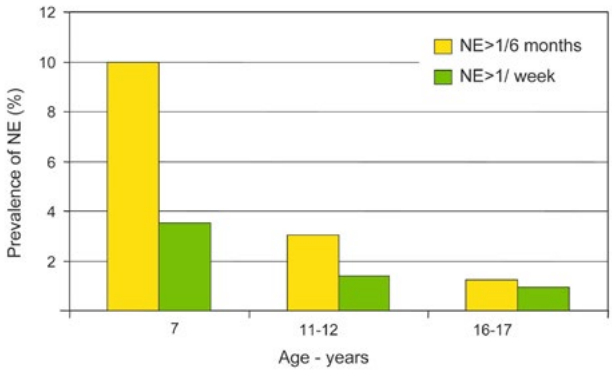

Figure 1. Prevalence of nocturnal enuresis (NE) by frequency of enuretic episodes and age. The data were obtained from metaanalyses of the epidemiological studies included in table III.1. NE>1 episode/6months: at 7 years [18, 21, 23-27, 39, 40], 11-12 years [18, 21, 23-26, 42] and 16-17 years [26, 41, 43]. NE>1 episode/week: at age 7 years [25, 26, 39, 40], 11-12 years [25, 26, 42] and 16-17 years [26, 41].

At age 11-12 years, the prevalence of NE had decreased and in most of the studies summarized in Table I the prevalence varied between 1.7% and 5.4%. In eleven of the studies, the number of non-enuretics and enuretics were available and the definition of NE was similar (once/month or more), apart from Swithinbank's [42] study (once/3 months or more). In these studies, the total number of children included was 15 924, with a total number of children with NE 589, giving a prevalence of 3.7%. So, of those children with NE at age seven years, almost 15% spontaneously grow out of the wetting every year. In a Japanese study a higher resolution rate was reported in children with MNE compared to NMNE in children 7 to 12 years of age (21% and 15%, respectively) [24]. Similar results were found in a study from Hong Kong in which the proportion of children with NMNE was significantly greater in adolescent boys than in boys aged 5-10 years (32% vs 14.6%), even if the total prevalence of NE was decreasing as in other studies [26]. The variation in the prevalence of NE at 11-12 years between the studies is less than that seen at age seven years.

At age 16-17, four cross-sectional studies show a further reduction in prevalence to 0.5-1.7%. Two of the studies re-investigated children who had previously been studied; at age seven years [41] and 11-12 years [42] respectively. The prevalence when the cohorts were added together was 1.3% (cohort=5679, NE=72) [26, 37, 41, 43], which gives a spontaneous cure rate of 11% a year among those who wet at age 11-12 years.

In a study of 13,081 adults randomly sampled in the Netherlands [48], an overall prevalence of NE of 0.5% was found. There was no significant difference between age groups. Primary NE was reported by 50% of the men and 19% of the women, indicating that a small group of the enuretic children remain enuretic as adults. Yeung et al found persistent primary NE in a 2.3% of Hong-Kong adults aged 16-40 years[49] and 1.9% had monosymptomatic enuresis. Enuretic symptoms in this adult population were more severe than in children, and of those with NE 53% wet > 3 nights a week and 26% every night[49]. In this later study the prevalence remained unchanged with increasing age indicating that NE persistent in early adulthood have a high risk of remaining.

2.2. Prevalence of monosymptomatic enuresis (MNE)

Few studies make a distinction between MNE and NMNE and it is therefore difficult to obtain relevant figures for MNE (Table 2). In two studies from Scandinavia dealing exclusively with seven-year-olds, there was agreement between the studies; 6.4% [40] and 7.4% [39]. A Japanese study gave similar figures for MNE; 6.2% at age 7 years. In this latter study MNE corresponded to approximately 60% of all NE in ages from 7 to 12 years [24]. When it comes to studies in which all ages were mixed (5-12 years), eight studies were identified in which those without daytime voiding problems could be identified. However, the difference in prevalence of MNE varied in these studies from 3.5% to 15%.

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

Author	Year	Prevalence of MNE (%)	
		Age 7 years	All ages included
Järvelin [40]	1988	6.4	
Hellström [39]	1990	7.4	
Yeung [19]	1996		3.5
Bower [50]	1996		15
Neveus [52]	1999		6.9
Kanaheswari [27]	2003	9	6.2
Lee [23]	2006	13.6	9.4
Kajiwara [24]	2006	6.2	3.5
Srivastava [32]	2011	15.5	12.6
Fockema [44]	2012	11.3	14.4
Mota [16]	2015	9.8	

2.3. Prevalence of NE versus gender

Almost all epidemiological studies of NE report a higher prevalence in boys than in girls, with the most reported ratio of 2:1 in western countries [16, 18-25, 28, 31, 32, 39, 40, 42, 50-52] . It appears that the gender difference diminishes with age and becomes less visible and less proven among older children [41, 43, 53] (Fig.2).

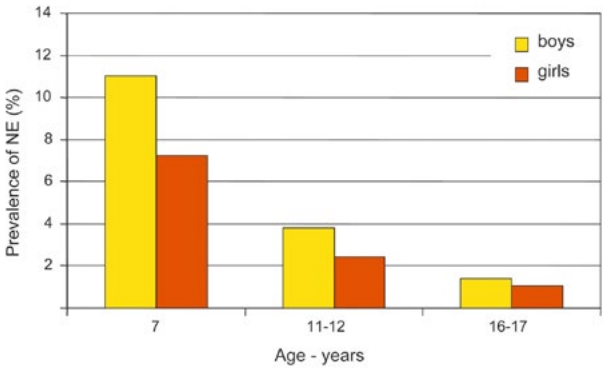

Figure 2. Prevalence of nocturnal enuresis (NE) >1 episode/6months, by gender and age. The prevalence data were obtained from metaanalyses of the following epidemiological studies: at age 7 [18, 24-26, 39, 40], age 11-12 [18, 24-26, 42] and age 16-17 [26, 41, 43].

2.4. Prevalence of NE versus ethnicity

In a study from The Netherlands [20], a higher prevalence was reported in the Turkish/Moroccan group (14%) than in Dutch children (6%) (OR 3.76 (95%CI 1.98-7.12)). An equally high prevalence was found in a Turkish study of children with NE [22] at age seven years (15.1%). In a study from Korea [23], the same high prevalence at age 7 years was identified (16.4%). However, other studies from South-East Asia had comparable [21, 24, 26] or even lower levels of prevalence to those in western countries. In fact, two Chinese studies have shown a low prevalence of NE [19, 54], 3.6% and 4.3% for children aged 4-12 and 6-16 respectively, which they attribute to earlier nocturnal urinary control in Chinese children, due to earlier toilet training. A recent survey from Mainland China showed a significant increase in prevalence of NE during the last decade (7,3% compared to 4.07%) and reported longer use of disposable diapers and delay of elimination communication to be significant risk factors for PNE [37].

2.5. Prevalence of NE versus frequency of wet nights and age

Yeung et al showed in a large epidemiological study that that the relative proportion of subjects with frequent bed-wetting increased with age [26,55]. Over all 82% of the adolescence had >3 wet nights/week versus enuretic children aged 5-10 (42%) (Fig.3). Such a relationship is also evident in Fig 1, in which the proportion of children with severe NE increase with age, even if the total number decrease. Further support for severe NE to remain in a higher proportion as compared to children with infrequent bedwetting was results in a study by Butler and Heron [15]. Findings in epidemiological studies also show a correlation between severity of the NE and NMNE [15, 18, 56], meaning that NE in adolescents often is combined with LUT dysfunction.

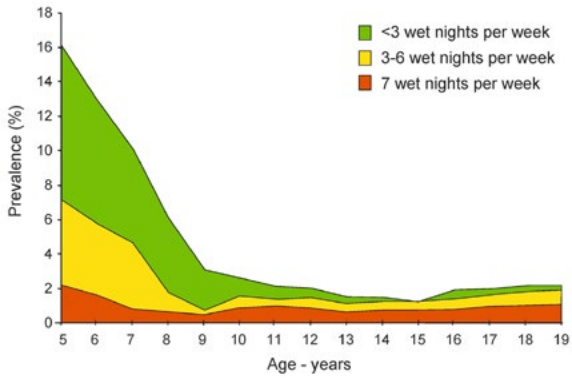

Figure 3. Prevalence of nocturnal enuresis by frequency of enuretic episodes and age. Data from [26].

3. POTENTIAL RISK FACTORS FOR NE

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

3.1. Daytime UI and LUT dysfunction

Daytime UI, a symptom of LUT dysfunction, have in epidemiological studies been shown t**o** be the strongest predictor for NE (OR 4.8 (2.9-7.9)) and have been identified in a third of the patients (NMNE) ([56]). However, poor concordance was revealed (kappa 0.25),

which confirmed the two to be separate entities that should be evaluated and treated separately.

3.2. Family history
NE is a hereditary disorder and this has been demonstrated in many studies [18, 19, 22, 31, 32, 34, 35, 40, 50, 52, 57]). The mode of inheritance appears to be autosomal dominant. Järvelin [40] showed that, if both parents were enuretics as children, the RR (95% CI) for the child to have NE was 16 (6.3-20.1), while if only one was enuretic, the RR was 7.8 (5.1-9.8). It has recently been shown that the risk for the child to have hereditary NE is increased with the severity of the enuresis. Children with severe NE (>2 episodes/week) were combined with odds ratio for maternal NE 3.63 (2.56-5.14), whereas mild and moderate NE (<2 episodes/week) had 2.14 (1.74-2-64) [58]. The association with paternal NE was less pronounced, but a similar increased association to severe NE was observed. Using molecular genetic methods, foci have been found on chromosomes 13, 12, 8 and 22 [59, 60]. A picture of pronounced heterogeneity for both genotype and phenotype emerges [61]. Time to spontaneous resolution of MNE also seems familial with a positive correlation between the age of cessation of MNE of the child and their mothers and fathers [62]

3.3. Psychopathology
There are evident connections between childhood enuresis and mental well-being [13, 14, 54, 57, 63-66]. The children are increasingly negatively affected by their NE with increasing age [67]. Evidence is accumulating to show that psychological consequences are probably caused by enuresis and not by the cause of primary NE, which has been thought for a long time [64]. The findings presented by Feehan [14] support this latter statement, as he only found an association between psychopathology and secondary NE, while children with primary NE did not display a connection of this kind.

3.4. Developmental delay and ADHD
Children with developmental delay and mental retardation have been shown to have a higher prevalence of NE [12, 20, 40, 68]. Spee-van der Wekke [20] found that children who were given special education in school, including both those with and without mental retardation, had an OR of 3.74 (95%CI 2.32-6.03) for NE.

Perinatal events such as toxaemia and low birth weight, possibly involving an increased risk of minor neurological dysfunction, have also been shown to be associated with NE [12, 40, 57]. A connection between NE and minor neurological dysfunction of this kind has also been shown by Lunsing [69] in 12-year-old enuretic children. Furthermore, children with attention deficit hyperactivity disorders (ADHD) are more likely to have enuresis than the general child population [65, 70-72] The other way around was also confimed in a case control study by Yosefichaijan who found a threefold increase of ADHD in children with MNE compared to a control group[73]

3.5. Sleep and arousal
The main pathology behind NE in children is the inability to wake up to the sensation of a full bladder. Parents often say that their enuretic child “sleeps very deeply”. Some recent studies support this view. By using auditory signals [74], computerised EEG [75] or questionnaires [52], a defect in arousal has been largely validated. In the study by Neveus [52], the odds ratios were significantly high for a high arousal threshold (2.7), pavour nocturnus (2.4) and confusion when awoken from sleep (3.4). Computerised EEG energy analysis has indicated both greater depth of sleep and impaired arousal in enuretics [76]. Difficulties in arousal from sleep has also been shown in children with NE compared to children with isolated daywetting problems and controls, by using a scoring system in a questionnaire [77]

3.6. Socio-cultural factors
Differences in the prevalence of NE [19, 22, 23, 54, 78] at early ages in different parts of the world are probably partly due to socio-cultural differences and not to differences in genetic predisposition [20]. It has been suggested that socio-economic status correlates with NE in some studies [18, 65], whereas in others no correlation was found [12]. Habits of tea-drinking in the evenings have also been identified as a risk-factor for NE[29, 33].

3.7. Other risk factors
Obstructive sleep apnoea (OSA) has been associated with enuresis in some patients [79]. In an epidemiological study an association between severe OSA and NE in girls was shown [28], but when including both sexes and all forms of OSA no difference was seen. In another study dealing with OSA patients versus controls, a significant correlation between NE and OSA was found (OR 5.1 (2.4-10.7) [80]. Removal of large adenoids or tonsils causing upper airway obstruction in children with NE significantly reduced or cured NE [81]. There are recent studies presenting an independent association between asthma and allergic disease and NE [82] Constipation (see co-morbidity below) may cause secondary NE or make primary NE persist [83]. Enkopresis has been shown to be a risk factor for NE in an epidemiological study (OR 2.7 (1.6-4.4)), while no association with constipation could be identified [56]. The correlation between encopresis and NE was also confirmed in an epidemiological study from Brazil [16]. Children suffering from obesity has also shown increased risk of having NE compared to non-obese children[84]. Children with Sickle Cell Disease are found to have increased prevalence of NE with studies reporting prevalence of 30-32% in paediatric populations with Sickle Cell Disease [85, 86]. Sexual abuse must also be included among the factors that may lead to NE [87], with increased prevalence of enuresis, compared to expected for age, in children referred for allegations of sexual abuse[88] Organic conditions such as infravesical obstruction and neuropathic bladder may also present as NE. In most cases, however, additional symptoms are present to make detection possible. Type1 diabetes was reported to be a risk factor for secondary MNE due to the polyuria seen at presentation [89]

4. PREVALENCE OF FUNCTIONAL INCONTINENCE IN CHILDREN

In children with functional LUT dysfunction, OAB is far more common than dysfunctional voiding. In a urodynamic study of 1,000 patients with functional LUT dysfunction, approximately two-thirds had an overactive bladder and one-third had dysfunctional voiding [90]. Based on clinical information, another study comprising 226 children revealed that 76% were considered to have OAB and only 1% dysfunctional voiding. The difference illustrates that different inclusion criteria influence the prevalence rate [91].

When considering the total prevalence of UI (all frequencies of UI included) (Table 3), there was a variation between 3.2% and 11.2% in different studies at the age of seven years. In the earliest studies the prevalence was lower (3.2%-5.0%), whereas in the studies performed later than 2000 [16, 23, 25, 92-94], the prevalence was higher 6.3%-11.2%. One explanation for the difference was probably an increased recognition of the problem in the population through information via media etc. At 11-13 years the reported prevalence varied between 0.9% and 12.5%. Swithinbank’s study [42]

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

Author (ref)	Sample size	Prevalence (%)			
		<1/week	>1/week	Total day+night	day only
Children aged 7 years:					
Järvelin [40]	Total: 2892 Boys:1444 Girls: 1445			3.21 2.7 3.7	1.8 1.3 2.3
Hellström [39]	Total: 3555 Boys: 1834 Girls: 1721	2.3 1.7 2.9	2.5 2.1 3.1	4.92 3.8 6.0	2.7 1.7 3.7
Bloom [103]	Total: 101			5.04	
Lee [23]	Total: 1325			6.73	3.9
Kajiwara [92]	Total: 984 Boys: 532 Girls: 452			9.03 9.2 8.9	9.0 9.2 8.9
Söderström [25]	Total: 715 Boys: 367 Girls: 348	3.0 3.2	3.8 2.6	6.33 6.8 5.8	
Joinson [93]	Total: 8213 Boys: 4222 Girls: 3991			7.83 6.9 8.8	
Swithinbank [94]	Total: 13973 Boys: 7217 Girls: 3991	6.4 6.0 7.0	0.9 0.7 1.2	7.3 6.8 8.8	3.3 5.8
Akil [104]	Total: 416				13.5
Mota [16]	Total: 3601 Boys: 1872 Girls: 1729			11.23 10.3 12.2	8.1 7.1 9.1
Doganer [35]	Total: 958			4.3	
Children aged 11-13 years:					
Bloom [103]	Total: 165			1.24	
Swithinbank [42]	Total: 1171 Boys: 510 Girls: 661	11.9 7.0 15.7	0.6 0.2 0.9	12.55 7.2 16.6	
Lee [23]	Total: 913			1.13	0.9
Kajiwara [92]	Total: 761 Boys: 366 Girls: 395			2.53 1.0 3.9	
Söderstrom [25]	Total: 763 Boys: 398 Girls: 342			4.23 4.1 4.3	
Doganer [35]	Total 342			0.9	
Children aged 15-17 years:					
Bloom [103]	Total: 81			1.24	
Hellström [41]	Total: 651 Boys: 344 Girls: 307	1.5 0.3 2.9	0.3 0.0 0.7	1.82 0.3 3.6	1.8 0.3 3.6
Swithinbank [43]	Total: 940 Boys: 411 Girls: 529			3.02 0.9 4.7	

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

showed a high prevalence (12.5%) and differed most from the rest (0.9%-4.2%). The difference could probably partly be explained by different limits for frequency of UI (occasionally [42] vs once/month or more). The fact that the studies were performed in different parts of the world was also a possible explanatory factor (UK, Turkey and Korea).

The frequency of UI decreased with age (Table 3), which was clearly demonstrated in the subjects with frequent episodes of UI (>1/week) (Fig.4). The prevalence at 7 years, 11-13 years and 15-17 years was 2.6%, 1.1% and 0.3% respectively. There were only two authors who investigated the same cohort of children on two occasions; Hellström [39, 41] in Sweden and Swithinbank [42, 43] in the UK. According to the studies by Hellström, the reduction from seven years to 17 years was 0.2% per year in those with wetting at least once a week and 0.3% when including all kinds of wetting. Swithinbank reported a far higher frequency for all kinds of wetting at age 11-12 years but not at 15-16 years and the reduction in his cohort of children was therefore approximately 2% per year.

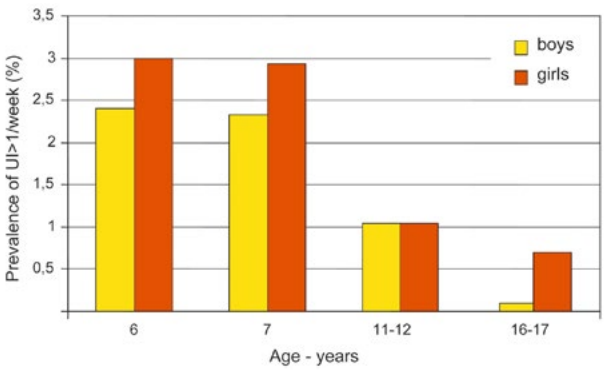

Figure 4. Prevalence of day UI (including mixed day/night) >1 episode/week by age and gender. Data are from: at age 6 years [98], 7 years [25, 39], 11-12 years [25, 42] and 16-17 years [41]

UI was more common in girls in most studies, especially in the older age groups (Table 3, fig. 4). From the prevalence found in the different studies, daytime UI could be suggested to be 1.5 times more common in girls than in boys at age seven years, whereas at age 16 years the difference was even more pronounced: 5-10 times more common in girls than in boys (Table 3). Overall in a population based study in 2856 children between 4.8-12.8 years, female gender was an independent riskfactor for UI (OR 5.4 (2.6-11.1), [95].

4.1. Prevalence of overactive bladder (OAB)

In a Japanese study [92], the prevalence in children between 7 and 12 years of age, OAB was seen in 17.8%, with no significant difference between boys and girls. There was a gradual decrease in prevalence from 19.8% at the age of 7 years to 12.8% at 12 years.

4.2. Comorbidity:

4.2.1. Prevalence of NE

NE in combination with UI is denoted as NMNE as mentioned above. NE has been identified as an independent risk-factor for day-UI (OR 7.2 (3.4-15.2)) [95]. Association of NE to day UI was more often reported in children with frequent UI (≥ 2 episodes/week), as compared to infrequent UI (< 2 episodes/week) at 7.5 years [94]. In boys NE was seen in 70-80% of those with frequent day UI compared to about 50% in those with infrequent. Corresponding figures for girls was about 55% and 30%, respectively.

4.2.2. Prevalence of Bowel problems

Urinary and fecal incontinence often coexist in different combinations. Constipation in childhood is a very common condition and when functional FI is seen, constipation is often the cause. The term encopresis can be used synonymously with functional FI. An increasing number of epidemiological studies reporting the frequency of bowel problems have been published, either as constipation or functional FI, in children with daytime wetting. Table 4 shows that the prevalence of bowel problems in day-wetting children approximately corresponded to a third of the children (21%-35%) [25, 77, 92, 93, 95, 96], with even higher prevalence in the subgroup with dysfunctional voiding (43%) [96]. A significant association between daywetting and bowel problems was shown [25]. These results support the new treatment concept of day-wetting children, with

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

Author	Number children bowel problems in day-wetting group	OR (95%CI)	Number children bowel problems in NE	OR (95%CI)
Söderstrom 2004 [25]	35%	7.2 (4.1-12.7)		1.2 (0.6-2.5)[2] 2.0 (0.6-6.3)[3]
Kajiwara 2004 [92]	33%			
Von Gontard 2004 [96]	25%[4]		0%-16%[1]	
Chandra 2004 [77]	24%		1%-24%[1]	
Joinson 2006 [93]	33%			
Sureshkumar 2009 [95]	21%	3.3 (1.4-7.7)[2]		
Fockema 2012 [44]			15.8%	
Sarici 2015 [34]			13.2%	1.52 (0.92-2.5)[3]

[1]low value represents MNE, high value NMNE, [2]OR for fecal incontinence, [3] OR for constipation, [4] Subgrouping of daywetting in OAB, VP and DV the prevalences are: 18%, 25% and 43%, respectively.

treatment of bowel problems as the first step. MNE, on the other hand, seldom have bowel problems (0%-1%), whereas in NMNE it is more common (16%-24%) [77, 96].

In an epidemiological study from Japan including 5282 children, aged between 7-12 years, 81.5% were reported to have daily bowel movements. A significant higher prevalence of NMNE was found in those with constipation, compared to among those with regular daily bowel movements (3.4% vs 2.2%) [24].

5. POTENTIAL RISK FACTORS FOR DAY WETTING

5.1. Family history

Day wetting, also including those subjects with mixed day and night wetting, has been shown to be correlated to hereditary factors, in parallel to what is known about children with NE. However, the number of studies is limited (Table 5). Hereditary factors have been shown to be more pronounced in those with severe UI (>2 episodes/week), especially when paternal day UI is present (Table 5) ([58, 97].

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

Author	RR (95% CI)	OR (95% CI)	Positive history (%)
Järvelin [57]			
-enuresis in mother	10.1 (3.4-29.3)		
-enuresis in father	5.9 (1.9-17.8)		
Sureshkumar [98]			
-daytime wetting in male sibling		5.3 (1.6-18.2)	
-daytime wetting in paternal lineage		9.3 (3.2-27.3)	
Chiozza [18]*			
-enuresis in parents		12.3	
Bower [50]			
-family history of enuresis			70**
Neveus [52]			
-family history		2.0 (1.1-3.7)	
Von Gontard [58]			
<2 episodes/week			
-maternal NE		1.2 (0.9-1.6)	
-paternal NE		1.3 (0.9-1.8)	
-maternal day UI		2.6 (1.4-5.1)	
-paternal day UI		5.5 (2.4-12.5)	
>2 episodes/week			
-maternal NE		2.1 (1.2-4.0)	
-paternal NE		2.1 (1.0-4.3)	
-maternal day UI		3.3 (0.8-13.7)	
-paternal day UI		10.1(2.3-44.1)	

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

5.2. Psychopathology

Children under stress as a result of marital separation, for example, have a higher incidence of diurnal or mixed UI, according to some authors [18, 57, 98]. Moreover, psychopathology investigated by Järvelin [57] using the Children's Apperception Test (CAT) revealed a significant increase in the signs of repression, including an inability to express one's emotions and feelings (p=0.027), when comparing day wetting children with controls. Neveus [52] found that day-wetting children had more difficulty falling asleep (OR 2.4, CI 1.4-4) and he interpreted them as "anxious children". Lettgren [99] found a significant increase in attention problems and delinquent behaviour in a certain form of day-wetting children (voiding postponement) using the Child Behaviour Check List (CBCL, Achenbach). In a recent paper [100] similar results were found with the highest rate of psychiatric comorbidity in children with UI due to voiding postponement and the lowest in children with MNE. In the group with encopresis 65% were considered to have severe behavioural problems [96], meaning that children with both wetting and bowel problems are at the highest risk for psychopathology.

In a population-based study investigating psychological problems associated with day UI, 8213 children were included of whom 643 suffered from daytime wetting at median age of 7.5 years [93]. Over all the results indicated a rate of psychological problems that was twice the rate reported for children with no daytime wetting, particular notable was the increase in externalizing problems. After adjustment for developmental delay, gender, stressful life events, variables associated to family sociodemographic background and soiling, there was still an independent association of daytime wetting and behaviour problems (OR 2.04, CI 1.67-2.51). In another epidemiological study UI was found to be associated with parenteral concerns about the child's social behaviour (OR 3.4 (1.4-8.3)), [95]. It is not clear whether the behavioural problems described in these studies are a cause or a consequence of daytime wetting.

5.3. Minor neurological dysfunction and developmental delay

Children with minor neurological dysfunction have also been shown to have an increased rate of day wetting. Duel [70] found that children with ADHD are three times more likely to have daytime UI than controls (p<0.0005). Von Gontard and Niemczyk also found children with daytime urinary incontinence to have a significantly higher risk for ADHD and opposite deficient disorder (ODD) symptoms [101, 102]. Also in children with delayed maturation or with mental retardation, the risk of day wetting is increased (OR 1.9 and 4 respectively), according to studies by Järvelin [40]. Perinatal events, which can also be suggestive of minimal brain dysfunction, have also been shown to be over-represented in day-wetting children. For example, Järvelin [57] found that the children of mothers who had suffered from toxaemia had an RR of 8.5 (CI1.4-51.9) for day UI.

5.4. Other risk factors for daytime UI

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

In many papers, UTI is regarded as a risk factor for daytime UI. Järvelin [57] found a RR of 8.6 (2.3-32.3) for UTI in daytime UI children. Neveus [52] was able to demonstrate similar connections; OR 2.3 (1.3-3.9) and similar results were seen in Sureshkumar´s study

[95]; OR 5.6 (2.0-15.6). However, these infections should probably be regarded as a consequence of the functional bladder disturbance with UI and not the other way round as a cause of the UI.

6. SUMMARY POINTS

Nocturnal enuresis (NE)

- The prevalence of NE at age 7 seems to be around 11% for most countries, at age 11-12 years around 3.7% and at age 16 around 1.3%.
- The spontaneous cure rate seems to be around 15% annually between 7 and 12 years, and between 12 and 17 years 11%.
- In an adult population the prevalence of NE seems to be 0.5-2%. The prevalence was 1% when including only those with childhood enuresis. Thus the risk of having persistent NE as adult if having the condition at 7 years of age can be calculated to 1%.
- Potential risk factors for NE in children include OAB, polyuria, family history, psychopathology, developmental delay, mental retardation, socio-cultural factors, sleep and arousal problems, sleep apnoea, constipation, sexual abuse and organic conditions such as infravesical obstruction.

Functional incontinence

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

IV. EPIDEMIOLOGY OF URINARY INCONTINENCE IN WOMEN

This section presents a narrative account of a targeted selection of high quality studies that illustrate what is currently understood about the prevalence, incidence, and risk factors for UI including its common subtypes, stress UI, urgency UI, and MUI.

1. GENERAL COMMENTS AND DEFINITIONS

Current terminology for female UI is drawn from the 2010 IUGA/ICS joint terminology report [105], but in most instances is entirely compatible with current terminology for men [106], and children [107]. In considering the epidemiology of female UI, researchers have mainly addressed the epidemiology of the symptom of UI, defined as the complaint of involuntary loss of urine. There remains a paucity of work at a population or community level concerning either the sign of UI, defined as observation of involuntary loss of urine on examination, or on the formal laboratory diagnoses of USI or DO.

A large majority of epidemiological studies have either not considered subtypes of UI, or only reported on SUI (complaint of involuntary loss of urine on effort or physical exertion), UUI (complaint of involuntary loss of urine associated with urgency), and MUI (complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing). A small number of studies have reported prevalence and risk factors for adult NE (complaint of involuntary urinary loss of urine which occurs during sleep). With a lack of validated questionnaire items for less common subtypes, the current literature is almost silent regarding the population prevalence and risks for postural incontinence, continuous incontinence, insensible incontinence, and coital incontinence, although they are sometimes grouped as “other incontinence”. Finally, there remains a separate category of incontinence, so called “functional incontinence”, more typical of institutionalised older adults, for whom physical or cognitive impairment limits their ability to use a toilet.

There are a large number of urinary symptom questionnaires employed in epidemiological research all with varying evidence of validity. Most questionnaires were initially developed using secondary care, i.e. hospital and institutional samples, with criterion validity demonstrated in comparison to bladder diaries, pad tests, or urodynamic diagnoses. Quite widely varying terminology is used in the items assessing SI and UI in different questionnaires (see Table 1 overleaf), and some items do not capture all aspects of the standardized definitions. Even the surrounding context for the items is known to strongly affect prevalence estimates [108-109], and small variations in terminology from different questionnaires may have similar effects.

The optimal assessment of incontinence subtypes remains controversial [110-111], but it is clear that self-report of symptoms differs systematically from detailed clinical evaluation. In particular, for women, MUI is more common than would be expected by chance, at least using questionnaire evaluation [112], and is reproduced less frequently using urodynamics [113-114]. SUI and UI have different treatment options, and are presumed to have different underlying pathophysiology. Caution is therefore needed when comparing epidemiological studies that either do or do not report a separate MUI subgroup, and when generalizing from population level data on MUI to clinical practice.

Self-report of UI symptoms should reflect the woman’s own experience of incontinence, but may bear little relationship to felt or expressed need for treatment. Across multiple measures, incontinence severity is shown to be only a moderate predictor of incontinence specific quality of life impairment [115-116]. It is important therefore to characterize both the severity of symptoms, through frequency of leakage and/or quantity of loss, and the perceived bother or impact on activities. Most questionnaires in contemporary use, including the ICIQ-SF, ICIQ-FLUTS and DAN-PSS, therefore ask patients to report both the frequency of UI, and its perceived bother (Table 6). Cautious interpretation should be made of high prevalence rates obtained with case definitions that do not incorporate some measure of symptom bother or impact.

UI is a stigmatizing condition in many populations [117], which creates a high risk for respondent bias in UI epidemiology [118-119]. Perhaps because of stigma, incontinence is also associated with low rates of presentation for care. Surveys assessing UI in healthcare settings may therefore also be highly prone to both medical

Table 6 Stress incontinence and urgency incontinence items from a range of validated questionnaires widely used in epidemiologic research

Questionnaire	Validation Paper	Stress Incontinence Item	Urgency Incontinence Item
King's Health Questionnaire	Kelleher et al., 1997 (127)	Urinary leakage with physical activity e.g. coughing, running	Urinary leakage associated with a strong desire to pass urine
BFLUTS & ICIQ-FLUTS	Jackson et al, 1996 (128)	Does urine leak when you are physically active, exert yourself, cough or sneeze?	Does urine leak before you can get to the toilet?
Dan-PSS (English version)	Schou et al, 1993 (129)	Do you experience leakage of urine when you physically exert yourself (e.g. coughing, sneezing, lifting)?	Is the compulsion to pass urine so strong that urine starts to flow before you reach the toilet?
OAB-q	Coyne et al, 2002 (130)	N/A	Urine loss associated with a strong desire to urinate
Urogenital Distress Inventory	Shumaker et al, 1994 (131)	Do you experience urine leakage related to physical activity, coughing or sneezing?	Do you experience urine leakage related to the feeling of urgency?
EPIQ	Lukacz et al, 2005 (132)	Do you experience urine leakage related to activity, coughing, or sneezing?	Do you experience urine leakage related to a feeling of urgency?
PFDI	Barber et al, 2005 (133)	Do you usually experience urine leakage related to laughing, coughing, or sneezing?	Do you usually experience urine leakage associated with a feeling of urgency; that is, a strong sensation of needing to go to the bathroom?

surveillance bias, in which presentation to care for other reasons results in a diagnosis of UI; and Berkson bias, in which selection of cases from within hospitals tends to reduce generalizability to the population, and may suggest associations with spurious risk factors. We therefore focus on community or population based samples with response rate over 60% [120]. To further minimize differential effects of such biases, where possible we report outcomes stratified by age, by type of UI, and by major subgroups of interest.

The majority of work reviewed in previous editions of this chapter, originated from the OECD countries. There have been many recent studies from both BRIC and developing countries [121] which are now reviewed. Subsequent discussion excludes however the epidemiology of obstetric vesico-vaginal fistula, which is covered in a later chapter.

2. PREVALENCE

Among general population studies unadjusted prevalence estimates for the most inclusive definitions of UI ('ever' 'any' or 'at least once in the past 12 months') have ranged from 5% to 69% [122], with most studies reporting a prevalence of any UI in the range of 25% to 45%. This enormous variation between studies is seen both within and between countries, and with few studies reporting age standardized rates, largely precludes meaningful comparison between countries. If there is variation in true prevalence rates between countries, it is obscured by cultural differences in the perception of UI and willingness to report UI, as well as methodological differences [123], including in the wording of questionnaire items, in the method of administration of questionnaires, and perhaps most importantly, with differences in case definitions employed [124-125]. There remains a severe lack of studies from the developing world [126].

Very few studies have used the same survey tools and methods to report female UI general population prevalence in more than one country (Table 7). Four studies have attempted to assess the relative prevalence in western nations [134, 136,138-139]. Across all countries surveyed, all these studies find that SUI is the most common subtype, followed by MUI, and then UUI. Hunskaar and colleagues surveyed 29,500 women in France, Germany, the UK and Spain [134]. By demonstration of similar age trends across all countries, they suggested both lower overall prevalence of incontinence in Spain, and a relative excess of urgency incontinence in France. The EPIC (Epidemiology of Incontinence) and EpiLUTS (Epidemiology of Lower Urinary Tract Symptoms) studies [136,140] used similar questionnaire items explicitly based on standard definitions. However, there was inconsistency between studies. The EpiLUTS study found similar prevalence of each UI subtype in the US, UK, and Sweden, while the EPIC study reported a more than 3-fold variation in prevalence between countries, with Sweden having a prevalence of 29.5% and Italy only 9.3%. The disparity in results could be explained by differences in sampling methods, or different response rates (58%, 33% and 59% respectively). A further study set in Senegal, Mauritania, and Chad, reports substantial variation in prevalence across countries, even after age stratification [135]. Finally, in a recent survey using identical methods across Russia, the Czech Republic and Turkey (n=3,130) [141] there was noted similar prevalences in Russia and Czech Republic, but an excess of urinary storage symptoms (including UI) in Turkey. Again, it is unclear whether such differences are due to linguistic differences in questionnaires, differences in response proportion, or true cultural or biological differences. The lack of consistency in between country comparisons, even for large surveys set in western nations, makes it impossible to assess the extent of true variation between countries. It also remains difficult to establish stable, meaningful prevalence rates for female UI, when there is no consensus about what constitutes significant UI. Again, extreme caution is needed in making direct comparison of crude prevalence rates.

Although between study comparisons of female UI prevalence are largely unrewarding, we can meaningfully compare within study distributions of UI by age and UI subtype. Table 8 summarizes prevalence estimates by age for female UI from community or population based studies with response rate >60%. Again a 10 fold variation in

unadjusted prevalence rates is evident between studies, so where available, overall prevalence rates are given by UI subtype, while age trends are depicted with sparklines. These depict the variation in age specific prevalence across the full age range of each study.

Table 7 Population prevalence rates for female UI from studies sampling in more than one country.

Reference	Method	Age	Country	Sample	Overall Prevalence %			
Hunskaar et al., 2004 (134)	Postal	18+	France	3,881	All UI SUI UUI MUI	44 13.6 11.9 15.0		
			Germany	3,824	All UI SUI UUI MUI	41 16.4 6.6 15.6		
			Spain	6,444	All UI SUI UUI MUI	23 9.0 4.8 6.0		
			UK	2,931	All UI SUI UUI MUI	42 17.2 6.7 14.3		
Niang et al., 2010 (135)	Postal	16+			Age	<30	30-59	60+
			Senegal	682	All UI	31.4	30.9	25
			Mauritania	740	All UI	8	13.2	22.7
			Chad	648	All UI	8.7	17.5	95
Irwin et al., 2006 (136)	Direct or phone interview	18+	Sweden	19,165	All UI	29.5		
			Italy		All UI	9.3		
			Canada		All UI	13		
			Germany		All UI	11.4		
			UK		All UI	14.9		
Coyne, Margolis, Kopp, & Kaplan, 2012 (137)	Web Based	40+	US	10,584	All UI SUI UUI MUI	67.0 23.1 6.7 21.1		
			UK	3,983	All UI SUI UUI MUI	69.0 28.6 7.1 19.6		
			Sweden	1,293	All UI SUI UUI MUI	67.1 26.9 7.9 16.		

Table 8 Population based studies with response rate >60%, reporting prevalence of female UI by age, published Jan 2008-July 2016 (earlier studies reviewed in Abrams et al., 2009)

Reference	Country	Sample Size	Survey Method	Age Range	Overall Prevalence (%)		Age Trend
Espuña-Pons et al., 2009 (142)	Spain	9,063	Postal	15+	All UI	12.2	
Herschorn et al., 2007 (143)	Canada	518	Telephone	18-90	SUI UUI	25.5 9.3	
Tahtinen et al 2016 (144)	Finland	2,002	Postal	18-79	SUI UUI	11.2 3.1	
Tennstedt et al., 2008 (145)	US	3,205	Direct Interview	30-79	All UI SUI UUI MUI Other UI	10.4 2.8 1.1 5.9 0.7	
Lee et al., 2008 (146)	South Korea	13,484	Direct Interview	19+	All UI SUI UUI MUI Other UI	24.4 11.9 1.9 10.2 0.5	
Zhu et al., 2008 (147)	China	5,300	Direct Interview	20+	All UI SUI UUI MUI	38.5 22.9 2.8 12.4	
Nygaard et al., 2008 (148)	US	1,961	Direct Interview	20+	All UI	15.7	
Martinez-Agullo et al., 2009 (149)	Spain	3,090	Direct Interview	25-64	All UI	4	
Bodhare et al., 2010 (150)	India	552	Direct Interview	35+	All UI	9.6	
Ojengbede et al., 2011(151)	Nigeria	5,001	Direct Interview	15+	All UI SUI UUI MUI	2.8 2.3 1.0 0.6	
Ahmadi et al., 2010(152)	Iran	800	Direct Interview	40-95	All UI	38.4	
Liapis et al., 2010 (153)	Greece	2,000	Direct Interview	20-80	All UI SUI UUI MUI Other UI	27.0 11.9 3.0 11.1 1.1	
Amaro et al., 2009 (154)	Brazil	685	Postal	22-96	All UI	27	
Lopez et al., 2009 (155)	Puerto Rico	276	Direct Interview	21-64	All UI SUI UUI MUI	34.8 16.7 4.0 14.1	
Correia et al., 2009 (156)	Portugal	1,483	Telephone	40+	All UI	21.4	
Slieker-ten Hove et al.2010 (157)	Netherlands	1,397	Postal	45-84	All UI SUI UUI MUI	58.8 30.6 6.1 23.2	

Reference	Country	Sample Size	Survey Method	Age Range	Overall Prevalence (%)		Age Trend
Ge et al., 2011 (158)	China	3,058	Direct Interview	20-96	All UI SUI UUI MUI	22.1 12.9 1.7 7.5	
Botlero et al., 2008 (123)	Aus	504	Postal	24-80	All SUI UUI MUI	6.8 4.8 0.7 1.3	
Wennberg et al., 2009b(159)	Sweden	1,023	Postal	20+	1991 All 2007 All	14.7 27.8	
Franzen et al., 2009 (160)	Sweden	4,609	Postal	18-79	All	28.9	
Zhu et al., 2009 (161)	China	19,024	Direct Interview	20-99	All SUI UUI MUI	30.9 18.9 2.6 9.4	
Lasserre et al., 2009 (162)	France	2,183	Direct Interview	18+	All SUI UUI MUI	26.8 12.1 2.9 11.2	
Onur, 2009 (163)	Turkey	2,275	Direct Interview	17-80	All SUI UUI MUI	46.3 21.3 19.9 16.7	
Zumrutbas et al., 2014 (164)	Turkey	919	Direct Interview	18+	All SUI UUI MUI	38.7 21.2 8.2 2.6	
Kwon & Lee, 2014 (165)	South Korea	9,873	Direct Interview	20+	All	7.9	
Liu et al., 2014 (166)	China	5,433	Direct Interview	20-100	SUI UUI MUI	14.0 3.0 6.3	
Wu et al., 2014 (167)	US	8,368	Direct Interview	20+	All	17.1	
Ebbesen et al., 2013 (168)	Norway	21,804	Postal	20+	All	29	
Osuga et al., 2013 (169)	Japan	1,218	Postal	40+	All SUI UUI MUI	6.6 5.4 3.2 2.1	
Horng et al., 2013 (170)	Taiwan	4,661	Direct Interview	35+	All	22	
Brito et al., 2012 (171)	Mexico	1,180	Direct Interview	45-65	SUI	15.3	

As in the studies comparing prevalence between countries, absolute prevalence rates vary widely in recent cross-sectional work. However, the distribution of UI subtypes is consistent. Isolated SUI accounts for approximately half of all incontinence, with most studies reporting 10-39% prevalence. With few exceptions, mixed incontinence is found to be next most common, with most studies report 7.5-25% prevalence. Isolated urgency incontinence is uncommon, with 1-7% prevalence, and where recorded at all, other causes of incontinence occur with approximately 0.5-1% prevalence. In summary, current data provide very disparate estimates of population prevalence for UI in women. Approximately 10% of all adult women report leakage at least weekly. Occasional leakage is much more common, affecting 25%-45% of all adult women. Prevalence rates from cross-sectional studies uniformly demonstrate an association with age, which is explored in more detail in the subsequent section on risk factors.

3. INCIDENCE AND REMISSION

Many prospective longitudinal studies have examined UI in women, either in the general population, or focused on pregnancy, menopause or old age. However, interpretation and comparison of incidence and remission rates is fraught with difficulties. Incontinence is not intuitively a condition, with fluctuating severity, indeed the popular perception in both the medical community and the general public, is of a chronic condition. However, misclassification due to the unreliability of symptom assessment tools may cause the appearance of symptom fluctuation. Measuring the short term test re-test reliability for the BFLUTS questionnaire [128], the DAN-PSS [172], the IIQ [173], or any of the other commonly used questionnaires suggests that only 80-85% of item responses are stable over even a brief retest period. Thus even when a longitudinal study is able to use the exact same item for assessment across even relatively long periods of follow up, the effect of misclassification due to questionnaire unreliability may obscure a true effect of incidence or remission. Even non-differential misclassification bias, can have serious consequences both for estimates of absolute cumulative incidence, and relative incidence risk, and such effects are largest for conditions such as UI, with high prevalence and low incidence [174].

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

Annual incidence rates for broad definitions of UI (“monthly” or “any”) range from 0.9% to 18.8%, while rates for weekly UI show less variation at 1.2-4.0%. There is a significant negative correlation between the length of a study and its reported annualized incidence rate, suggesting that short studies of 1-2 years overestimate incidence due to a dominating effect of misclassification. Limiting comparisons to studies with >5yr follow up suggests incidence of 1.3-4.9% even for inclusive definitions of UI. Fewer studies have reported remission rates, and again estimates vary widely between 1.2 and 42%. Again, limiting the comparison to longer studies of >5yrs suggests rates of 2.1 to 5.0%. Overall these results are compatible with findings from cross-sectional studies, with modest increases in UI prevalence across the whole female population of 0.5-1% per year. Although the extent of cohort effects has rarely been reported, current data suggests that earlier cohorts are less likely both to report incontinence [167, 175], and to seek care for it [176].

Table 9 Studies reporting incidence and/or remission for UI in women

Study	Country	Period (years)	♀ Sample Size	Loss to Follow Up (%)	Baseline Age	Case Definition	Prevalence at baseline (%)	Prevalence at follow up (%)	Annual Incidence (%)	Annual Remission (%)
Samuelsson et al., 2000)(177)	Sweden	5	457	16.4	20-59	Any UI	23.5	27.5	2.9	5.9
Hagglund et al., 2004 (178)	Sweden	4	338	26.6	20-50	Any UI	45.6	47.5	4.2	4
Wehrberger et al., 2006 (179)	Austria	6.5	925	52.3	20+	Any UI Weekly UI	32.0 n/a	43.3 n/a	3.9 2.1	2.9 n/a
Townsend et al., 2007a (180)	US	2	64,650	18.4	36-55	Monthly UI Weekly UI	52.5 n/a	48.3 n/a	6.9 1.9	7.0 n/a
Dallosso et al., 2003 (181)	UK	1	6,424	48.9	40+	Monthly SUI	17.3	n/a	8.3	n/a
McGrother et al., 2004 (182)	UK	1	12,036	20.2	40+	Any UI	34.2	n/a	8.8	25.2
Donaldson et al., 2006 (183)	UK	3	12,750	33	40+	Any SUI	16.9	n/a	6.1-7.3	33.7-34.9
Waetjen et al., 2007 (184)	US	5	3,301	18.1	40-55	Monthly UI Weekly UI Monthly SUI Monthly UUI Monthly MUI Other UI	46.7 15.3 32.2 9.2 13.8 2.7	n/a	11.1 1.2 5.0 3.2 2.4 0.5	n/a

Study	Country	Period (years)	♀ Sample Size	Loss to Follow Up (%)	Baseline Age	Case Definition	Prevalence at baseline (%)	Prevalence at follow up (%)	Annual Incidence (%)	Annual Remission (%)
Liu et al., 2002 (185)	Australia	2	2,272 (♂&♀)	13.9	65+	Any SUI Any UUI	12.1 38.4	15.4 37.4	15.4 18.8	n/a n/a
Goode et al., 2008 (186)	US	3	490	5	65+	Monthly UI	0.41	n/a	9.7	13
Ostbye et al., 2004 (187)	Canada	10	5,332	60.2	65+	Any UI	19.5	28.8	1.8	n/a
Wennberg et al., 2009a (176)	Sweden	16	2,911	51.6	20+	Any UI	14.6	27.8	1.3	2.1
Moller et al., 2000 (188)	Denmark	1	2,860	20.1	40-60	Weekly SUI Weekly UUI	13.1 7.3	11.0 6.7	4.0 2.7	41.4 42.0
Hotledahl et al., 1998 (189)	Norway	1	507	3.6	50-74	Monthly UI	30.6	29.8	0.9	1.4
Byles et al., 2009 (190)	Australia	9	12,432	42.4	70-75	Sometimes UI	20.7	27.3	1.62	n/a
Lifford et al., 2008 (191)	US	2	58,703	10.4	54-79	Monthly UI Weekly UI	45.2 n/a	51.6 n/a	4.6 1.8	6.6 4.4
Jackson et al. 2006 (192)	US	2	1,017	19	55-75	Any UI	66	63.1	9.6	7.1
Nygaard et al., 1996 (193)	US	6	2,025	n/a	65+	Any SUI Any UUI	40.3 36.3	n/a n/a	4.77 4.75	5.02 3.68
Iglesias et al., 2005 (194)	Spain	5	486	34.9	65+	Any UI	41	54	7.2	2.8
Herzog et al., 1990 (195)	US	2	1,154	30.2	60+	Any UI	37.7	52.7	15.8	7.5
Burgio et al., 1991 (196)	US	3	541	61.9	42-50	Monthly UI	30.7	n/a	2.7	n/a
Melville et al., 2009 (197)	US	6	5,820	18.1	57-67	Monthly UI	13.5	n/a	3.5	n/a
Jahanlu et al., 2010 (198)	Norway	10	2,331	13	40-44	Any UI	38.9	43.9	4.9	n/a
Legendre et al., 2014 (199)	France	12	4,127	7.4	46-50	Any UI	24.5	34.7	3.3	6.2

4. POTENTIAL RISK FACTORS

This section summarises the most important reported demographic, social, environmental, and lifestyle correlates of urinary incontinence in women. Familial risk factors for UI and POP are considered together in the section on genetic epidemiology.

While a majority of previously cited studies have reported associations with incontinence, great caution is again needed in assigning these as causal risk factors. As already seen, a large majority of studies are cross-sectional in design, providing no evidence of causation, since the temporal association of the putative risk factor and the onset of UI cannot be assessed. Where possible we therefore try to focus on risk factors for incident UI, from longitudinal studies. Again though, with the exceptions of mode of delivery, menopause hormone therapy, and weight loss, there remains a dearth of interventional studies. Even the highest quality observational studies may suffer from residual or unmeasured confounding, further limiting conclusions about causality.

4.1. Age

The age distribution for UI of all causes reported in the widely cited EPINCONT study [200], depicts a steady increase in moderate and severe UI throughout the adult lifespan, but with a distinct peak in slight UI around the time of the menopause. Other large studies have, however, reported a steady increase in prevalence for both slight and severe UI, without a distinct menopausal peak [201]. The timing and causes of a fifth and sixth decade peak has been explored in a number of high quality longitudinal studies of menopausal transition, discussed subsequently. Where such a peak is identified from cross-sectional studies, it is most pronounced for SUI [134,202]. Across most cross-sectional studies isolated SUI declines into old age, as MUI becomes relatively more common [200,203]. Besides methodological differences, disparity in age ranges, severity thresholds, and proportion of each subtype of UI probably therefore explains the modest differences in age trends seen in Table 8. These age trends, drawn from cross-sectional studies, may in any case be biased by cohort or period effects.

While most cross-sectional studies find an increase in prevalence into old age, some high quality studies have identified a peak in all cause UI, with a decline in the eighth and ninth decade [165]. Such a large disparity might be explained by sampling strategies that include or exclude institutionalized adults. The epidemiology of UI in this vulnerable group deserves special attention, and of course remains of key interest to geriatricians. The epidemiology of UI in nursing home residents has been the subject of one systematic review [204]. Only one primary study provides data from more than one country, allowing cross-border comparisons. From a population of 279,191 elderly people in care homes, from Denmark, France, Iceland, Italy, Japan, Sweden, and the US, the prevalence of female UI was relatively stable at 42.0-72.5% [205], with much of that variation accounted for by differences in age structure, and proportion of residents with functional or cognitive impairment. Indeed variability in prevalence estimates for female care home residents across the entire literature is much less than for the general population [204], ranging from 42.0% in Japan [205] through to 78.4% in the US (using a much more inclusive definition) [206]. UI is associated with nursing home admission from the community [207]. This may in part explain the apparent steeper increase in prevalence with age in nursing homes compared to community dwelling samples [206]. Loss to follow up certainly limits our ability to accurately assess age trends in the elderly from cross-sectional studies.

Given the difficulties in establishing robust incidence estimates, most longitudinal studies do not provide good evidence of age trends in incidence. Studies have variably reported no change in incidence with age, or a stable incidence in middle age, with a sharp increase in old age. However, the large Nurse's Health Study cohort [180] provided good evidence of a decrease in incidence of SUI following the menopause, which has more recently been explored in analyses of the SWAN study [208], the 1946 British Birth Cohort [202] and the Hordaland Women's Cohort [209]. All these studies provide consistent evidence of a peak in UI at the time of the menopause, with pre- and peri-menopausal status being associated with increased incidence of UI and decreased remission of UI compared to post-menopause. As will be discussed in the section on menopausal replacement therapy, part of this peak may be iatrogenic. Consistent with evidence from cross-sectional studies [134,200] the peak is attributable mainly to mild SUI.

While the association between age and female UI is clearly important for planning healthcare resource allocation, in many studies this is not an independent association. Other risk factors associated with age, including parity, co-morbidities, and BMI attenuate the association with UI [201], and additional adjustment for relevant co-morbidities typically eliminates the association [145]. Confounding factors adequately explain the association between age and UI, and therefore UI in women should not be considered as an intrinsic consequence of the aging process itself.

4.2. Obesity and Adiposity

Obesity is perhaps the most clearly established risk factor for UI in women. There is a wealth of cross-sectional, longitudinal, and interventional data demonstrating positive association between BMI and UI, which has been subject of several systematic reviews [210-212]. Across a wide range of studies obese women have approximately double the risk of UI. A typical pattern of association, taken from the large (n = 83,355) Nurses' Health Study II [213] is demonstrated in Figure 5. The ORs for UI by severity are plotted against BMI, from underweight through to obese. Although the Nurses' Health Study II is limited to middle aged women, such findings are consistent across all age groups, both within studies [214] and between studies [210]. This association is quite minimally attenuated by adjustment for other risks for UI.

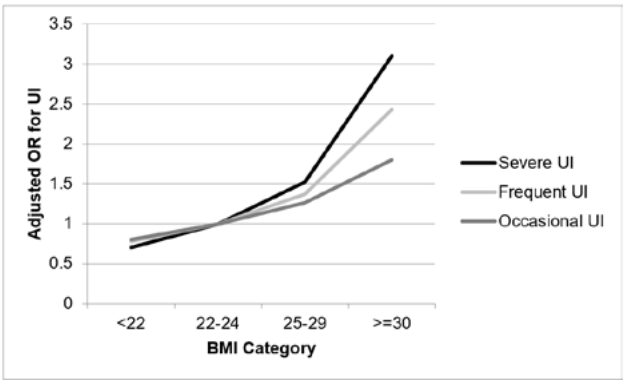

Figure 5 Associations between BMI and UI severity from the Nurses' Health Study II. Original figure created based on data reported in Danforth et al, AJOG 2006 [213].

Data from the EPINCONT survey also demonstrate the same positive association between BMI and more severe UI. Additionally they indicate that such associations hold for the major subtypes of UI (Figure 6), but are most pronounced for mixed UI, and relatively modest for UUI. Similar findings were reported for data from the Heart and Estrogen/Progestin Replacement Study [215] and the 1946 British Birth Cohort [216] with the associations with BMI being greater for SUIor MUI compared with UUI.

The temporal association between BMI and UI is also established with data from the 1946 British Birth Cohort, SWAN, MRC Incontinence [181] and the Nurses' Health II studies demonstrating that earlier onset of obesity is associated with increased risk for UI in middle age [217] and that both higher BMI and greater weight gain are associated with increased risk of incident UI [181,184, 218]. Although again it is hard to compare between studies, it appears that BMI may be a greater risk factor for incident UI than for prevalent UI adding credence to the association [184]. As for cross-sectional studies, the association is stronger for incident SUI and MUI, compared with incident UUI [181, 184].

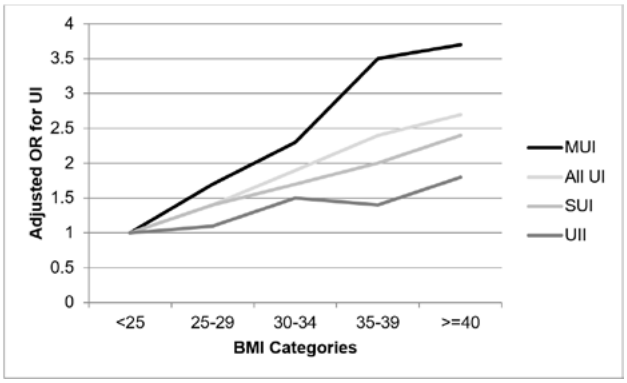

Figure 6 Associations between BMI and UI subtype from the EPINCONT study. Original figure created based on data reported in Hannestad et al, BJOG 2003 [231].

There is adequate evidence [219-220] that obesity increases intra-abdominal pressure, predisposing to SUI, while metabolic syndrome associated with obesity predisposes to UUI [221-224]. Consistent with this, waist circumference and waist to hip ratio appeared to be associated only with stress UI, and not with urgency UI in the SWAN [184] and HERS studies [215]. More recent data from BACH [225] and KNHNES [226] indicate that measures of central adiposity are also correlated with UUI.

Finally, intervention studies for weight reduction have reported that even modest weight loss is associated with improvement or resolution of both SUI and UUI, with the probability of resolution correlated to the degree of weight loss [219, 227-230]. Despite the complex interplay between weight and other risk factors for UI, we still have robust evidence to support a causal role of BMI in the development of UI.

4.3. Parity, pregnancy & mode of delivery

Parity is considered by the laity as among the most important risk factors for UI. This is reflected in almost all large cross-sectional surveys (Figure 7). Some early studies reported a threshold effect at one delivery and little or no additional risk with increasing parity [232-234] but in most subsequent work, increasing parity is associated with increased risk of UI. A single delivery is typically associated with adjusted OR of around 1.3-1.6 for UI, and further deliveries linearly increasing the risk up to an adjusted OR of 1.5-2.0 [184,201,213,235].

As expected these effects are strongest in the third and fourth decades, with substantial attenuation through middle age, and in many studies no persistent effect in old age [214,235-237] as other risk factors come to dominate. Although the EPINCONT [235] and SWAN [184] studies reported only association between parity and SUI or MUI, other studies have also suggested, a reduced but significant association with UUI [238-239].

There is a substantial difference in effect between vaginal delivery and caesarean delivery, that has also been the subject of systematic reviews [250-252]. Over short term follow-up meta-analysis of data from four large cross-sectional studies [253-256] suggested a significant protective effect of caesarean on stress UI (OR 0.56) and MUI (OR 0.70). For long term follow up, meta-analysis of 15 studies again found almost double the risk of SUI after any vaginal delivery (spontaneous, or assisted) compared to any caesarean section (adjusted OR 1.85, absolute risk difference 8.2%), with a smaller effect on UUI (adjusted OR 1.30, risk difference 2.6%). In meta-regression of long term studies the effects on SUI were much more pronounced for younger women, further adding to our confidence in assigning a causal role for vaginal delivery.

Generally across all observational studies, women delivering exclusively by caesarean have similar prevalence for UI as age matched nulliparous women. While the existing interventional studies remain significantly underpowered, the same direction of effect for caesarean is still seen [257].

Pregnant women, and those in the early post-partum period are typically excluded from population-based studies of UI, but a large body of work considers the specific epidemiology of UI in and around pregnancy. A systematic review [258] including 33 population-based studies, each with response rate over 50% concluded that the prevalence of UI in the first three months post-delivery was 30%, with infrequent SUI being the most common. The difference in UI rates between women delivering vaginally and those delivering by caesarean is evident immediately after delivery. As demonstrated in Table 5 (adapted from Abrams et al 2009 [122]), there is a gradual decrease in prevalence during the first post-partum year.

Despite the protective effect of caesarean, for many women the onset of UI is during pregnancy itself. The point prevalence of UI is low in the first trimester, rising rapidly in the second trimester and increasing slightly in the 3rd trimester [259-260]. In the population based Norwegian Mother and Child Cohort Study, (n=43,279), the prevalence of SUI from before to during pregnancy, rose from 9% to 31% in nulliparous women, and from 24% to 42% in parous women [261]. In contrast, MUI showed a similar rise in both groups (from 6% to 16% and from 8% to 20%, respectively). UUI remained virtually unchanged in both groups at less than 5%. In follow up of these women, the onset of UI during pregnancy was strongly predictive of post-partum UI (adjusted RR 2.3, 95%CI 2.2-2.4), with little modification by mode of delivery. Such an effect seems to persist into long term follow up [262-265] even for women who return to full continence in the immediate post-partum period. It seems that the temporary physiological changes during pregnancy may reveal women with a predisposition to UI in later life, in a manner analogous to gestational diabetes [266].

There are other suggested potentially modifiable obstetric risk factors, including induction of labour, forceps delivery, and use of episi-

Table 10 Prevalence of urinary incontinence in the first post-partum year among primiparous women by type of delivery

Reference	Country	Type of delivery	N	Type of UI	Severity of UI	Prevalence (%) by months post-partum		
						1 to 3 months	4 to 6 months	7 to 12 months
Chaliha et al., 1999 [240]	UK	VD	289	All Stress	Any	15 13		
		CS	131	All Stress	Any	9 8		
Eason et al., 2004 [241]	Canada	VD	467	All	Any >Weekly Daily	31 10 3		
		CS	104	All	Any >Weekly Daily	12 2 1		
Eftekhar et al., 2006* [242]	Iran	VD	357	Stress	Any		16	
		CS elCS emCS	345	Stress	Any		12 11 25	
Ekstrom et al., 2008 [243]	Sweden	VD	197	Stress Urge	Any	20 4		15 6
		elCS	192	Stress Urge	Any	4 3		5 5
Pregazzi et al., 2002 [244]	Italy	VD	379	Stress Urge	Any	8 6		
		SVD	218	Stress Urge	Any	16 1		
Farrell et al., 2001* [245]	Canada	SVD	313	All	Any	23	22	
		CS elCS emCS	125 27 98	All	Any	8 4 9	10 5 12	
Groutz et al., 2004* [246]	Israel	SVD	145	Stress	Fortnightly			10
		elCS emCS	118 100	Stress	Fortnightly			3 12
Glazener et al., 2006* [247]	New Zealand, UK	VD SVD IVD	2805 1954851	All	Any	32, 29 31, 28 33, 30		
		CS	569	All	Any	16, 12		
Schytt et al., 2005 [248]	Sweden	VD SVD IVD	750 617 133	SUI	Any			20 19 22
		CS elCS emCS	165 43 122	Stress	Any			9 0 11
Borello-France et al., 2006 [249]	USA	VD	356	All Stress Urge Mixed	Any	35 17 4 15	31 14 3 14	
		elCS	116	All Stress Urge Mixed	Any	25 11 4 10	23 14 1 8	

Table adapted and updated from Abrams, Cardozo, Khoury and Wein 2009
VD=all vaginal deliveries; SVD=spontaneous vaginal delivery; IVD=instrumental vaginal delivery (forceps and/or vacuum); CS=all Caesarean Sections; elCS=elective Caesarean Section (prior to labor); emCS= emergency Caesarean Section (after onset of labor)
**** Prevalence estimates restricted to women with no UI prior to pregnancy***

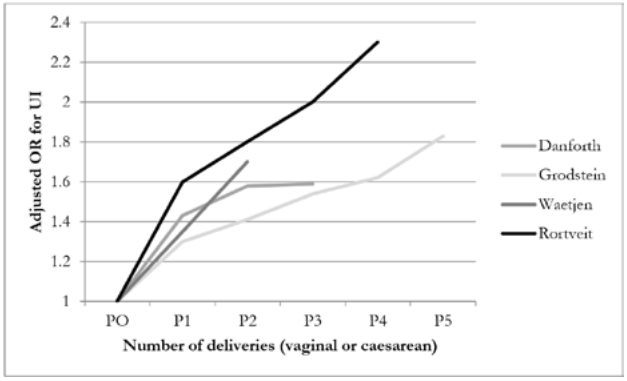

Figure 7 Adjusted OR for UI from selected large cross-sectional surveys. Figure created for this chapter combining data in references (Danforth et al., 2006; Grodstein et al., 2003; Rortveit et al., 2001; Waetjen et al., 2007) [184,201,213 och 235].

otomy. Regardless of conflicting observational evidence of an effect of episiotomy (for example references 241,249,267-268) there are a large number of interventional studies that have not shown either harm or benefit [269]. Similarly while forceps delivery has conflicting evidence from observational studies (for example references 245,269,270-272) within the context of the second stage of labour, maternal UI is of secondary importance in decision making regarding choice of delivery instrument [273]. In a similar vein, while induction and augmentation of labour, and use of epidural anaesthesia have each been identified as being associated with both early postpartum and persistent UI [244, 274-276] it is doubtful whether this should have any effect on current obstetric practice.

Many other suggested obstetric risk factors, including age at first delivery, and birth weight, are perhaps not meaningfully modifiable. Several studies have suggested that older age at either first or last birth is associated with UI [216,277-279] although more recent data from the RRISK study suggested a U shaped distribution [275] with very young mothers also at increased risk. Inadequate adjustment for socio-economic class may explain all these effects. Numerous studies have suggested that greater birth weight at a single delivery, or maximum weight of infant across all deliveries may also be associated with UI [236,247,275,280]. Although elective caesarean would be protective, birth weight is still challenging to predict, and again pragmatic randomized interventional trials are needed before making clinical recommendations.

4.4. Menopausal Replacement Therapy

Menopausal oestrogen replacement therapy was once widely prescribed as a treatment for UI during or after menopause, on the basis of rather heterogeneous data from clinical trials [281] and inconsistent associations in cross-sectional studies [276,282]. While current evidence overall continues to support prescribing of topical oestrogen [283], the Nurse's Health Study [284], the Heart Estrogen/Progestin Replacement Study (HERS) [285], and Women's Health Initiative (WHI) Hormone Replacement Trial [286] all provided strong evidence that oral oestrogens, with or without combined progestogens were associated with increased incident UI. In the placebo controlled HERS trial, women randomized to conjugated oral oestrogen plus medroxyprogesterone were more likely to experience worsening of their incontinence over 4 years (39% vs. 27%, p<.001) [285]. In the randomized WHI trial, continent women receiving oestrogen, with or without progestogen, were approximately twice as likely compared to women receiving placebo to have developed SUI at 1 year (16% vs. 9%, p<.0001) [286]. The risks of MUI and UUI were also significantly increased, though more modestly. Further trials including oestrogen arms have subsequently been reported during development of selective estrogen receptor modulators (SERMs), confirming these findings [287]. Some SERMs have themselves been associated with an increased risk of UI [288], although raloxifene appears safe [289].

4.5. Hysterectomy

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

Among a sample of 1,517 Taiwanese women aged 65 years and over, hysterectomy was associated with OR 1.8 for UI, with no difference between abdominal and vaginal hysterectomy [290]. Earlier trials had, however, suggested either no effect [177, 198] or rather more modest effects [291]. Where an association is found, it is strongest with case definitions consistent with "severe UI" [192,213,254] perhaps reflecting high rates of mild UI in controls. Using a sample of more than 900,000 women from the Swedish Population Register, abdominal hysterectomy for benign disease was associated with a hazard ratio of 2.1 for subsequent SUI surgery, while vaginal hysterectomy for prolapse was associated with a hazard ratio of 6.3 [292]. Similar results were observed comparing hysterectomy and endometrial ablation in the Scottish Morbidity Returns database [293]. Recent data from a randomized trial of levonorgestrel-IUS versus hysterectomy [294] does confirm this effect. In follow up of 236 women, increased incidence of stress UI (OR 1.83 95%CI 1.01-3.22) was first apparent at 10 year follow, with significantly higher rates of treatment for both SUI and UUI.

Overall, hysterectomy appears to be associated with development of subsequent UI symptoms, and particularly with the need for SUI surgery. One potential mechanism is loss of pelvic floor support at the time of surgery. The data from observational studies should still be considered cautiously, as findings may be influenced by both healthy responder bias and medical surveillance bias, the latter of which may also affect unblinded interventional studies.

4.6. Diet

Many dietary constituents including coffee, tea, alcohol and carbonated beverages have all implicated in the pathogenesis of UI. Dietary data are difficult to obtain reliably [295] and women may change dietary intake in response to UI, making cross- sectional studies of diet and UI difficult to interpret.

The consumption of coffee or other caffeinated drinks as a risk factor for UI has been most widely studied. While some studies report a positive association associated with an increased risk of UI [187,296-298] others have either report no association [299-301] or a protective effect [181,302]. Even within the large EPINCONT study there were conflicting findings regarding coffee, with a positive association with mixed UI, but a negative association with SUI [231]. The WHI study demonstrated a dose-dependent positive association between caffeinated coffee and UUI, but not for decaffeinated coffee or for other UI subtypes [303]. The EPINCONT study suggested a positive association between tea drinking and SUI or MUI [231] while analysis of the Swedish Twin Registry Cohort showed an association only with OAB [302]. The Leicester MRC Incontinence study is one of two studies to have used food

frequency questionnaires, and found no association with tea [181]. It is unclear whether tea consumption contributed significantly to the overall association between UI and dietary caffeine in the WHI study [303]. At a population level the overall picture is therefore unclear, despite suggestive evidence of improvements in symptoms reported from interventional trials of caffeine reduction [304].

Anecdotally, alcohol consumption may be acutely associated with urinary urgency and UI. A positive association between alcohol consumption and UI has been reported by some studies [305] but is found to be either protective [181,306] or of no significance [231] in other studies. Differences between studies may reflect confounding associations between age and alcohol consumption.

The most comprehensive assessment of diet as a risk factor for UI comes from the Leicester MRC study [181]. Besides effects reported above, this study also found increased incidence of SUI with increased intake of carbonated drinks, and reduced incidence of OAB with increased intake of bread, potato and vegetable consumption. While these effects certainly provide interesting avenues for further research, there is no evidence of a causal association, and instead these dietary components may be surrogates for other unidentified socioeconomic risks. Overall there is a lack of consistency in reports of dietary associations with UI that most likely reflects methodological limitations rather than differences between populations.

4.7. Socio-economic status

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

Table 11. Selected studies reporting associations between socioeconomic status and UI in women. Directions of effect summarized across multiple measures of SES. Positive association reported where statistically significant association (OR or RR) of more UI among women of higher social status, and vice versa for negative association.

Reference	Country	♀ Sample	SES Measure	Incontinence Definition	Direction of Association
Huang et al.., 2006 [307]	US	2,109	Educational level	Bothersome UI*	Negative
Sampselle et al., 2002 [308]	US	3,302	Educational level Financial strain	Any UI Bothersome UI*	Positive Negative
Waetjen et al., 2007 [184]	US	2,702	Educational level Social Support	Monthly UI Monthly UUI	Negative Positive
Kraus et al., 2007 [309]	US	654	Occupation	Bothersome UI*	Negative
Tennstedt et al., 2008 [145]	US	3,205	Composite Index	Weekly UI	Nil
Melville et al., 2005 [254]	US	3,506	Educational level Income	Monthly UI Monthly UI	Negative Negative
Saadoun et al., 2006	France	2,640	Educational level Occupation	Monthly UI Monthly UI	Nil Nil
Roe & Doll, 2000 [280]	UK	2,699	Occupation	Monthly UI	Nil
Kuh et al., 1999 [216]	UK	1,333	Educational level Educational level	Monthly SUI Monthly UUI	Positive Nil
Coyne et al., 2009a [311]	US/UK/ Sweden	15,861	Educational level Occupation	Monthly UI Monthly UI	Negative Negative
Ge et al., 2011 [158]	China	3,058	Educational level Occupation	Monthly UI Monthly UI	Negative Negative

Defined using either quality of life questionnaire, or symptom bother rating.

4.8. Smoking

Data from observational studies on smoking is again quite inconsistent. It has been reported to be an independent risk factor for UI in women in some cross-sectional studies [156,213,231,308, 312] but not in many others [145,158,251]. Within studies that do find an association, former smokers have a risk intermediate between never smokers and current smokers, and some dose response effect is evident, adding plausibility.

However, with one exception longitudinal studies have consistently failed to find a significant association between either past or current smoking and incident UI in multivariate analysis [184,187,191,213]. Only in the Leicester MRC study [181] was current smoking associated with increased risk for incident stress UI. The conflicting data from cross-sectional studies and lack of association between smoking and incident UI in most prospective studies suggests that smoking is probably not a causal risk factor for UI.

4.9. Exercise

Evaluating associations between physical activity and UI remains complex. It is clear that high impact exercise such as gymnastics [313-314] or trampolining [315-316] leads to SUI, with a dose dependent deleterious effect. However, women who suffer with UI, and particularly stress UI, may feel less able to engage in such sports [317]. Furthermore with increasing interest in core training as a treatment for UI [318] there are theoretical reasons to believe that low impact exercise might have a direct therapeutic effect. With these competing mechanisms at play, unsurprisingly cross-sectional studies have again produced conflicting evidence (see for example [145,147,319]. However, among cross-sectional studies, comparison of low impact and high impact exercise is suggestive that as hypothesized, high impact sports might be harmful, while low impact sports might be protective [231,320].

Evidence from longitudinal studies overall suggests that exercise does have a protective effect against incident UI, but perhaps only mediated via an effect on weight. In the Leicester MRC study, women who reported that they exercised less frequently were at increased risk for both incident SUI and OAB in a model that adjusted for physical functioning, although notably this association was eliminated in a full model, adjusting for obesity [181]. In a study of 4,291 older women exercise at baseline was not associated with incident UI at 10 year follow up after multivariate adjustment [187]. Perhaps the strongest evidence comes from the Nurses' Health Study [321]. In this population of US nurses aged 54-79, a higher level of physical activity across 14 years of follow-up, was associated with a reduced risk of UI overall, and specifically SUI, although after adjustment for BMI and other factors, the overall effect was small.

4.10. Comorbidities: Diabetes, Urinary Tract Infection, Cognitive Impairment, Ischaemic Heart Disease, Physical Impairment, and Depression

In cross-sectional studies many different comorbidities have been associated with UI in univariate analysis [282,311,322]. However, in most cases these have no explicatory power, being neither a cause nor consequence of UI, but only associated with other known or unknown mediators of UI, or differentially diagnosed due to medical surveillance bias. In this section, we therefore concentrate on studies that are able to adjust for a wide range of confounders, and again give priority to associations of incident UI.

Many cross-sectional studies have reported UI to be more common in women with either type 1 or type 2 diabetes, than among women with normal glucose levels, even after extensive adjustment for known risk factors [168,184,191,254,311,323-324]. There are conflicting data regarding a dose dependent association, e.g. between HbA1C and UI severity [323,325]. Longitudinal evidence is also conflicting. In the Nurses' Health Study cohort [326] Type 2 diabetes was a slight but significant predictor of incident UI (RR=1.21), and the magnitude of the association was seen to increase both with duration of diabetes and with severity of incontinence. Despite significant associations with prevalent UI in the SWAN study, no association with either incident UI [184] or worsening UI was found [184]. Perhaps the best evidence however comes from recent analyses of women enrolled in the Epidemiology of Diabetes and its Complications study. Over 7 years of follow up, more than 10 years after a diagnosis of type 1 diabetes, HbA1C was shown to be a powerful predictor of incident incontinence (odds ratio 1.41, per % HbA1c increase) [327] even after careful adjustment. There are plausible pathophysiological mechanisms by which diabetes might induce incontinence, and it seems likely based on the totally of current evidence that it truly has a causal role.

Acute UTI is a direct cause of transient UI [328] but caution is required regarding a causal association with chronic UI. UTIs are often diagnosed and treated based on symptoms alone, and there may therefore be a risk of misclassification between exposure and outcome. Many cross-sectional studies have found that women with UI are more likely to report having had one or more lifetime UTIs [225,321,329,331] and longitudinal data suggest both that UI can cause UTI, and that UTI can lead to UI. Two prospective studies found that baseline UI was a risk for incident UTI [332-333] among middle aged and elderly women, and in the Leicester MRC study, a history of UTI was associated with both incident SUI (OR 1.9) and incident OAB (OR 2.1) in women aged >40 [322].

Prevalent UI has a clear association with dementia [261,334] but until recently longitudinal studies did not identify an association with incident UI. One longitudinal study of 6,349 community dwelling women found that a decrease in mental functioning as measured by the modified mini mental status exam (MMSE) was not associated with increased frequency of UI over 6 years, but did predict a greater impact [345]. Despite strong associations with baseline UI in the Canadian Study of Health and Aging, moderate or severe cognitive impairment, again defined by the modified MMSE, was not associated with incident UI over 10 years [187]. However, in a sample of 12,432 women aged 70-75, followed up for 9 years, the Australian Longitudinal Survey of Women's Health did demonstrate an association with diagnosed dementia (OR 2.34) [190]. In a 9 year follow up of 1,453 women aged 65 years and over enrolled in an US HMO, diagnosed dementia was strongly associated with incident diagnosis of UI (RR 3.0 95%CI 2.4-3.7) [335]. Given the strength and consistency of associations with prevalent and incident UI, and given that treatment for reversible dementia can improve UI [336-337] a causal role seems certain.

Ischaemic heart disease is associated with many risk factors for UI, but perhaps because of Neyman's bias, caused by exclusion of participants who have died, cross-sectional studies have often failed to identify an association with UI itself even in univariate analysis [287,338].The BACH study reported a strong association only among Black participants (OR 2.52) in multivariate analysis [145]. In the Leicester MRC study [322] a history of ischaemic heart disease was associated with baseline SUI and OAB only in univariate analysis, and with no association with incident symptoms. In contrast, the Nurses' Health Study found that coronary heart disease was associated with incident weekly UI (OR 1.46), and incident severe UI (OR 1.79) [212]. If ischaemic heart disease is a risk factor for incident UI, its effects might be mediated by cardiac failure [335] or polypharmacy [339-340].

Several cross-sectional studies have documented an association between depression and UI [184,254,291,341,-342,396]. In the SWAN study, depression was not associated with incident UI, but in the UAB Study of Aging, in a sample of 490 women aged 65 years and older, baseline depression was weakly associated with incident UI (OR 1.2) over 3 years of follow-up [186]. Similarly in the Health and Retirement Study participants (n=5,820), major depression was a modest predictor of incident UI (OR 1.46) over six years of follow-up, and including extensive adjustment for confounders. Baseline UI did not predict incident depression in the same study. In a follow up of women aged 65 years and older enrolled in an HMO, diagnosed depression was also associated with incident diagnosed UI over 9 years (OR 1.6) [335]. Although it seems plausible that the stigma of UI leads to depression (for example by reducing a woman's social network), current evidence supports causality in the opposite direction, most likely as depression increases the bother of UI symptoms.

Functional impairments, particularly mobility limitations, a history of falls, arthritis, dizziness, use of a walking aid, and poor lower extremity strength, have been correlated with UI in many community-based and nursing home studies [145, 270,272,343-344]. In the Nurse's Health Study osteoarthritis and functional limitations were plausibly associated only with incident UUI (RR 1.86 and 2.10 respectively), not with incident SUI or MUI [191]. In a study of 2,025 older women, improvement in Activities of Daily Living was associated with remission of UUI at 3 year follow up [272]. Other longitudinal studies have shown similar findings [181,345]. It remains unclear whether UI is a direct consequence of difficulties in getting to the bathroom and/or removing clothing, or whether mobility limitations and UI may both be consequences of general frailty in older age or of an underlying systemic illness.

4.11. Ethnic Variation

Ethnic variation in any disease provides only limited evidence for any underlying genetic predisposition. Environmental or cultural differences rather than genetic differences may explain differences in prevalence between populations. As there are very wide variations in UI prevalence between studies, meaningful comparison by race and ethnicity can be made only where such data has been reported within one study. Almost all population-based studies comparing the prevalence of UI among women from one or more racial or ethnic groups originate from the US, which may limit generalizability of conclusions. Results are summarized in table 7. In general, across all studies, white women have a higher prevalence of UI, and in particular SUI than all other groups.

The starkest and most consistent contrast is in rates of SUI for black and white women. In most studies (Table 12), black women have half the prevalence of SUI compared to white women, with differences persisting after adjustment for age, parity and BMI. In comparing prevalence of MUI and UUI for white and black women, there is less consistency. Most studies suggest similar prevalence of urge UI and MUI, however, the BACH survey found very high rates of MUI [145] among black women, while the EPI study reported very high rates of pure urgency UI [257]. These cross-sectional data are supplemented by longitudinal studies. In the SWAN study [184] black women were at half the risk of incident SUI, but nearly double the risk of incident UUI. In the Nurse Health Studies [346]4 black women had lower risk of both overall UI, and SUI after adjustment. The consistency of this difference across both cross-sectional and longitudinal studies, employing different case definitions suggests a real difference in prevalence rather than simply reporting bias.

Table 12 (overleaf): Population-based studies reporting ethnic variation in incontinence prevalence (Table updated from Abrams, Cardozo, Khoury and Wein, 2009) [122].

Reference	Age	Sample Size	Case Definition	Prevalence (%)			
				White	Hispanic	Black	Asian
Fultz et al., 1999 [349]	70+	3,991	Any UI	23	-	16	-
Nygaard et al., 2003 [272]	50-69	5,701	Any UI	17	10	10	-
Nygaard et al., 2008 [286]	20+	1,961	Monthly UI	16	16	14	-
Burgio et al., 1991 [196]	42-50	541	Monthly UI	32	-	18	-
Grodstein et al., 2003 [201]	50-75	82,936	Monthly UI Weekly UI	35 18	28 16	21 10	26 13
Danforth et al., 2006 [213]	37-54	85,670	Monthly UI Weekly UI	18 26	19 26	14 22	14 18
Sampselle et al., 2002 [308]	42-52	3,258	Any UI	66	42	50	52
Waetjen et al., 2007 [184]	42-52	3,002	Monthly UI Weekly UI Monthly SUI Monthly UUI Monthly MUI	57 20 32 8 16	28 11 21 1 5	39 13 13 12 13	39 9 27 4 7
Anger et al., 2006 [347]	60+	23,477,726	Any UI Monthly UI Weekly UI Daily UI	41 35 25 15	31 27 25 8	20 17 15 11	-
Jackson et al., 2004 [267]	70-79	1,558	Weekly UI Weekly SUI Weekly UUI	27 12 11	-	14 5 7	-
Dooley et al., 2008 [327]	20+	4,229	Any UI Any SUI Any UUI Any MUI	53 27 8 19	50 26 8 17	38 12 11 15	-
Fenner et al., 2008 [330]	35-64	2,814	Monthly UI Weekly UI Monthly SUI Monthly UUI Monthly MUI	33 21 13 4 7	-	15 9 4 4 4	-
Markland et al., 2009 [343]	65+	421	Any UI	45	29	-	-
Markland et al., 2008 [270]	65+	490	Monthly UI	41		25	
Tennstedt et al., 2008 [138]	30-79	3,205	Weekly SUI Weekly UUI Weekly MUI Weekly Other UI	35 13 44 7	14 11 69 6	9 3 82 5	-
Thom et al., 2006 [119]	40-69	2109	Monthly UI Weekly UI Daily UI Weekly SUI Weekly UUI Weekly MUI	45 30 12 15 9 3	51 36 17 18 10 5	37 25 12 8 14 2	34 19 9 8 7 3

Typically smaller groups of East Asian or Hispanic women have been included in these studies, which precludes clear conclusions. Broadly though, Asian women report lower prevalence of both SUI and UUI. There is less consistency in comparisons of Hispanic and non-Hispanic white women, with some studies reporting higher, and others lower overall prevalence. This heterogeneity may be explained, at least in part, by differences in prevalence among sub-populations, with Mexican-American women being at higher risk than other Hispanic women [347] or differences in extent of adjustment for covariates.

These studies therefore clearly demonstrate wide variation in self-report of UI, and particularly SUI between women of different ethnicities. There may be substantial differences between women of different ethnicities in major risk factors for UI, including BMI, and perhaps parity, which might explain differences in UI. However, variation in prevalence might also reflect true differences in genetic susceptibility, particularly since in some studies the wide disparity in rates persists even after adjustment for the major known environmental risk factors.

5. THE GENETIC EPIDEMIOLOGY OF INCONTINENCE IN WOMEN

Geneticists have historically pursued a specific sequence of studies to establish the genetic basis of diseases [348]

The first step was measurement of familial correlations, followed by formal twin or adoption studies. Analysis of segregation patterns in extended pedigrees was used to identify the likely mode of inheritance. This information was used to inform linkage studies, designed to identify putative chromosomal risk loci. Only once these steps were complete would association studies be attempted. Although it remains relevant to establish the heritability of a trait, this traditional sequence of investigations has been supplanted by the success of GWAS, with many new discoveries now coming from association studies without the prior steps. Nonetheless here we recapitulate the history of our understanding of UI as a complex genetic disease, with multiple genetic and environmental risk factors, and review the studies that formed the basis for the genetic epidemiology of incontinence.

5.1. Family Studies

The existence of both acquired and inherited risk factors for UI was first recognized more than 150 years ago [395] by observation of familial aggregation. However, familial aggregation provides limited evidence of heritability, since it fails to control for the effects of shared environmental factors. For UI, exposures to all major lifestyle risk factors are likely to be at least partly determined by socio-cultural values that are shared within families. Such effects are at least plausible for family size, smoking, socio-economic status, care seeking behaviour, physical exercise, dietary and drinking habits, and toilet training. As UI is considered stigmatizing in all populations, family studies may be at risk of differential misclassification bias. This might be expected to have particular impact on the validity of estimates obtained from studies employing the family history method, and any study with non-random sampling of families, for example those relying on probands recruited in secondary care, or those recruiting volunteers via advertisement. Finally, while age correction of risks is possible, to account for increasing disease prevalence with age, this has typically not been employed in family studies of UI.

Although family studies may not provide robust evidence, there have been many studies that examined prevalence of UI (Table 13) among relatives of women with incontinence [204,350-354]. Despite considerable variation in case ascertainment and sampling methods, almost all studies have demonstrated increased risks for UI among first degree relatives of probands. This appears to have a plausible biological gradient, with higher risks among relatives of women with severe UI.

Table 13: Family studies of urinary incontinence among women.

Study	Setting	Design	Age range	n (♀ probands and controls)	Proband phenotype	Family member outcomes	OR or RR (95%CI)
Diokno et al, 1990 [204]	Population Based	Family History Method	>60	1,154	Any UI	Either parent with UI as adult	2.04 (1.55-2.68)
						Any sibling with UI as adult	1.85 (1.32-2.60)
					Urge UI	Either parent with UI as adult	1.89 (0.93-3.82)
						Any sibling with UI as adult	0.68 (0.20-2.28)
					Stress UI	Either parent with UI as adult	1.74 (1.12-2.70)
						Any sibling with UI as adult	1.59 (0.92-2.75)
					Mixed UI	Either parent with UI as adult	2.63 (1.91-3.61)
						Any sibling with UI as adult	2.32 (1.58-3.40)
					Other UI	Either parent with UI as adult	0.23 (0.06-0.99)
						Any sibling with UI as adult	0.70 (0.21-2.34)

Study	Setting	Design	Age range	n (♀ probands and controls)	Proband phenotype	Family member outcomes	OR or RR (95%CI)
Mushkat et al, 1996 [354]	Secondary Care	Direct ascertainment	>18	424	Urodynamic Stress UI	Stress UI among all first degree relatives	3.00 (2.06-4.38)
						Stress UI among mothers	3.68 (2.10-6.45)
						Stress UI among sisters	3.39 (1.89-6.08)
						Stress UI among daughters	2.43(0.68-8.65)
Hannestad et al, 2004 [353]	Population based	Direct ascertainment	>18	8,771 (mothers) 2,866 (older sisters)	Any UI	Any UI among daughters	"1.31(1.19-1.44)* 1.94(1.26-3.00)**"
						Any UI among younger sisters	1.59(1.34-1.89)*
					Stress UI	Stress UI among daughters	"1.52(1.28-1.81)* 2.98(1.11-8.03)**"
						Stress UI among younger sisters	1.77(1.34-2.33)*
					Urge UI	Urge UI among daughters	1.80(0.83-3.92)*
					Mixed UI	Mixed UI among daughters	"1.55(1.21-1.99)* 2.07(0.92-4.64)**"
						Mixed UI among younger sisters	1.74(1.08-2.82)*
Elia et al, 2002 [351]	Secondary Care	Family history method	>18	667	Any UI	Any UI among any relatives	4.51(2.833-7.20)
Ertunc et al, 2004 [352]	Secondary Care	Direct ascertainment	>18	513	Surgery for Stress UI	Stress UI among mothers	3.71(1.84-7.47)
						Stress UI among sisters	2.49(1.49-4.16)
Buchsbaum et al, 2006 [355]	Community Based	Direct ascertainment	Post menopause	143	Nulliparous with any UI	Any UI among parous sisters	2.89(1.46-5.70)
Lapitan et al, 2001 [356]	Secondary Care	Family history	>18	5,502	OAB	Any family history	1.62(1.42-1.83)
Andrada Hamer et al, 2013 [357]	Population based	Direct ascertainment (registry)	Any age	3,678,556	Surgery for Stress UI	Surgery for Stress UI among sisters	6.09(5.73-6.48)$
						Surgery for Stress UI among mothers	2.56 (2.27–2.89)$

RR adjusted for age, BMI, and parity **RR adjusted for age, BMI, and parity and restricted to subgroup of daughters of mothers with severe UI $ RR adjusted for age and parity. Note: unadjusted risks generally higher across all outcomes, indicative of substantial concordance/correlation in age, BMI, and parity between family pairs.

The most modest estimates come from the EPINCONT study, which is also least likely to be affected by bias, with the direct ascertainment method employed in a large population representative sample [353]. With a total sample of 8,125 pairs of probands and their daughters or younger sisters, they found less than two-fold increased risk of stress UI among daughters of women with SUI (RR 1.52 95%CI 1.28-1.81), and a non-significant but directionally consistent increased risk of UUI among daughters of women with UUI (RR 1.80 95%CI 0.83-3.92). Similarly, in a survey spanning 11 countries in South and East Asia (n=5,502), a family history of OAB was also a modest predictor of OAB symptoms including UI (OR 1.62 95%CI 1.42-1.83) [356]. In the studies that have used multivariate analyses, it appears that these familial risks are attenuated but not eliminated by adjustment for classic risk factors for UI including age, parity, and BMI.

Risks seem particularly elevated in relation to incontinence surgery. For example in a registry based study of 3,678,556 Swedish women, surgery for SUI among sisters was associated with greatly increased odds (OR 6.09 95%CI 5.73-6.48) [357]. This exaggerated association might be a consequence of low rates of presentation for care, such that care seeking rather than the underlying symptoms are particularly familial. In contrast to the twin studies discussed in the next section, family studies have demonstrated much more clearly that SUIrather than UI is familial. This might be a reflection of more stigma around UI, or simply lack of statistical power for a rarer condition.

Three studies have also assessed family history as a risk factor for incident post-partum UI, with some evidence of familial aggregation [317,358-359]. Again, however, estimates from these studies may be compromised by use of the family history method, rather than direct ascertainment. A single large study has assessed correlations between adult UI and childhood daytime wetting, using the ALSPAC cohort [97]. Using a sample of 8,145 children aged seven they reported excess risks associated with incontinence in the children for UI among their mothers (OR 2.64, 95%CI 1.38-5.07) and particularly among their fathers (OR 5.47, 95%CI 2.39-12.50).

In summary, a family history of UI is associated with approximately two to three fold increased risk. Such an effect appears to hold for all subtypes of UI, although the evidence is more robust for SUI. Among adults there is plausible evidence that family history is associated with both earlier onset, and more severe phenotype. Additionally, there is also clear evidence that this familial predisposition stretches right across the lifecourse. These effects are however partly explained by known environmental risk factors, and family studies cannot exclude the risk of further unmeasured confounding from shared environmental risks. For this we should consider evidence from classical twin studies.

5.2. Twin Studies

Twin studies compare the concordance in a trait or condition between monozygotic (MZ) twins and same-sex dizygotic (DZ) twins, to estimate heritability. Heritability, and here specifically broad-sense heritability, is defined as the proportion of phenotypic variation (V_P) that is due to variation in genetic values (V_G). For genetically determined traits higher concordance is observed in MZ twins compared to DZ twins, while for entirely environmentally determined traits, concordance should be the same in both types of twin pairs.

This idea is illustrated by consideration of a fully penetrant autosomal single gene disorder, which will display 100% concordance in MZ twins, while in DZ twins will have only 50% concordance for a gene with dominant mode of inheritance.

A fundamental assumption of analyses of classic twin studies is that both types of twin pairs share equal environment. This assumption is clearly violated both antenatally, and in later life. This bias can be further investigated in studies of twins reared apart, or in adoption studies, but these designs have not been applied to the study of UI A second central assumption is that MZ twins are genetically identical, which again is violated both by epigenetic effects, and by somatic mutation.

Three major twin resources have been used to assess genetic influences on UI: the US Twins Days festival, the Danish Twin Registry, and the Swedish Twin Registry. The Twins Days festival relies on volunteers, and the resulting recruitment bias is likely to overestimate concordance for many traits for both MZ and DZ twins. In the sample of 1,764, predominantly MZ, middle-aged twins from Twins Days, concordance of symptomatic SUI was 79.5% for MZ and 78.6% for DZ twins [397]. Such a result suggests no significant genetic contribution to SUI at all.

Among a sample of 2,336 twins surveyed as part of four surveys from the Danish Twin Register, concordances for both MZ and DZ twins were much lower not only for SUI, but also for urgency and mixed incontinence [360]. With cohorts for middle-aged and elderly women, heritability was calculated separately in each age group. As in the Twins Day sample, genetic factors were not significant for SUI in middle-aged women, but rose to a heritability of 39% in the elderly women. Similarly heritability increased with age for UUI(42% rising to 49%), and MUI (27% to 55%).

Women participating in the Swedish Twin Register have provided relevant data as part of two separate analyses [361-362]. Treatment codes corresponding to SUI and POP surgery from a nationwide surgical register were used to estimate heritability for a sample of 16,886 twins aged >50. Concordances for surgical treatment were low, but produced heritability estimates of 41% for SUI surgery, and 43% for POP surgery. Similarly for female twins aged 20-46 from the same register (evaluable sample 4,550), using self-completed questionnaires, produced an estimate of 34% heritability for SUI. From the same survey, heritability was estimated for UUI (37%), MUI (18%), “any” UI (51%), nocturia (48%), and urinary frequency (40%). It was however noted that because of sample size limitations, an absence of genetic effects cannot be entirely precluded for SUI, or MUI.

The mechanism of these probable genetic effects has also been explored in analyses of joint hypermobility and pelvic floor mobility in twins [363-364] which is one pathophysiological correlate of SUI. These data suggest heritability of 59% for oblique bladder neck descent on Valsalva in nulliparous twins aged 18-24, with a shared genetic component to both pelvic floor and elbow mobility.

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

5.3. Segregation Analyses

Despite the large number of family studies for UI in adults, there have been few studies to examine segregation among extended pedigrees. Studies of families affected by nocturnal enuresis [365] have however included some adults affected by UUI. Analysis of different enuretic families has usually suggested autosomal dominant inheritance with high penetrance, but low penetrance and autosomal recessive modes have also been reported. These findings could be a consequence of selection or ascertainment bias. In contrast results from more recent association studies strongly suggest that polygenic inheritance is most likely across the population as a whole.

5.4. Linkage Studies

A linkage study can be used to map a condition to one or more genomic loci by demonstrating co-segregation of the trait among an extended family with specific genetic markers. The association between two SNPs is measured using Linkage Disequilibrium (LD) statistics, typically D’ or r^2. With the success of the International HapMap Project [366] and the 1000 Genomes Project [367] LD has been established for the majority of all known common SNPs. Although there are more than 60 million catalogued human SNPs, common SNPs less than 10 kb apart are often highly correlated. Thus without a requirement for dense genotyping, linkage studies can successfully identify loci containing a causal genetic variant [368]. Given the power constraints of assembling extended families for study, this technique is most successful for monogenic or oligogenic traits in which the causal variants have large effect sizes. Several linkage studies have been conducted using families of chil-

dren affected by nocturnal enuresis, and two studies have considered uniquely adult symptoms. Earlier reports suggested a range of loci associated with nocturnal enuresis [365,369] and in the largest attempted replication using a collection of 32 families with at least three members with nocturnal enuresis, there was evidence in favour of a locus at chromosome 22q11 (cumulative logarithm (base 10) of odds (LOD) score 3.63), and weak evidence for loci at 13q13 (cumulative LOD score 1.53) and 12q(cumulative LOD score 1.95) [370]. Allen-Brady and colleagues genotyped women from 32 families, including 70 patients needing surgical treatment for POP. There was strong overlap with other pelvic floor disorders including a high prevalence of treatment for both SUI and UUI [371]. Using a set of 27,157 markers from a predesigned array, they observed a significant peak at 9q21 (maximum HLOD 3.41), and further suggestive peaks at 9q31(maximum HLOD 1.90), and 1q42(maximum HLOD 1.89). Subsequent unpublished work from the same group did not however replicate these findings specifically for SUI surgery [372] but suggested separate loci on chromosomes 2, 4, 8,10 and 11 (maximum HLOD scores 2.15-2.98). Such problems with replication of linkage studies [373] have been recognized right across medicine, and may be particularly pronounced with multiple common variants each with small true effect sizes.

5.5. Gene Association Studies

A recent systematic review has summarized all prior candidate gene and genome-wide association studies [374]. Replication is an essential step in establishing the validity of genetic associations, and yet meta-analyses were possible for only three polymorphisms.

Variation in the beta-3 adrenoceptor, particularly of the rs4994 SNP, also known as Trp64Arg, has been extensively investigated in association with obesity, type 2 diabetes mellitus, and other metabolic syndrome phenotypes. The beta-3 adrenoceptor is highly expressed in bladder, and mediates detrusor muscle relaxation [375]. A beta-3 adrenoceptor agonist has recently been approved for treatment of OAB symptoms [376-377]. One conference abstract and two published papers[378-380] provided relevant information on the common rs4994 missense mutation, of which two could be included in a meta-analysis. In the initial report, in a heterogeneous Japanese sample of 13 men and 31 women, with diverse urological pathologies including neurogenic bladder and benign prostatic hyperplasia, the rs4994 SNP was not associated with LUTS (OR 1.20 95%CI 0.32-4.47) [379].

. Results were not available stratified by gender, and could not be included in quantitative synthesis. Subsequent reports used larger samples of Japanese women (n=100) [378] and Brazilian women (n=49) [380] and looked specifically at the OAB phenotype, finding a large effect size (pooled OR 2.46 95%CI 1.67-3.60), with no heterogeneity. Despite a lack of information about genotyping QC, and some risk of population stratification, this large effect size confers some protection from bias, providing moderate epidemiological credibility.

rs1800012 also known as the Sp1-binding site polymorphism of collagen, type I, alpha 1, modifies transcription factor binding and gene expression. It has been most extensively studied in association with osteoporosis, where the minor allele is modestly associated with reduced bone mineral density and increased fracture risk [381]. Collagen, type I, alpha 1 is a major structural component of the vaginal epithelium and endopelvic fascia [382]. The available data on gene and protein expression in pelvic tissue from women with POP or SUI are heterogeneous but suggest increased *COL1A1* expression with reduced type 1 collagen content (see a previous comprehensive review [382].

Two studies of Polish [383] and Greek [384] women reported associations of the same polymorphism with SUI, in both cases using a combined symptomatic and objectively measured case definition. The pooled effect size was large (OR 2.09 95%CI 1.35-3.22) with no heterogeneity (I^2=0%). There was significant deviation from Hardy-Weinberg equilibrium in one sample, and therefore only weak epidemiological credibility for this finding.

Matrix metalloproteinase-1, also known as interstitial collagenase, is one of a number of enzymes that cleave collagen type 1. The *MMP1* gene is upregulated in pelvic tissues of women with POP [385]. Common variants of this gene have been extensively studied in association with chronic obstructive pulmonary disease [385] cardiovascular disease [398] and a number of cancers including of lung, colon and breast. Two studies tested associations with SUI [387-388] and the pooled effect was non-significant (OR 0.87 95%CI 0.63-1.20), with no heterogeneity.

Finally there remain a number of candidate gene studies of UI for which no replication has been reported. Statistically significant associations have been suggested between UI and the CAG copy number variant of *AR*, the androgen receptor [389] between UI and the rs6313 polymorphism of *HTR2A*, the serotonin 2A receptor [390] and between SUI and both the rs2165241 and rs1048661 variants of *LOX-L1*, lysyloxidaselike-1 [391]. Following the Venice recommendations [392] these nominally significant but unreplicated associations are all assigned weak epidemiological credibility.

As the first genome wide association studies (GWAS) for UI are reported, these results from candidate gene studies are all likely to be overturned. Initial GWAS results from the WHI found no replicable loci for UUI [393] while a subsequent consortia of European and US studies have reported one replicated locus for SUI close to the *EN1* gene and one for UUI close to the *EDN1* gene [394]. Notably no previously suggested gene for UI was re-identified in either of these studies.

6. SUMMARY POINTS

- Despite a vast literature, there remain many uncertainties about the aetiology of UI.
- Despite wide consensus on the definitions of the symptoms of UI and its subtypes, there is no universally accepted threshold for clinically or biologically significant UI, and no objective tests that can be applied in the community.
- For these reasons, even the prevalence of UI is not well established, and the incidence and remission are even less clear.
- Family studies and twin studies have provided convincing evidence of genetic predisposition to UI with genetic variation contributing up to half of population phenotypic variability.
- Heritability is most pronounced for UUI.
- Although some families may be affected by severe dominant monogenic forms of incontinence, for the general population no clear mode of inheritance is apparent, consistent with our understanding of both SUI and UUI as complex polygenic conditions.
- Linkage studies have not yielded consistent results, nor led to identification of any candidate genes.
- The few available candidate gene studies are underpowered for large genetic effects, but suggest the possibility of *ADRb3* as a candidate gene.
- Emerging results from GWAS are likely to substantially change our understanding of the genetic architecture of these conditions.

V. EPIDEMIOLOGY OF URINARY INCONTINENCE IN MEN

1. GENERAL COMMENTS

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

Recent community-based studies consistently report lower prevalence rates of UI in men than in women by a 1:2 ratio [399-401]. The type and age distribution of UI appears to be different between the sexes, and risk factors, although less investigated in men, are distinct from women. It is also important not to consider UI as an isolated problem in men, but rather as a component of a multifactorial problem. Often other urogenital symptoms (LUTS) such as weak stream, hesitancy, and dribbling, or erectile dysfunction, exist.

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

2. PREVALENCE

Several surveys from the general population have been conducted to determine the prevalence of UI in men (Table 14). Prevalence rates ranging from 1 – 40% have been published. The wide range of results may be explained by the variation in the population studied, the definition of UI used, and the methods used in the surveys. A systematic review of 21 studies reported a prevalence of UI in older men ranging from 11-34% (median = 17, pooled mean = 22%), while that among middle-aged and younger men was from 3% to 5% (median = 4%, pooled mean = 5%). In the same review, the prevalence of daily UI in men ranged from 2-11% (median = 4%, pooled mean = 5%) [402]. A more recent systematic review of 69 prevalence studies on UI in community-dwelling men showed overall prevalence rates from 4.81% to 32.17%, with prevalence increasing with age [403]. A wide definition of UI, older age, the inclusion of institutionalized men, and the use of self-reporting methods tend to result in higher prevalence rates [402,404-405].

Table 14 Examples of prevalence studies of UI among men (study population at least 400)
A. General Population Sampling, all adult age groups

Author and year [ref]	N	Response rate (%)	Country	Population (age)	Definition of UI used	Method of assessment	Prevalence (%)
Akbar 2021 [413]	1446	94 %	USA	45-84 yrs	based on the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF)	Interviewer administered questionnaire	11.1
Tsui 2018 [435]	1059	76.4 %	UK	68 yrs	ICIQ-SF	postal questionnaire	7
Donnelly 2018 [425]	2955	29.60%	Northern Ireland	≥40 years	any degree of urinary leakage	postal survey	35.6
Helfand 2018 [539]	477	92 %	USA	≥18 years	leakage of urine in any of the described occasions (based on the LUTS tool definition)	Patient-reported urinary symptoms	32
Pöyhönen 2016 [540]	7470	58.70%	Finland	30-80 years	definition from the Danish Prostatic Symptom Score	postal questionnaire	40
Gonzalez-Sanchez 2016 [541]	1041	78%	Mexico	>18 yrs	ICIQ-SF used to assess the presence (with score of 1) and severity of incontinence	Printed on-site questionnaire and on-line survey	24.7
Wackerbarth 2015 [542]	1111	(not reported)	Nepal	> 14 yrs	any report of leaking of urine	Cluster-Randomized Survey	4.5 (95% CI 1.9–10.8)
Park 2015 [543]	5830	92.80%	South Korea	>= 19 yrs	based on Urogenital Distress Inventory-6 (UDI-6) definition	Face-to-face interviews	5.5

Author and year [ref]	N	Response rate (%)	Country	Population (age)	Definition of UI used	Method of assessment	Prevalence (%)
Wu 2015 [432]	3604	88.90%	USA	≥50 yrs	At least weekly leakage or (of any volume) or monthly leakage (of volumes more than just drops)	Interviewer administered questionnaire	6.4 (95% CI 5.4-7.5)
Kim 2014 [544]	1842	26.80%	Korea	>=40	Any UI by EPIC questionnaire; based on ICS definitions	Interviewer administered questionnaire (EPIC questionnaire)	9.1 (95% CI 7.8-10.5)
Kogan 2014 [141]	1516	(not reported)	Russia, Czech Republic, Turkey	>=18	Any UI by EPIC questionnaire; based on ICS definitions	Structured telephone interviews	7
Zumrutbas 2014 [411]	636	74%	Turkey	≥18 yrs	ICIQ-SF The frequency and amount of UI were determined by the relevant questions of ICIQ-SF in the questionnaire.	Self-administered questionnaire	9.9
Osuga 2013 [545]	1198	32%	Japan	>=40	involuntary loss of urine ≥ times per week.	Self-administered questionnaire (missing data followed up by interviewer)	3.3
Yoshimura 2013 [412]	3224	(not reported)	Japan	≥30 yrs	ICIQ-SF Definitions: Mild UI = once or less per week; Moderate UI = two or three times per week; Severe UI = once or more per day.	Self-administered questionnaire (missing data followed up by interviewer)	Any UI : 13.7 Mild UI : 10.4 Moderate UI : 1.4 Severe UI : 1.9
Lee 2011 [546]	888	22.00%	Korea	>=18	Involuntary urinary leakage	Telephone interview using a questionnaire	2.9% (other UI = 1.3, SUI = 0,9)
Markland 2011 [547]	9071	(not reported)	US	>=20	Positive response to SUI/UUI/Other	Personal interview	13.9% SUI = UUI = 8.3% (7.6-9.0)
Malmsten 2010 [418]	4072	80%	Sweden	45-103	2002 ICS definition	answering a postal questionnaire	10.5
Markland 2010 [415]	5297	(not reported)	US	>=20	Score of 3 or greater on a validated incontinence severity index (moderate to severe leakage)	interview	4.5 (3.8-5.4)
Correja 2009 [548]	451	59.60%	Portugal	>=40	at least one episode of urine leakage in the previous month	Structured telephone interviews	7.65 (95% CI 4.8-10.4)
Espuna-Pons 2009 [549]	15929	(not reported)	Spain	>=15	(not reported)	questionnaire	3.6
Diokno 2007 [407]	21590	66.5 %	US	>=18	Involuntary leakage or loss of urine in the past 30 days	Postal questionnaire	12.7

Author and year [ref]	N	Response rate (%)	Country	Population (age)	Definition of UI used	Method of assessment	Prevalence (%)
Irwin 2006 [136]	19165	33%		>=18	ICS 2002 definition	Telephone interview	5.4 (95% CI 1.9-5.9)
McGrother 2004 [550]	92491	60.2 %		>=40	In the last year, did you ever leak urine when you don't mean to?	Postal questionnaire	14.2
Boyle 2003 [414]	4979	28-72%	France, Netherlands, UK, Korea	40-79	Lack of control over bladder function which caused urine leakage at times	Self-administered questionnaire	7 (France), 16 (The Netherlands), 14 (UK), 4 (Korea)
Brocklehurst 2003 [551]	1883	(not reported)		>=30	Ever suffered from bladder problems such as leaking, wet pants, damp pants	Interview	6.6 overall, 3.8 incontinent in the previous year, 2.8 in the previous 2 months
Finkelstein 2002 [431]	25400	88.7	Canada	>=30	urinary incontinence diagnosed by a health professional	interview	1.4 (per 100 population)
Parrazzini 2002 [552]	9613	97.5		>=50	Involuntarily leaked in the past 3 months		8.3 (95 % CI 7.7-8.9)
Van Oyen 2002	7266	(not reported)		> =15	(not reported)		1.4
Schmidbauer 2001 [305]	1236	(not reported)		Mean 49	(not reported)		5
Maral 2001[408]	1000	90		> = 15			1 (SUI), 3 (UUI)
Bortolotti 2000 [554]	2721	-		> 50	Any urine loss in the last year	Telephone interview	3 32 (last year), 14 (weekly)
Roe 2000 [555]	12529	53	US				5.3
Smoger 2000 [556]	840	85		25-93, VA clinic	Incontinence in the past 12 months	Self- administered questionnaire	32.3
Ueda 2000 [406]	3 500	52.5	Japan	> 40		Mailed self-administered questionnaire	10.5 (UUI)
Roberts 1999 [557]	778	-		> 50			25.6 (95 % CI 22.5-28.8)
Roberts 1998 [558]	2 150	-		> 40	Urinary leakage in the previous 12 months	self	18
Schulman 1997 [559]	2499	(not reported)		> 30	(not reported)		5.2
Malmsten 1997 [417]	10 458	74%		> 45	(not reported)		9
Legace 1993 [560]	2830	86%		>-20	Any urine loss in the past 12 months	Self-administered questionnaire	11 (95% CI 9-13)
Obrien 1991 [561]	2496	79%			(not reported)	Self- administered questionnaire	7.4 (95% CI 6.4 – 8.4)

Table 14 Examples of prevalence studies of UI among men (study population at least 400)
B. General Population Sampling, Older Group

Author and year [ref]	N	Response rate (%)	Country	Population (age)	Definition of UI used	Method of assessment	Prevalence (%)
Bauer 2019 [444]	1298	87%	USA	70-79	monthly UI of any type	interviewer-administered questionnaires from prior large observational studies	22
Lee 2018 [399]	2013	-	UK	50-90+	complaint of any involuntary leakage of urine	face-to-face interviews and self-completion questionnaires	6.9
Noguchi 2016 [562]	1705	-	Australia	>/= 70	Urinary incontinence was defined as leaking urine at least once a day	questionnaires	7.2 (95 % CI 6.0–8.5)
Marques 2015 [563]	616	-	Brazil	>60	positive response to the question: Is it common for you to lose a bit of urine and accidentally get wet; either because there was not enough time to get to the bathroom, or because you were sleeping; or when you cough or sneeze, or push something?	individual interviews in households	17 (CI 14.0 – 19.9)
Vasilopoulos 2014 [564]	1514	-	USA	62-90 yrs, community- dwelling	Any UI in last 12 months.	Self-administered and interview administered questionnaires	62-69 : 25.8 (SE 2.3) 70-79 : 38.4 (SE 3.0) 80-90 : 40.5 (SE3.6)
Ramage-Morin 2013 [565]	6639	92.10%	Canada	>=65	UI diagnosed by a health professional and had lasted, or was expected to last, at least six months	Structured telephone interviews	All men : 9.2 (8.3-10.2) 65-74 yrs : 6.4 (5.4-7.7) 75-84 yrs : 11.6 (9.8-13.6) ≥85 yrs : 18.7 (15.4-22.6)
Osuga 2013 [545]	1198	99.8 %	Japan	60.7+/-12.5 years	involuntary loss of urine ≥ times per week.	Self-administered questionnaire (missing data followed up by interviewer)	60-69 : 2.9 70-79 : 5.3 >=80 : 15.1
Kwong 2010 [566]	1705	47 %	Australia	>=70	Urinary leakage at least 2x/week over the past 4 weeks	Self administered-questionnaire	14.8
Smith 2010 [567]	572		US (Latinos)	older			26.9
Yu 2009 [568]	743		China (rural)	>=60		Face to face interview	33.38
Janssen 2007 [443]	2216	57%		>= 65	Leaked or lost control of urine in the past year	Interview	13.1
Landi 2003 [420]	5372			>= 85	MDS urinary incontinence scale of >=1	Health care professional assessment	49
Stoddart 2001 [569]	1000	79 %		> 65	Incontinence in the previous month		23
Aggazzotti 2000 [570]	893	90 %		> 65, Community and residential homes	Involuntary loss of urine at least 2x/month	Questionnaire, review of clinical record	39.2

Author and year [ref]	N	Response rate (%)	Country	Population (age)	Definition of UI used	Method of assessment	Prevalence (%)
Gavira-Iglesias 2000 [571]	827	-		> 65	-	-	29 (95% CI 25-38)
Smoger 2000 [556]	840	85 %		25-93, VA clinic	Incontinence in the past 12 months	Self-administered questionnaire	32.3
Umlauf 1996 [428]	1 490	53 %		Elderly	Uncontrolled urinary leakage of any amount the month before	Mailed self- administered questionnaire	29
Thom 1997 [335]	1420	-		>=65		Review of database	5.3
Herzog 1990 (MESA study) [572]		66% - 72%		>=60	In the past 12 months about on how many days have you lost any urine, even a small amount beyond control	Interview	18.9

SUI: Stress UI, UUI: Urge UI, MUI: Mixed UI

For any definition of UI, there is a steady increase in prevalence with increasing age (Table 15).

Table 15 Examples of prevalence of UI across age spectrum in men

Author and year [ref]	N	Distribution by age	Prevalence [1] (%) (95%CI)
Noguchi 2016 [562]	1705	70–74 75–79 80–84 85–89 90–97	4.9 (3.3–6.6) 7.6 (5.4–9.9) 7.2 (4.3–10.1) 15.0 (9.0–21.1) 14.0 (3.6–24.3)
Aniuliene 2016 [573]	86	<50 50-59 60-69 70-79 >80	1.5 13.8 26.2 40.0 18.5
Kim 2014 [544]	1842	40-49 yrs 50-59 yrs ≥60 years	7.2 (5.6-9.3) 9.4 (7.3-11.9) 11.6 (9.1-14.8)
Zumrutbas 2014 [574]	636	18-29 yrs 30-39 yrs 40-49 yrs 50-59 yrs ≥60 years	5.2 7.9 9.0 11.0 18.3
Kwong 2010 [566]	1,705	70-74 >=90	12.0 16.3
Correja 2009 [405]	451	40-49 50-59 60-69 70-79 ≥80	7.6 (4.8–10.4) 4.0 (0.0–9.1) 3.9 (0.0–8.4) 8.6 (2.4–14.8) 13.2 (6.3–20.0) 21.6 (6.9–36.3)
Espuna-Pons 2009 [549]	15929 (men and women)	45-64 65-74 >=75	2.8% [2] 10.2% [2] 22.7% [2]
Shamliyan 2009 [403]		19-44 45-64 65+ 80+	4.81 (3.69-5.94) 11.2 (10.14-12.26) 21.13 (19.9-22.35) 32.17 (29.62-34.73)
Diokno 2007 [407]	21590	18-34 35-44 45-54 55-64 65-74 75+	7.25 7.17 10.98 15.58 23.82 30.19

Author and year [ref]	N	Distribution by age	Prevalence [1] (%) (95%CI)
Mariappan 2006 [575]	353	40-49 50-59 60-69 >=70	6.6 7.9 10.6 10.3
McGrother 2004 [550]	92491	40-49 50-59 60-69 70-79 >=80	7.4 11.1 16.8 23.2 30.5
Finkelstein 2002 [441]	25400	30-39 40-49 50-59 60-69 70-79 80+	0.2 0.4 1.1 2.7 5.7 6.4
Aggazzotti, 2000 [570]	839	<65 65 – 74 75 – 84 85+ >= 95	19 23 52 53 57
Bortolotti, 2000 [299]	2721	51 – 60 61 – 70 70+	2 3 7
Smoger, 2000 [556]	840	<40 41 – 50 51 – 60 61 – 70 71 – 80 >80	25.4 30.9 31.4 36.3 33.2 20.0
Temml, 2000 [576]	1236	20 – 39 40 – 59 60 – 69 70+	2 4 8 12
Ueda, 2000 [406]	3500	40 – 59 60 – 69 70+	2 4 4
Malmsten, 1997 [417]	10458	45 50 55 60 65 70 75 80 85 90+	3.6 4.1 3.3 5.1 6.1 7.3 9.6 19.7 21.8 28.2
Schulman, 1997 [559]	2499	50 – 54 60 – 64 70+	5 6 14
Thom 1997 [335]	1420	65-74 75-79 >=80	2.8 5.6 7.6
Obrien 1991 [561]	2496	35-44 45-54 55-64 65-74 >=75	2.4 5.5 5.7 12.1 15.4
Diokno,1986	805	60+	19

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

Table 16. Relative proportion of types of urinary incontinence in men.

Author Year	Population	Age group	UUI	SUI	MUI	Others
Akbar 2021 [413]	1446	>= 55	8.6	0.8	1.6	-
Tsui 2018 [435]	1059	68 y	12	1.5	1	-
Aniuliene 2016 [573]	86	>=40	60	9.2	30.8	-
Park 2015 [543]	5830	>=19	1.9	1.1	1.7	
Shamliyan 2009 [403]	*	19-44 y 45-64 65+ 80+	68.2 59.3 54.2 65.9	16.3 28.9 8.0 0	15.5 11.7 17.9 34.1	-
Diokno 2007 [407]	21,590	>=18 18-34 35-44 45-54 55-64 65-74 75+	44.6 30.0 35.4 38.9 46.8 53.8 56.3	24.5 38.1 35.8 30.8 19.3 16.7 13.2	18.8 14.8 12.6 16.5 21.0 22.6 22.4	12.1 17.1 16.2 13.8 13.0 6.9 8.1
Herschorn 2007 [143]	482	>=18 y	58	27	15	-
Irwin 2006 [136]	19,165	>=18 y	22.2	11.1	11.1	53.7
Nuotio 2003 [341]	171	>70	70.8	8.3	25	
Liu 2002 [577]	2087 (total)	>=70 y	17.4	11.9	-	-
			30.4	20.7	-	-
Damian 1998 [429]	589	>=65 y	52.2	10.6	16.1	21.1
Diokno 1986 [578]		>= 60 y	34.9	7.9	28.9	28.3

Due to differences in the pathological anatomy and pathophysiology of UI in men and women, there is a different distribution in incontinence subtypes. A predominance of urge incontinence (40-80%), followed by mixed forms of UI (10-30%), and stress incontinence (<10%) is observed [331]. The pooled prevalence rates in a systematic review confirmed that such distribution pattern across the different types of UI is consistent across the different age groups [403]. (Table 16).

The higher percentages of the urge and mixed types of UI are more significant in studies involving older people. The increasing prevalence of any UI by age in men is largely due to the contribution of UUI rather than SUI. One study demonstrated an increased rate of urge UI from 0.7% between age 50-59, 2.7% between 60-69, and 3.4% for 70 years and older respondents. SUI was steady at 0.5%, 0.5% and 0.1% for the above groups, respectively [406]. A similar trend of increasing proportions of urge and mixed UI with increasing age is demonstrated in the large population-based study in the US [407], and a smaller population-based Canadian study [143]. On the other hand, Maral and coworkers reported increasing prevalence also of SUI with age, from 0.9% between age 35-44 to 1.2% between 45-54, 3.8% between 55-64, and 4.9% at age 65 and older [408].

Most studies report a significant proportion of other/unclassified types of UI. One study reported that a majority of men with UI had overflow and functional types of UI[299], while another found constant dribbling in 7% of their respondents [409]. Terminal dribbling or postvoid dribbling is another type of leakage in men that is difficult to assign to the conventional subtypes of UI. In an Australian survey, 12% of respondents reported frequent terminal dribbling [410].

When it comes to severity, the distribution in men follows that of women. Available data have shown that the overall prevalence of UI in men is largely due to mild UI. Men reporting moderate to severe UI are significantly less than those reporting mild UI [411-412]. Estimates for severe UI in older men tend to be about half that of older women [331].

Few studies have studied the impact of race or ethnicity on the prevalence of UI among men. Akbar and colleagues [413] utilized the data from the Multi-Ethnic Study of Atherosclerosis to analyze the variation and distribution of UI subtypes among non-Hispanic White, Chinese, non-Hispanic Black, and Hispanic. The prevalence of any UI was highest among non-Hispanic Blacks (15.7 %) followed by Hispanics (15.3 %), non-Hispanic Whites (7.9 %), and Chinese (5.8 %) [413]. A four-country study presented lower prevalences of reported UI among men from Korea (4%) and France (7%) than in men from Britain (14%) and Denmark (16%) [414]. On the other hand, unpublished data from the MESA study did not indicate differences in prevalence among white male respondents compared to African American respondents. Similarly, the National Health and Nutrition Examination Survey did not find any difference in the prevalence of UI by racial/ethnic group [415].

Literature on the incidence of male UI is scarce. One recent prospective cohort study of community-dwelling Medicare enrollees has reported on this issue. From the University of Alabama at Birmingham Study of Aging, 77 men with no UI at baseline were followed for 42 months for evaluation of incident UI, which occurred in 38% of men [416]. The MESA study [331] found a one-year incidence rate for men older than 60 years at 9-10%. In a population-based survey in the UK among men with at least 40 years of age, the one-year incidence of UI was noted to be 3.8% [182]. A

review of a health organization database of males at least 65 years old revealed a UI incidence of 23.8 per 1000 person-years. Malmsten [417] analyzed the age of onset of UI for each age cohort. The mean debut age for all men was 63 years. The mean duration was about 8-10 years in the cohorts. A longitudinal population-based study in Sweden showed that 8.6% (212/2471) of those without UI at the initial survey was found to have UI at the survey done 11 years later [418].

Substantial remission rates for UI in males were noted by the MESA study, higher among men (27-32%) than women (11-13%) [331]. A similarly high one-year remission rate of 39.6% was noted among British males [182]. In the Swedish longitudinal study, 47.8% (55/115) of those found to have UI at the initial survey did not present with the problem at the time of the follow-up survey 11 years later [418].

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

3. POTENTIAL RISK FACTORS FOR UI

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

3.1. Age

As in women, increasing age is correlated with an increasing prevalence of UI in men (Table 15). Multivariate analyses in several studies have shown that age is an independent risk factor for incontinence [405,407,412,419-425] Compared to women, however, there seems to be a steadier increase in the prevalence in men with increasing age. The National Health and Nutrition Examination Survey in the US reported an odds ratio for moderate to severe UI of 1.8 (95% CI 1.6-2.0) for every 10-year increase in age in a cohort of 5,297 men 20 years or older [415].

3.2. Lower Urinary Tract Symptoms (LUTS) and Infections

In postal and telephone surveys of community-living incontinent men, a majority has experienced a variety of other medical conditions, many of which may cause or aggravate UI. LUTS like urgency, nocturia, feeling of incomplete voiding and reduced flow are typically associated with UI [305,426-428]. In one study, UI was reported by 15% of men without voiding symptoms, frequency, or urgency and by 34% of those with such symptoms [426].

Studies have also reported that urinary tract infections and cystitis are strongly associated with male UI [409,429], with an odds ratio of 3.7 for UI in men reporting cystitis [406] and an odds ratio of 12.5 among men with recurrent infections [299]. The meta-analysis of 5 studies including the previously mentioned studies showed a significantly higher risk of UI among men with UTI, with a pooled odds ratio of 3.6 (95% CI 2.17-6.00) [403]. It should be noted that most reports indicating a positive association between UTI and UI involved men aged older than 60 years.

3.3. Functional and Cognitive Impairment, Physical Activity

Mobility problems such as the use of a wheelchair or aids to walking, as well as diagnosed arthritis or rheumatism or having a fall the last year, were significantly greater among incontinent than continent men [282,429]. The Canadian National Population Health Study involving 25,400 men found that those afflicted with arthritis were more likely to have UI with an odds ratio of 1.59 (95% CI 1.07-2.38) [431]. The same study demonstrated that men with back problems were 2x more likely to have UI (OR 2.1, 95%CI 1.50-2.93).

Several other reports identified frailty and functional dependency as more significant associations to male UI than chronological age. A Japanese study on community-dwelling men noted that UI is more likely among men whose activities of daily living (ADL) are impaired, specifically those who are unable to change clothes and unable to walk outside, with an odds ratio of 17.4 and 4.36 respectively [406]. A Canadian study found odds ratios of 1.8 and 6.4 for partially and totally immobile men aged 65+, respectively, for daily UI compared to those with normal ambulatory function. Similarly, the Silver Network Home Care project among the frail older persons in Italy showed that those with higher ADL scores (i.e., greater functional impairment) had 2-4x higher odds of having UI [420]. A survey of nursing home residents in Wisconsin identified dementia and poor ADL as risk factors for the occurrence of UI [422]. These results were corroborated by a recent population-based cross-sectional study that identified ADL impairment as a risk factor (OR=2.4, 95% CI=1.2-4.9) for UI among 3604 men included in the National Health and Nutrition Examination Survey [432]. Among hospitalized older adults, the incidence of UI was more common in frail subjects (at discharge: 24.3% vs 9.6%, p-value= .038; 6 months: 43.2% vs 21.7%, p-value = .020; and 12 months: 56.8% vs 33.3%, p-value = .020) compared to the control group in a 1-year prospective cohort study [433]. Hence, the current scientific evidence recognizes functional and cognitive impairment as risk factors for UI.

Congruent with the previous observations, the association between physical activity and UI has been studied by Kikuchi and co-workers among the elderly, community-based population in Japan [437]. They found that men with middle-level physical activity have lower UI prevalence compared to those with low-level physical activity, with an odds ratio of 0.38 (0.17-0.78). High-level physical activity showed similar relations but was not statistically significant [419,435,437].

Finally, 383 Men from the I-Lan Longitudinal Ageing Study (ILAS) in Taiwan were evaluated to identify the association between muscle mass, muscle strength, physical function, and UI based on the assumption that pelvic muscle architecture decreases along with whole-body muscle mass. The investigators found that walking speed was the only independent risk factor for UI (HR 0.05, 95% CI 0.003–0.987, P ¼ 0.049) and sarcopenia has a non-significant association with UI [436].

3.4. Neurological disorders

Many specific neurological diseases may lead to UI [437]. DO is seen commonly in mengingomyelocele patients and spinal injuries, Parkinson's disease, and multiple sclerosis. Areflexic bladder dysfunction due to a cauda equina lesion or diabetes might cause overflow or a paralysed pelvic floor and hence SUI. A meta-analysis of 5 studies showed that men who suffered a stroke were at an increased risk for UI with a pooled odds ratio of 2.68 (95% CI 1.31-5.45) [403]. Another study reported that men who had suffered a stroke were at increased risk for UI with an odds ratio of 7.1 [406]. The Canadian National Population Health Survey showed that stroke in men increased their odds of having UI by 8x (OR = 8.26,

95%CI 3.63-18.8) [431]. A case-control study by Jorgensen [438], age-matched long-term stroke male survivors with controls showed a higher prevalence of UI among stroke survivors compared to controls (17% vs 9%). A retrospective observational study including 6327 men also showed an increased risk of UI with dementia (HR 1.68 95 % CI 1.43–1.98) and stroke diagnosis (HR 1.72, 95 % CI 1.35–2.19) [439].

In addition, among UI sufferers, the stroke survivors were found to have a higher frequency and more leakage than controls. In a study of 235 stroke patients, the occurrence of UI correlated with motor weakness (OR 5.4), visual defects (OR 4.8, and dysphagia (OR 4.0) [440]. In the UK, recent research involving a cohort of 1059 men from the Medical Research Council (MRC) National Survey for Health and Development showed that men diagnosed with previous stroke or TIA report more UUI (OR 2.6, CI 1.4-4.8) [435].

3.5. Diabetes

The results of studies on the association of diabetes mellitus with UI are conflicting. Several reports have not found diabetes as a factor significantly associated with UI in men. This includes the Canadian population-based study involving more than 25,000 men showing no increased risk for UI among men with diabetes [441]. However, the Japanese survey found that diabetics had twice the odds of having UI than non-diabetics [412]. Tsui and colleagues also reported an increased risk of UUI in patients diagnosed with diabetes (OR 1.94 CI 0.99-3.81) [435]. An earlier review reporting the pooled analysis of 6 studies showed that diabetic men were significantly more likely to have UI with an odds ratio of 1.36 (95%CI 1.14-1.61) [403].

3.6. Alcohol and Smoking

Two recent reports showed a significant association between alcohol consumption and UI in men. A Japanese survey showed an odds ratio of 1.84 (95%CI 1.2-2.82) [412], and a survey among Chinese men showed an odds ratio of 1.42 (95% 1.1-1.8) [423].

The prevalence of incontinence based on the Overactive Bladder Symptom Score (OABSS) and International Consultation on Incontinence Questionnaire-Short Form(ICIQ-SF) was reported to be higher among current and ex-smokers than non-smokers [442]. Smoking was also found to be significantly associated with UUI in non-obese men with an odds ratio of 1.79 (95% CI: 1.01-3.17) in a separate study [430].

3.7. Obesity

Previous studies did not reveal a significant association between increased BMI and UI [443]. However, a more recent prospective analysis of 1298 community-dwelling men, aged 70 to 79, in the multicenter Health, Aging, and Body Composition Study provided evidence of increased UI prevalence with higher BMI (OR 1. 49, 95% 1.21-1.83) and fat mass (OR 1.23, 95 % 1.05-1.45) [Bauer 2019]. In a study including a younger population in Australia, obesity was associated with UI with an odds ratio of 3.2 (1.2-9.0) [421]. A population-based survey in the UK involving 1059 participants from the National Survey for Health and Development also supports the increased risk of UI associated with increased BMI with an OR 1.26 (CI 1.12-1.4) [435]. Hence, contemporary studies are already consistent in identifying obesity as a strong risk factor for male UI.

3.8. Treatment for Benign Prostate Disease (monopolar TURP vs newer endoscopic treatment, open prostatectomy)

TURP has been associated with an incidence of stress incontinence of about 1%. A randomized controlled trial comparing TURP, laser prostatectomy, and vaporization of the prostate for benign disease showed comparable UI rates immediately and up to 12 months postoperatively [Van Melick 2003]. Resection and enucleation techniques using any modality have similar long-term UI rates but short-term transient UI was a concern in enucleation methods (odds ratio 1.92, 1.39 to 2.65) [446-447]. Holium laser enucleation which is commonly employed recently for large prostates (>100 g) was associated with 10% SUI rate postoperatively [448] while photoselective vaporization of the prostate was associated with 14.3 % de novo UUI after 6 months [449].

3.9. Treatment for Malignant Prostate Disease (radical prostatectomy and focal therapies)

Since the last edition of this text was published, significant progress in the study of post-radical prostatectomy UI has been made especially with the refinements in the techniques and technologies associated with the procedure. Radical prostatectomy seems to induce UI at a much higher rate than TURP. The most recent systematic review including 4 randomized controlled trials comparing RP and deferred treatment (watchful waiting and active surveillance) for localized prostate cancer showed a UI rate of 173/1000 men undergoing RP [450]. The overall prevalence of post-radical prostatectomy UI ranges from 2 to nearly 60% (Table 17). This wide range may be explained by many factors, including differences in study characteristics, population characteristics, study site, the definition used, and the timing of assessment of continence in relation to the surgery. The era in the development of the procedure has also been found to be associated with the prevalence rates [451], as well as the various procedural modifications of the surgery (see below).

Table 17. Examples of studies on the prevalence of post-prostatectomy incontinence

Author/Ref	Procedure	N	Follow up	Definition	Prevalence (%)
Mazariego 2020 [510]	RP	1642	15 yrs	needing to wear one or more pad per day owing to weak urinary control and frequent leakage	18.2 % (nerve-sparing RP); 27 % (non-nerve sparing)
Xu 2018 [511]	RP	1995	15 yrs	use of pads except for protection	12.80%
Schepens 2018 [579]	RP	1590		unknown	26.00%
Tienza 2018 [490]	RP	746	12 mo	complaint of any involuntary leakage of urine	23
Albkri 2018 [580]	RP	110	49.0 mo (5–160)	not explicitly stated	34.5% 26.8% (RRP) 46.3% (lap RRP) 28.5% (RARP)
Steentjes 2018 [581]	RP	842	2–18 yrs	Unknown	Early 14.9% Late 19.6%
Tyson 2018 [489]	RP/ RARP	1291	3 yrs	any urine leakage	Low risk PCa: 63 % Intermediate risk Pca: 68 % High risk PCa: 78 %
Leow 2017 [582]	RP	5082	30 days	unknown	7.3-7.9 %
Barocas 2017 [583]	RP	1523	3 yrs	EPIC questionnaire; any urinary leakage	14.00%
Wilt 2017 [584]	RP	731	19.5 years	use of absorbent pads	17.3
Daugherty 2017 [585]	RP	136	Not stated when the assessment for UI done in relation to the treatment	Validated 2-item incontinence severity index Incontinence based on an index value of 3 or greater (scale of 1-12), corresponding to moderate or severe incontinence	23.2 (14.0-35.9)
Carlsson 2017 [586]	RP	338	1 yr	Urinary continence was defined as less than one pad changed per 24 hour ; otherwise, incontinent	16.00%
Tasci 2015 [587]	RARP	1499	1 yr	Continence was defined as the use of no pads or only a safety pad usage; otherwise, incontinent	11.30%
Gavin 2015 [588]	RP	934	≥24 (2-18 yrs)	Unknown	27.8% (95%CI 24.9–30.8)
Kumar 2015 [481]	RARP	800	34.1 months in <70 years 37.2 months in >70 years	based on the EPIC questionnaires	8.7 % in <70 years 12.7 % in >70 years
Geiger-Gritsch 2015 [589]	RP	253	12 months	International Consultation on Incontinence Questionnaire(ICIQ)	Mild UI : 29.9% Moderate UI : 18.1% Severe UI :15.0 %
Holm 2014 [478]	RP	844	12 months	used pads daily/ occasional dribbling without pads	74.0% (40 % used pads daily, 34 % occasional dribbling)
Schiavina 2014 [465]	RRP	778	1 yr	use of 1 or more pads	7.70%
Kopp 2014 [589]	RP	362	Mean 6.3 (SD 4.8) years since diagnosis	Any UI UI < 1 /week UI 1 /week UI 1 /day Pad use	79.0% 21.8% 15.5% 41.7% 21.7%
Resnick 2013 [491]	RP	1164 842	24 60 180 (5 yrs)	No control or frequent leakage	9.6% 13.4% 18.3%
Peterson 2011 [508]	RP	1618	> 12	Self-report of UI in every followup	9.70%

Author/Ref	Procedure	N	Follow up	Definition	Prevalence (%)
Hu 2003 [591]	RP	12079	> 36	unknown	4-20 %
Augustin 2002 [592]	RP	368	12	Any protection	27.00%
Sebesta 2002 [593]	RP	674	> 24	Use of pads	32.00%
Potosky 2000 [594]	RP	1156	24		10.00%
Bishoff 1998 [497]	RP	907			
Peterson 2012 [508]	RRP	1616	> 1 year Median 50.7 months (range 12–216 months) since surgery	Patient-reported, do you ever leak urine?	90.30%
Kundu 2004 [472]	RRP	2737	>= 18	Use of pads	7.00%
Salomon 2003 [595]	RRP	205	12	Use of pads	34.00%
Moinzadeh 2003 [464]	RRP	200	12-15	Use of pads	2.0% 1.0%
Maffezzini 2003 [596]	RRP	300	?		SUI : 9.0% SU
Deliveliotis 2002 [504]	RRP	149	12		6-8%
Benoit 2000 [597]	RRP	25 651	12		8.00%
Poon 2000 [500]	RRP	220	Mean >12		3-7%
Catalona 1999 [479]	RRP	1 870	>12		8.00%
Horie 1999 [462]	RRP	104	12	Use of pads	22.00%
Goluboff 1998 [461]	RRP	480	12	Any UI Daily or pad use Continuous	57.0% 7.0% 1.0%
Weldon 1997 [460]	RRP	220	18		5.00%
Lowe 1996 [459]	RRP	180	12	Any protection	12.00%
Gray 1999 [470]	RRP/RPP	209	Median 32		25.00%
Olsson 2001 [452]	Lap RP	228	12	Use of pads	21.60%
La Fontaine 2000 [598]	Lap RP	522	Mean 31	Use of pads	15.00%
Galli 2006 [599]	Lap RP	150	12	Use of pads	8.30%
Novara 2011 [476]	RARP	242	12		11.00%
Novara 2010 [600]	RARP	308	12		10.00%
Lee 2010 [601]	RARP	107	Mean 7.6	Use of pads	9.00%
Reynolds 2010 [602]	RARP	1005	24	Use of pad	10.00%
Van Hemerlrijck 2012 [603]	RRP RARP	1377	12	Unknown	54.0% 48.0%
Nilsson 2011 [477]	RRP RARP	1288	> 1 year Median 2.2 years (range 1-5 years) since surgery	Using > 1 pad / day	10.50%
Shikanov 2010 [604]	RARP	1436	12 mo	Use of pads	31.00%
Martin 2011 [605]	RARP	315	12 mo	Use of pads	22.00%
Xylinas 2011 [606]	RARP	500	12 mo	Use of pads	22.00%
Link 2008 [607]	RARP	1847	12 mo	Use of > 1 pad daily	7.5.0%

RRP: radical retropubic prostatectomy
RPP : radical perineal prostatectomy
RP: radical prostatectomy, unspecified or combined
Lap RRP: laparoscopic retropubic prostatectomy
RARP : Robotic-assisted radical prostatectomy

Post-prostatectomy incontinence rates based on symptoms reported by patients are generally 2-3x higher than those based on physicians' observations. Studies that have performed both assessments in the same population confirm this observation that doctors underestimate postprostatectomy UI by as much as 75% [452-455]. This was conflicting to the recent report of Wagner and associates where practitioners significantly overestimate UI at 3 months post-RARP (48% vs 39%) [456]. A higher UI rate is also seen after self-reported questionnaire assessment compared to pad testing [457-458].

Incontinence rates after prostatectomy seem to steadily decline with time and plateau 1 - 2 years after surgery [459-465] (Table 18). This emphasizes the need for a long follow-up period to establish continence status postprostatectomy. An actuarial study among 647 postprostatectomy men estimated an UI rate of 13% at one year and 7% at two years postsurgery [466]. The Prostate Cancer Outcomes Study reported that the 5-year postprostatectomy incontinence rate among 1, 288 men was 14%, which was higher than the 10% rate reported after 2 years [467]. After 3 years of follow-up, a large nationwide population-based study found that 3% of the cohort studies eventually underwent post-prostatectomy UI surgery [468].

Table 18. Examples of studies on postprostatectomy UI rates at different times of assessment

Study	Type of Prostatectomy	N	UI Rates by Time of Assessment of Continence (%)				
			1 mo	3 mo	6 mo	12 mo	24 mo
Chen 2017 [608]	RP	469	-	45.6	-	32.3	33
Wagner 2016 [456]	RARP	482	-	52	37	24	-
Prabhu 2014 [609]	RRP	1788	-	27.4	-	-	4.5
Schiavina 2014 [465]	RRP	778	59.4	41.1	29	22	-
Basto 2014 [528]	RARP	262	62 (<70 years); 87 (>70 years)	34 (<70 years); 40 (>70 years)	23 (<70 years); 18 (>70 years)	11 (<70 years); 8 (>70 years)	-
Berg 2014 [610]	RARP	232	-	71.11	38.11	16.81	-
Springer 2013 [611]	RRP (nerve sparing)	128	71.9		26.6	10.6	
Penson 2008 [467]	RP	1213	-	-	33	18	15
Moore 2007 [475]	RP	228		43		15	
Harris 2007 [612]	RPP	210	48	29	15	6	-
Moinzadeh 2003 [464]	RRP		-	18	9	1.5	-
Jacobsen 2007 [516]	RRP, Lap RRP		-	42 (RRP), 70.4 (lapRRP1), 60 (lapRRP2)	-	12.8 (RRP), 20.7 (lapRRP1) 14.5 (lapRRP2)	-
Ates 2007 [613]	Lap RRP	939		30.2		11.8	8.3
Galli 2006 [599]	Lap RRP	150	45	26.2	12.1	8.3	-
Link 2005 [614]	Lap RRP	122	-	83.01 49.02	47.81 10.12	33.31 6.62	-
Springer 2013 [611]	Lap RRP	125	60		31.6	3.2	
Patel 2011 [440]	RARP	1111		14%1	6 1	41	
Finley 2009 [615]	RARP			31%1			
Greco 2009 [616]	RARP			352	212	112	

[1] – continence defined as 0 pads
[2] – continence defined as <= 1 pad daily

Several preoperative patient characteristics and intraoperative factors postulated to influence the risk of UI post-radical prostatectomy have been investigated.

Older age at the time of surgery has been associated with a higher prevalence of post-prostatectomy UI [461,469-478]. One study showed a doubled risk for every 10 years of age beginning at age 40 [479]. Another showed that age at surgery predicted % per year [477]. However, other studies failed to demonstrate that age is an independent predictor for incontinence [454,480]. Kumar also conducted an age-stratified comparative analysis of functional outcomes among those who underwent robot radical prostatectomy and found that UI rates are comparable in younger and older men with the average time to continence also similar to both groups (3.1 vs 3.2 months, respectively) [481]. Other studies suggested that rather than age affecting final continence, elderly men need a longer time to achieve continence after surgery [462,482].

The weight and body mass index of patients has been identified as a risk factor for postoperative UI [469,483] or as a predictor of a longer interval before return to continence [461,473]. A meta-analysis [484], which included 6 trials with 2890 participants, showed that obesity (BMI ≥ 30) increases UI risk at 12 months in patients who underwent robotic-assisted laparoscopic radical prostatectomy (OR 2.43, 95% CI 1.21, 4.88, p-value = 0.01) but not in those who underwent laparoscopic radical prostatectomy.

Other factors have been associated with a higher prevalence of post-prostatectomy UI, although not consistently. These include preoperative LUTS and sexual dysfunction, ECOG status, severity of cancer, clinical stage, PSA, prostate volume, bladder neck size, Gleason score, and the hospital volume where the RP is done [469,471-472,475,485-486-491]. The effect of prior TURP on post-prostatectomy UI has also been variable [492-494]. A retrospective analysis of 156 patients who underwent preoperative MRI of the prostate and were followed up post-prostatectomy showed that time to return to continence was associated with the variation in the shape of the prostatic apex. The prostatic apex that does not overlap with the membranous urethra was found to be significantly associated with an early return of continence [486]. The preoperative thickness and length of the membranous urethra were also considered influential in post-prostatectomy UI [490]. Multiple prostate biopsies have not been shown to significantly affect mid to long-term UI after prostatectomy [495]. The 5-year cohort study of the Prostate Cancer Outcomes Study found that among prostatectomy patients, race and ethnic differences were related to UI, with African-Americans having better recovery compared to non-Hispanic whites and Hispanics [496].

The technique of radical prostatectomy impacts UI rates. Modifications associated with lower UI rates in early reports include the perineal approach [470,497] and sparing of the neurovascular bundle [469, 471,484,498]. Bladder neck preservation affords an earlier return to continence compared with bladder neck resection, but with similar UI rates after one year [499-500]. One study showed earlier recovery of UI after tennis racquet reconstruction and bladder neck preservation compared with bladder neck resection with puboprostatic ligament preservation, but with similar UI rates at one year [501-504]. However, continence status assessed more than 12 months after surgery showed even lower rates of UI after bladder neck preservation (11.6%) compared to resection (4.9%) in one study [502]. These longer-term difference in continence rates was further supported by the more recent randomized controlled trial [505] of 208 men with 3,6 and 12- month continence rates of 55.3% vs 84.2% (p <0.001), 74.8% vs 89.5% (p = 0.05) and 81.4% vs 94.7% (p = 0.027) in the control and bladder neck preservation group, respectively. Bladder neck intussusception was found to be associated with earlier return to continence in prospective studies [506]. The literature on the impact of neurovascular preservation on postprostatectomy continence rates is conflicting [507-508]. Present literature reports decreased UI was associated with increased neurovascular bundle preservation with 18.2 % UI rate among patients receiving nerve-sparing RP vs 27 % in the non- nerve sparing RP group [509,570]. An unprecedented ligation-free technique of the dorsal venous complex during laparoscopic radical prostatectomy done in 180 patients showed lower UI of 60% vs 75.5 %, 45.6% vs 62.3%, and 26.1% vs 28.3 %, at 3, 6 and 12 months, respectively compared to standard ligation technique [511]. Simforoosh introduced a sutureless vesicourethral anastomotic technique based on the assumption that a reduction in the number of sutures utilized in the vesicourethral anastomosis improves continence recovery by causing less disturbance in the intrapelvic urethra. Promising low UI rates were achieved: 10 % at 3 months, 4.1 % at 6 months, and 3.6 % at the last follow-up visit [512]. Other technical aspects of the surgical procedure including the use of cautery when resecting the seminal vesicle; the degree of bundle preservation; excision of lymph glands; use of cautery near the urethra; and observation of a cutting suture in the bladder neck were not associated with UI [509].

Since the inception of laparoscopic and robotic surgeries and with the increasing performance of these minimally invasive procedures, several studies have investigated their impact on postoperative continence rates. Early systematic reviews with metaanalysis of studies comparing continence rates for open, laparoscopic, and robotic radical prostatectomy did not show any significant difference in the postoperative continence rates between the 3 techniques [513-515]. However, a prospective study of 239 men showed that UI after laparoscopic procedures seems to be higher initially but approximates that of open techniques by one year [516]. A larger population retrospective study with 12092 localized prostate cancer patients compared UI rates among those who underwent minimally-invasive RP (technique not specified) and open radical prostatectomy. Higher rates of UI (53.9 % vs 43.2 % in the younger age group and 56.5 % vs 51.8 % among the older age group) were seen after minimally-invasive RP [517].

A systematic review that focused on robotic radical prostatectomy showed better continence recovery after robotic prostatectomy compared with open retropubic prostatectomy (OR : 1.53, p=0.03) or laparoscopic radical prostatectomy (OR : 2.39, p=006) [518]. However, more recent large multicenter prospective non-randomized controlled trials reported a non-statistically significant difference in UI at 2-3 years (UI rate of 21.3 % for RARP vs 20.2 % for RRP in the study of Haglind; UI score for RARP 76 + 21.3 vs 78 + 21.7 for RRP in the study of Harlemann) [519-521]. These conclusions were further supported by a randomized controlled trial assigning 326 men to RARP and RRP. Both approach yielded similar functional outcomes at 24 months [522]. Immediate continence defined as no pad usage after catheter removal was also not significantly influenced by the surgical approach (robot vs open) but by surgeon volume (>100 procedures), preoperative erectile function and ECOG status, bilateral nerve-sparing, less blood transfusion, and Gleason score [521]. The global evaluative assessment of robotic skill (GEARS) score, whereby a higher score was associated with superior surgical skill, was utilized as a tool to validate the relationship of surgeon technical performance and early continence after robot-assisted laparoscopic radical prostatectomy. Higher scores were associated with better continence rates [523].

Several recent multicenter prospective studies, randomized controlled trials, and meta-analysis have compared the Retzius-sparing technique and the conventional RARP [524-526]. These studies demonstrated superior early continence up to 6 months, and quality of life in the Retzius-sparing group compared to the standard RARP group with UI rates of 38.9 % vs 66.5 %, 8.9% vs 32 %, and 5.4 vs 15 % at 1 week after foley catheter removal, 3 months post-surgery, and 6 months post-surgery, respectively [526]. Robot-assisted radical prostatectomy has also been done extraperitoneal with UI rates of 69.8 %, 49.7 % and 11.2 % at 1, 3 and 12 months post-RP, respectively but these comparable rates to intraperitoneal RARP were attributed to the nerve-sparing technique done [527]. The use of Rocco suture has not been shown to predict the time of continence recovery in robot prostatectomy [528]. Kováčik and colleagues introduced Advanced Reconstruction of Vesicourethral Support (ARVUS), a novel post-prostatectomy reconstruction technique involving anterior and posterior reconstruction of the pelvic structures during RALRP. Unfortunately, the technique performed worse in continence rates compared to the control group [529].

Additional observation worth mentioning is that men who underwent salvage radical prostatectomy after either EBRT or brachytherapy were found to have worse urinary continence outcomes than after focal therapy [530]. Conversely, salvage brachytherapy was associated with 18.3 % UI in a small retrospective cohort study [531]. Adjuvant radiotherapy has not been found to affect post-prostatectomy UI rates when assessed beyond 1 year [532-533].

With the well-established association of radical prostatectomy and UI, interest in focal therapies for localized prostate cancer has emerged and research endeavors have been set in motion to understand the effect of different focal therapies on UI. Despite reports of having superior functional outcomes compared to radical prostatectomy, He and associates conducted a systematic review and meta-analysis on the oncologic and functional outcomes of high intensity focused ultrasound (HIFU) and was able to observe incidences of 10 % (95% CI 0.06–0.14), and 2 % (95% CI 0.01–0.03) UI among men after whole gland and partial gland ablation, respectively [526]. These rates were consistent with later reports, limited to observational cohort studies [535-537]. No randomized controlled trials (against radical prostatectomy and other treatment options for localized prostate cancer) have been reported as of the writing of this text. 3dRT monotherapy as a form of focal therapy confers 7% UI rate [538] while EBRT and/or high dose brachytherapy was reported to have 14 % UI rate.

3.10. Factors with unclear association with UI in men

A diagnosis of hypertension was associated with an increased UUI risk in men OR 1.52 (CI 1.0-2.33) based on recent research in the UK involving a cohort of 1059 men from the Medical Research Council (MRC) National Survey for Health and Development [435].

Those with sleep apnea were more likely to have UI than those without (OR=2.73, 95% CI=1.51-4.95) [539]. Li and associates evaluated the association of major depression and vitamin D deficiency, and UUI in 1293 non-obese men in the National Health and Nutrition Examination Survey. Odds ratio of 2.60, (95% CI: 1.33-5.09) and 1.61, (95% CI: 1.01-2.59) were obtained, respectively [430]. These risk factors have not yet been validated in other studies.

4. SUMMARY POINTS:

- The epidemiology of UI in men has not been investigated to the same extent as for females. But it appears that UI is at least twice as prevalent in women as compared with men. There seems to be a more steady increase in prevalence with increasing age than for women.
- Most studies find a predominance of UI, followed by mixed forms of UI and SUI the least. Most studies have a large fraction of other/unclassified types.
- Literature on incidence and remission of male UI is still very scarce.
- Clear risk factors are more seldom scientifically documented, but several medical correlates have been reported. Established risk factors predisposing men to UI include increasing age, presence of LUTS, UTI'S, functional and cognitive impairment, diabetes, alcohol intake, obesity, neurological disorders, and prostatectomy.
- Substantial gains have been achieved on the study of the epidemiology of UI in men compared to the previous years. The conduct of more population-based prevalence studies permitted a better understanding of the problem of UI among men.
- UI after radical prostatectomy is frequent, ranging from 2-57%. Rates steadily decline from the time of surgery and plateaus at 1 to 2 years postoperatively.
- Factors affecting post-prostatectomy UI include the age at surgery, obesity, type of prostatectomy, and certain modifications in the technique.
- There is not enough evidence to demonstrate any significant difference in continence rates between open, laparoscopic and robotic-assisted radical prostatectomy.
- Modifications in the surgical technique of radical prostatectomy have variable impact on postoperative continence rates.
- Comparative studies of surgical procedures and focal therapies to address prostate disease and their various modifications should be performed to better assess their impact on postoperative continence rates.

VI. EPIDEMIOLOGY OF OVERACTIVE BLADDER AND NOCTURIA

1. GENERAL COMMENTS AND DEFINITIONS

OAB and nocturia were previously neglected topics in the medical literature [617-619]. Earlier research on epidemiology of LUTS focused either on LUTS suggestive of BPH and BPO in men or SUI in women [620]. However, there has been increased research interest in OAB and nocturia during the last quarter century [618-619,621].

OAB can be bothersome [622-624], and is associated with comorbidity [322], impaired quality of life [8], and reduced emotional well-being and work productivity [625]. Nocturia is a common cause of sleep maintenance insomnia [626-628]. Nocturia can be bothersome [629-636], and is associated with impaired mental health, physical health and quality of life [636-638]. Systematic reviews and meta-analyses found that nocturia is associated with increased risk of falls, fractures and mortality [639-640]. Also OAB has been suggested to be associated with increased risk of falls and fractures [641-642]. Indeed, urinary urgency and urgency incontinence, the cornerstone symptoms of OAB, and nocturia are among the most

bothersome urinary symptoms both on an individual and population-level [643].

In general, the definition of any condition is a critical factor in evaluating its epidemiology: OAB and nocturia are not exceptions to this rule [619,644]. To facilitate discussion and research related to LUTS, the International Continence Society (ICS) has produced standardisation reports [645-648]. We will use the ICS definitions as basis of this chapter. However, we acknowledge that these definitions are not perfect and we encourage further research and discussion [621,644-651].

OAB is a term to describe the clinical problem of urgency and UUI from a symptomatic rather than from a urodynamic perspective. Previously various terms, such as 'irritable bladder' or 'unstable bladder' have been used. According to the ICS, OAB is a symptom-defined condition characterised by urinary urgency, with or without UUI, usually with increased daytime frequency and nocturia [645-646]. The ICS defines *urinary urgency* as sudden compelling desire to pass urine, and the term OAB is appropriate if there is no proven infection or other obvious pathology [645].

It has been known for a long time that among healthy people urine production is lower during the night than during the day [652]. Urologists have traditionally defined nocturia as frequency of micturition at night without reference to urine amount, while internists have assumed that nocturia results from an increased amount of urine produced with less focus on other LUTS [653]. According to the ICS definitions, *nocturia* refers to waking at night one or more times to void, and *nocturnal polyuria* (NP) is the production of an abnormally large volume of urine during sleep [647]. Nocturnal UI or nighttime bed wetting (enuresis) differs from nocturia.

According to the ICS, as stated earlier, nocturia is also a component of OAB. However, there is a debate on the definitions, especially regarding urinary urgency and OAB [621,650-651,654-664].

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

2. PREVALENCE OF OVERACTIVE BLADDER

Prevalence estimates from as low as 2% [665] up to 53%[666] have been reported. Many studies on OAB have reported prevalence estimates between 10% and 20% [667-674]. However, many of the studies have been limited by not measuring bothersomeness.

Table 19 summarized population-based studies that assessed prevalence of OAB in adults of both genders. To identify these studies, a Medline search (English-language articles published before June 2016) was carried out on with the strategy (((Overactive bladder.mp) or (OAB$.mp)) and ((prevalence.mp). Non-population-based (i.e. based on doctor attendances or similar) studies or studies not conducted among both sexes were not included in Table 19.

Among these population-based studies identified, different populations, different sample selection and different data collection methods were often used (Table 19). Sample sized varied between 913 and 162,906, median being 3,366 individuals. Nine (39%) out of 23 studies did not report any response proportion. Among those 14 studies which reported, as many as eight (58%) had response proportion less than 50%. There was significant heterogeneity in symptom assessment, exclusion criteria, case definitions (some studies used grading of symptom severity whereas others did not), and in the time period during which the occurrence of symptoms was asked (Table 19). Hence, dissimilarities in study procedures likely explain the differences in prevalence estimates. Overall, median prevalence estimate of the studies was 16.5% (range 2-35% in men, and 3-41% in women) (Table 19). However, estimates of the prevalence of OAB have been smaller in many recent studies compared to earlier estimates (Table 19).

Table 19. Overview of published population-based studies assessing prevalence of OAB in both sexes (PubMed indexed English-language articles as of June 2016, in chronological order).

Origin	Data collection method	Sample source	Respondents (response proportion, %)	Age range (years)	2002 ICS Consensus Definition of OAB	Definition of normal - abnormal occurrence	Time period	Prevalence, %: Men/women
European [667]	Telephone interview / in person interview[a]	Telephone registry / electoral census[a]	16,776 (unreported)	40 – 75+	N/A	N/A	Undefined	**16 / 17**
USA [669]	Telephone interview	Telephone registry	5,204 (44.5)[b]	18 – 75+	N/A	N/A	Past 4 weeks	**16 / 17**
Canada [675]	Telephone interview	Telephone registry	3,249 (43.4)[c]	35 – 75+	N/A	N/A	Past month	15 / 21
Japan [671]	Mailed questionnaire	Not reported	4,570 (45.3)	40 – 100	N/A	N/A	Past month	14 / 11
Brazil [676]	Unreported	Not reported	913 (unreported)	15 – 55	Yes	Unreported	Undefined	14 / 23
Taiwan [677]	Questionnaire administered by nurse	Population registry	1,921 (67.0)	30 – 79	No	N/A	Past 4 weeks	16 / 18
International [674]	Telephone interview	Telephone registry	19,165 (33.0)	18 – 70+	Yes	No – Yes	Undefined	11 / 13
Finland [678]	Mailed questionnaire	Population registry	3,727 (62.4)	18 – 79	Yes	Rarely – often	Past 2 weeks	7 / 9
Korea [679]	Telephone interview	Telephone registry	2,005 (13.8)	40 – 89	No	N/A	Past 4 weeks	21 / 31
Canada [680]	Telephone interview	Telephone registry	1,000 (unreported)	18 – 90	No	N/A	Undefined	13 / 15
USA [681]	Mailed questionnaire / Telephone interview	Consumer panel	162,906 (62.7)	18 – 85+	No	N/A	Undefined	24 / 29
Portugal [682]	Telephone interview	Telephone registry	1,934 (59.6)	40 – 80+	No	N/A	Past 4 weeks	35 / 29
International [683]	Web-based interview	Consumer/ voter panel	30,000 (49.5)[d]	40 – 99	Yes	Rarely – sometimes (Sometimes – often)	Past 4 weeks	22 / 36 (5 / 11)
USA [684]	Web-based interview	Consumer/ voter panel	2,000 (42.1)[e]	40+	Yes	Rarely – sometimes	Past 4 weeks	26 / 41
USA [69]	In person interview	Community registry	3,483 (63.3)[h]	30 – 79	Noi	N/A	Past month[i]	9 / 14
Korea [685]	Telephone interview	Telephone registry	2,000 (22.1)	18 – 96	Yes	Unreported	Undefined	10 / 14
Korea [686]	Telephone interview	Post/address registry	2,000 (unclear)	30 – 60+	No	N/A	Past week[j]	19 / 27
China [687]	Interviewer assisted	Unreported	14,844 (69.0)	18 – 70+	Yes	<1 a week – ≥1 a week	Past week	6 / 6
USA [688]	Web-based interview	Consumer/ voter panel	10,000 (unknown)[f]	18 – 70	No	N/A	Past 4 weeks	16 / 30
Japan [689]	Web-based interview	Consumer/ voter panel	Unknown	20 – 60+	No	N/A	Past week[j]	10 / 9
Brazil [690]	In person interview	Local census tract	3,000 (unclear)	30 – 70+	Yes	Unreported	Undefined	5 / 10

Origin	Data collection method	Sample source	Respondents (response proportion, %)	Age range (years)	2002 ICS Consensus Definition of OAB	Definition of normal - abnormal occurrence	Time period	Prevalence, %: Men/women
China [691]	In person interview	Local census tract	9,805 (unclear)	40 – 70+	No	N/A	Past week	3 / 2
International [692]	Telephone interview	Unreported	3,130 (unknown)[g]	18 – 60+	Yes	No – Yes	Undefined	18 / 28

[a] In the European study, in five out of six countries, telephone interview was used (excluding Spain, where direct interviews were conducted due to lower proportion of households with telephone). Study sample was obtained from telephone number listings (except Spain, where electoral census data was used).
[b] Out of 11,740 participants (of 17,231 households contacted), 5,539 were considered ineligible. To calculate response rate, the number of respondents was divided by eligible participants (the former response rate). If same proportion of non-participants, as there were ineligible among participants (47%), were also considered ineligible, response rate was greater (the latter response rate).
[c] Out of 7,487 individuals, 3,239 completed the questionnaire (response proportion 43.4%).
[d] Invitation to complete email survey was sent to 88,150 members of the Internet-based panel. Of the members, 51,546 responded but 7,947 were excluded due to high rates of missing or inconsistent data, or discontinuation of the survey. Finally, 30,000 participants were randomly selected from the pool of respondents with completed surveys.
[e] Invitation to complete email survey was sent to 5,002 members of the Internet-based panel. Of the members, 3,058 responded, but only 2,106 members completed the survey. Finally, 2,000 participants were randomly selected from the pool of respondents with completed surveys.
[f] Invitation to complete email survey was sent to 38,469 members of the Internet-based panel. Of the members, 18,591 responded, but number of members completing the survey was not reported. Finally, 10,000 participants were selected from the pool of respondents with completed surveys.
[g] Authors reported that a large proportion of individuals asked to participate declined. However, the number of individuals asked to participate was not reported.
[h] Out of 5,503 individuals, 63.3% completed the questionnaire (n=3.483).
[i] In this study, individuals "were considered to have urgency if they reported difficulty postponing urination, had a strong urge to urinate (fairly often, usually or almost always) in the last month or a strong urge to urinate in the last 7 days (4 or more times)."
[j] Time period was not reported in the article. However, authors cited the original OABSS articles, which states that "patients were instructed to circle the score that best applied to their urinary condition during the past week" (Homma et al. Urology 2006).
[f] ICS, International Continence Society; OAB, overactive bladder; UTI, urinary tract infection.
[g] Cut-off point (threshold) used for normal vs. abnormal symptom occurrence. Reviewed only for studies using current ICS definition of OAB.1
h Time period during which the occurrence of symptoms was asked.

Only few population-based studies have evaluated OAB prevalence using the ICS definition *and* reported bother. Assessing perceived bother associated with OAB substantially decreases the prevalence estimates. In the FINNO Study (conducted in Finland among aged 18-79) [624], as many as 54% of men and 57% reported *any* (at least rarely) urinary urgency. However, prevalence of at least moderate bother from urgency was 7% for men and 9% for women. Overall, more than 96% of individuals with *rare* urgency reported no or small bother from it whereas 65% of individuals with urgency *often* and more than 70% with urgency *always* reported moderate or major bother (scale: none-small-moderate-major) [624]. These results are in concordance with two international studies [622-623]. In the EpiLUTS study (conducted in the US, UK and Sweden among people aged 40–99) [623], 22.4% of men and 35.7% of women reported urinary urgency at least sometimes (in scale: never-rarely-sometimes-often-almost-always) (Table 19). However, prevalence estimates were substantially lower when bother was taken into account. Only 6% of men and 12% of women reported "quite a bit" or more bother from urgency (in scale: not at all-a little bit-somewhat-quite a bit-a great deal) [623]. Bother analysis from the EPIC Study [622, 664] showed also that infrequent urinary urgency is not considered as very bothersome by most individuals. Out of OAB cases, 46% did not report symptom bother from it [622]. More recent studies [693-694] have had similar findings: i) definition of disease has strong impact on prevalence estimate, and ii) the more strict definition used, the bigger bother and quality of life impact. Overall, all these results suggest that i) bother measurement is essential in estimating the clinically relevant prevalence of OAB, and ii) most studies have overestimated the prevalence of patient-important OAB [5-8] (Table 18).

3. INCIDENCE OF OVERACTIVE BLADDER

The natural history of OAB has been systematically reviewed (English articles published between January 1, 1990, and September 20, 2009) [695]. Authors identified 7 longitudinal studies of OAB. OAB incidence varied between 3.7% and 8.8%; and included studies provided evidence for dynamic nature of OAB [80]. Indeed, longitudinal studies have confirmed not only that OAB prevalence increases with age but also that OAB is a dynamic condition [696-702].

In a population-based study (conducted between 1991 and 2007 in Gothenburg, Sweden) [693], the number of women with OAB with UUI ("OAB wet") increased from 6% to 16%, however, the proportion of women with OAB without UUI (OAB dry) did not differ significantly (11% vs. 10%). Among women with OAB dry in 1991, 23% remained OAB dry, 28% reported symptom progression to OAB wet and approximately half reported remission of OAB by 2007, supporting the concept of the dynamic nature of OAB. The rate of remission of OAB symptoms was greater for women who were OAB dry (49%) compared with those who were OAB wet (26%).

Finding that OAB is a dynamic condition was also reported in studies from Australia and Japan [701-702]. In the CHAMP study conducted among 1,705 men aged 70 or more living in metropolitan Sydney [701], one in three older men with OAB had sustained remission of symptoms without medical or surgical interventions. Of the men with OAB at baseline, 29% received treatment for OAB or benign prostatic enlargement over 5 years. In the Japanese longitudinal community-based "Fujiwara-kyo study" among more than four thousand people aged 65 years or more [702], the incidence rate of OAB was 12% and remission rate 30%.

4. RISK FACTORS FOR OVERACTIVE BLADDER

The causes of urinary urgency and/or OAB remain poorly understood. Identified risk factors are summarized below.

4.1. Age

In numerous cross-sectional studies older individuals reported more OAB than younger ones (Table 19). Furthermore, longitudinal studies have confirmed that OAB increases with age [695]. Besides increasing age, also having urgency in childhood predicts having urgency in later life [703-704].

4.2. Gender

In Table 19, we summarized population-based studies assessing prevalence of OAB among both genders. In most studies, OAB was more common among women (Table 19). Out of 23 listed studies, in only three (13%) the prevalence estimate of OAB was larger in men than in women. However, none of these studies [671,682,691] included younger age group. This is probably important as OAB is typically more common among women especially in younger ages.

4.3. Obesity

In a British, prospective study, obesity was a risk factor for the onset of OAB (OR 1.5, 1.0-2.1) in women [322] but not among men [688]). Ten studies were included in a systematic review examining the link between OAB and obesity [705]. There was a statistically significant link between obesity (measured by BMI) and OAB in eight studies. However, four of the studies that found a positive correlation were found to have low methodological quality. Three studies examined relation of OAB with waist circumference, two found relationship whereas one did not. Overall, unfortunately most studies were cross-sectional and did not often adjust for major confounders. A systematic review and meta-analysis of 33 observational studies (2190 patients, median follow-up 12 months) found that bariatric surgery is associated with improvement or resolution of any UI in 56% (95% CI 48-63%), SUI in 47% (95% CI 34-60%), and UUI in 53% (95% CI 32-73%) of patients [706].

4.4. Life-Style

In a prospective study among British women, neither alcohol, coffee nor tea consumption were risk factors for the onset of OAB (defined as having either urgency, UUI, or a combination of these) but use of carbonated drinks was [322]. Among men, neither tea, coffee nor wine consumption were associated with onset of OAB onset, but a negative association between beer intake at baseline and subsequent OAB onset was found [692]. However, this may be explained by a *systematic misclassification error* (individuals decrease or cease alcohol consumption due to ill health) [707-708], *residual confounding* (moderate drinkers have many other favouring lifestyle factors) [709-710], or direct biological effects. In a Swedish population-based study in young female twins [168], tea (but not coffee) drinking was associated with an increased risk for both OAB and nocturia. However, after controlling for confounders (including zygosity of twins) these associations did not remain significant. Concurring with these studies, among non-care seeking women [105], coffee or alcohol consumption was not associated with OAB. In a population-based study among women in Southern Sweden [306], OAB was not associated with alcohol consumption.

In a prospective British study, smoking was a risk factor for the onset of OAB (defined as having either urgency, UUI, or a combination of these) in women but not in men [696]. In a population-based study among Finnish women aged 18-79 [711], urgency was approximately three times more common among current and twice as common among former than never smokers. Parallel associations for urgency with smoking intensity suggested a dose–response relationship [99]. Other supporting findings have also been reported [712-714]. However, some other studies did not find smoking as a risk factor for urgency [168,682,306].

A prospective study among British men did not provide evidence of any specific dietary patterns as a risk factor for onset of OAB [697]. Furthermore, physical activity was not significantly associated with OAB onset in men [697]. Contradictory results were found among non-care seeking women [716] where physical activity was associated with decreased OAB.

4.5. Race/Ethnicity And Socioeconomic Status

Evidence regarding the role of race/ethnicity on OAB prevalence is emerging. In a small Taiwanese study [717], higher prevalence of urgency (7.7% vs. 4.3%, p=0.02), was found in indigenous woman than in non-indigenous women. In the US part of the EpiLUTS study [137], OAB was reported by 26% of White, 33% of Black, 27% of Asian and 28% of Hispanic men. In the multivariate analysis, OAB was significantly more common among African-American (OR 2.0, p<.001) and Hispanic (OR 1.7, p<.001) male participants. The authors reported no statistically significant differences among women after multivariate analysis, despite wide variation in crude prevalence (27% for Asian women, 43% for White, 46% for African-American and 42% for Hispanic) [137]. Hospital-based studies have reported conflicting results regarding prevalence of OAB by race/ethnicity [718-720].

4.6. Reproductive Factors And Pelvic Surgery

Urinary urgency is a common symptom during pregnancy [721]. In a Taiwanese study [722], only 1% of women reported having urgency before pregnancy, whereas corresponding estimates were 16% in the first, 25% in the second, and 31% in the third trimester. Other studies have also found increasing prevalence of urgency with advanced gestational age [723-724]. However, in a Nigerian study, women in the 3rd trimester did not report more urgency than women in 2nd trimester [725]. Although one quarter of pregnant women reported urgency, it was associated with moderate or severe bother for only 5% of symptomatic women.

The association of parity and urinary urgency is controversial. Some studies reported no association for parity with urgency or OAB [105,322,726-727] whereas others found increased prevalence of urgency among parous women [717,728-731]. However, there were substantial differences in methodologies between these studies. Regarding delivery mode, most studies demonstrated no effect on prevalence of urgency or OAB [682,726,730-733]. On the other hand, contrary findings have also been reported [734-735]. In a Swedish prospective study, weekly urgency was reported by 2.6% of women with a vaginal delivery and by 2.7% of the women with a cesarean section [715]. Corresponding figures were 7.9% for vaginal delivery and 2.7% for cesarean section groups at 9 months post-partum [734] concurring the results of a cross-sectional US study [734]. In a US study [715], for women with a history of at least one operative vaginal birth, the adjusted odds of OAB was more than quadrupled (OR 4.9, 95% CI 2.2-11; women who had delivered all their children by pre-labor cesarean as reference). A systematic review pooled estimates from 8 studies suggested an elevated risk of UUI after vaginal delivery versus cesarean section (adjusted OR: 1.30; 95% CI, 1.02-1.65; absolute risk difference: 2.6%) [736]. Similar findings were found for OAB in a prospective US cohort study following women for median time of 5 years post delivery [737].

The association of postmenopausal period with increased urgency or OAB has been reported in several studies [687,728,730-731,738-740]. Impact of hormone therapy on OAB is unclear [741]. The Cochrane Incontinence Group review of UI and estrogens (urgency or nocturia not as the primary objective of the study) found that there were less nocturnal voids and urgency episodes among women treated with local (but not systemic) estrogen [742]. There were no significant differences in OAB prevalence among women using either oral contraceptives or a levonorgestrel-releasing intrauterine device, in comparison to noncontraceptive users in a population-based study among young, Swedish women [743].

Radical hysterectomy is related with increased prevalence of pelvic floor problems [744]. For instance, patients treated for cervical cancer reported 2-3 times more commonly urgency than the matched controls: 36% of those with history of radical hysterectomy and pelvic lymph node dissection, 49% of those with surgery and adjuvant radiotherapy, and 48% of those with primary radiotherapy reported experiencing urgency [745]. However, the relation of urgency and hysterectomy for benign indications is less clear. Many studies did not find a significant association between hysterectomy with urgency [726-727,746-750]. However, some studies reported less [739,750-752] and some more [682, 728-729,753] urinary urgency after hysterectomy. No difference by route of hysterectomy on urgency has been found [750,752,754-755]. Both POPand stress incontinence surgery are associated with risk of (de novo) urgency or UUI in both hospital based, and population based studies [714,727,756-758].

4.7. Specific Conditions

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

Benign prostatic hyperplasia. Instead of OAB/urgency, observational, clinic-based studies have assessed relation of DO with BPH/BPO. Although patients with DO are less likely to get symptom improvement after BPH surgery than those without DO, many patients report less urgency after BPH surgery [759]. Similar findings were found in a prostatectomy study among men aged 47-85, 32% (n=49) reported urgency pre-operatively and 13% post-operatively (n=20) [760]. In another study, DO was present in 68% of patients (n=21) at baseline and in 31% (n=10) at follow-up (mean 2 years) in the prostatectomy group [761]. However, many patients remain symptomatic after prostate surgery, and prognostic factors for success remain largely unknown [762].

Pelvic organ prolapse. In community-based studies [730,763-765], POP was associated with 2-6 times higher risk of having UUI. Concurrent with this findings, hospital based studies have also found POP as a risk factor for UUI, and in interventional studies UUI is often (but not always) relieved [766].

Mental health. In the BACH survey [767], urinary frequency, urgency, and nocturia were associated with previously experienced sexual, physical, and emotional abuse for both genders and for all ethnic groups of the study (White, Black, Hispanic). Concurring results were found in a German, clinic-based study where 31% of women with OAB reported almost twice as often earlier physical or sexual abuse as did the women with SUI (18%) or women without

LUTS (18%) [768]. In an Iranian study, individuals with OAB had a higher prevalence of anxiety (28.2 vs. 8.8%; p=0.001) and depression (38.2 vs. 18.2%; P = 0.02) [679] concurring with findings from multinational EpiLUTS study and a longitudinal Japanese where increased depression and anxiety were found among individuals with OAB [707,7699]. Furthermore, postpartum depression has also been reported to be associated with UUI [770].

Other conditions. In the BACH survey [771], urgency was associated with almost double the risk of hypertension and heart disease in women and with more than double the risk of diabetes in men. However, In a Japanese study among the elderly, OAB was not associated with diabetes or kidney disease but was associated with depression, alcohol use, and increasing BMI [772]. In a UK prospective cohort study within a random sample of 19,241 women aged 40 or more identified from Health Authority lists of 108 general practices [322], predictors of OAB included bowel urgency, imbalance, osteoporosis, ankle swelling, diabetes, DVT and cystitis [322]. Urgency/OAB has also been reported to common among patients with irritable bowel syndrome [773-774], functional dyspepsia [775], diabetes [776-778], including gestational diabetes [779], stroke [780] and asthma [689].

5. PREVALENCE OF NOCTURIA

Most earlier studies assessing nocturia prevalence were conducted among elderly men [781-788]. They consistently found that nocturia 1) is a very common symptom and 2) increases with ageing. These finding have been confirmed in numerous comparative studies conducted in both sexes [629-630,635,673,680,789-802] (Figure 8).

Population-based studies assessing prevalence of nocturia in adults of both sexes included. A Medline search of the English-language articles published before June 2016 carried out with the search strategy ((nocturia.mp) and ((prevalence.mp)). Non-population-based (i.e. not based on doctor attendances or similar) studies, studies not conducted among both sexes of adults, studies with narrow age range (<40 years), or studies with percentage data unavailable not included.

In the FINNO Study, conducted among men and women aged 18 to 79 [793], approximately one out of eight men and women reported at least two voids per night. In addition, one in three reported one void per night. Young women reported more nocturia than young men, prevalence of nocturia in men and women equalized in the sixth to seventh decade of life, and in elderly men had more nocturia than women. Many other studies have supported these findings: higher prevalence of nocturia among young women than young men, and an equalization of prevalence in middle age [188,635,649,681,687,802-804] (Figure 8). As the gender difference has been found across different continents (Europe, Asia, Australia, North America, and South America) it probably not due to specific country, lifestyle or cultural factors. The reasons for the excess of nocturia among older men remain unknown, but prostatic enlargement is likely to be the predominant factor.

The Krimpen study, conducted in the Netherlands among elderly men [805], is one of the few studies where nocturia was assessed by using frequency-volume charts. One and a half or more voids/night (average of information on two to three nights) was present in 60% of men aged 70-78 years, whereas at least 2.5 voids per night was present in 20%, respectively. These estimations are comparable to questionnaire studies: most elderly people void at least once per night [803] (Figure 8).

6. INCIDENCE OF NOCTURIA

A comprehensive systematic review and meta-analysis summarized the incidence and remission of nocturia [806]. Authors conducted a search of PubMed, Scopus, and CINAHL databases as well as abstracts of major urological meetings until end of August 2015 and found 16 eligible studies [807-823]. Of the 16 included studies, 10 (62%) were at high risk and six (38%) at low risk of bias. Of these 16 studies, 14 (88%) accurately assessed noctu-

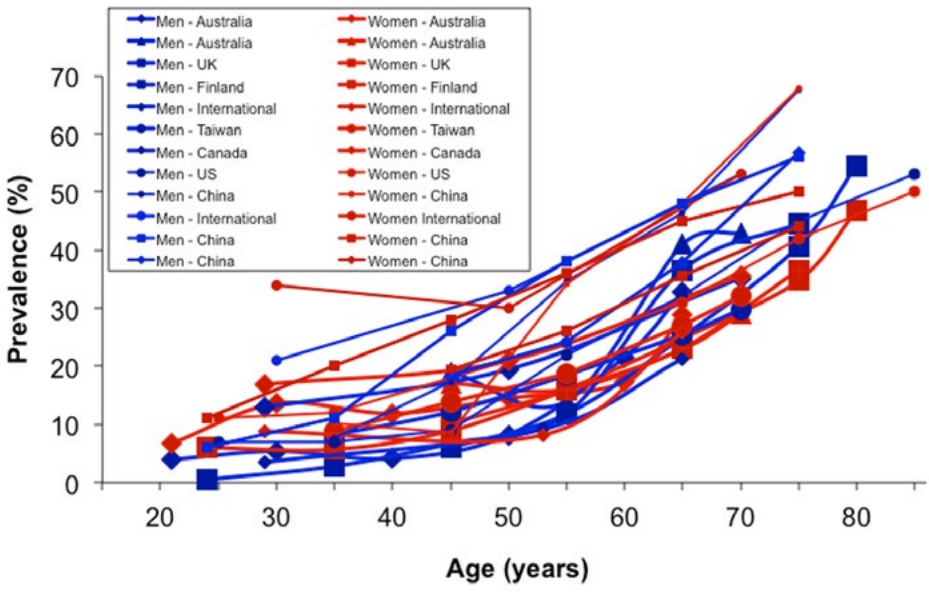

Figure 8. Prevalence of at least two voids per night across age groups by sex in population-based studies conducted among both sexes with wide age-range [14, 15, 20, 58, 65, 179-191].

ria both at baseline and at follow-up, nine (56%) had little missing data in the follow-up, and eight (50%) used representative source populations. Pooled estimates from 13 studies [810-823] with 114 964 person-years of follow-up demonstrated that annual incidence was strongly associated with age: 0.4% (0–0.8%) for adults aged less than 40 years; 2.8% (1.9–3.7%) for adults aged 40–59 years; and 11.5% (9.1–14.0%) for adults aged at least 60 yr. Of those with nocturia, each year 12.1% (9.5–14.7%) experienced remission.

7. RISK FACTORS OF NOCTURIA

The causes and risk factors of nocturia are not very well understood [650,785]. Available studies, that aimed to identify potential risk factors, are summarized below.

7.1. Age

There have been numerous studies showing that elderly subjects have more nocturia than younger people- age is one, if not the most important correlate of nocturia. For instance, in a community-based US study, less than 5% of those aged 18-24 reported two voids per night while the corresponding figures were approximately 15% and 25% for those aged 45-54 and 65-74 respectively [630]. Besides increasing age, also childhood nocturia and enuresis has been suggested to predict nocturia in later life [708,824].

7.2. Gender

Although there is no remarkable difference in overall prevalence of nocturia between genders, in more detailed age specific analyses differences have emerged between the genders (Figure 8). Many studies found higher prevalence of nocturia among young women than young men, and an equalization of prevalence in middle age [635,674,680,777,803,883]. Prostatic enlargement has been suggested as predominant factor for potential nocturia excess among elderly men [803].

7.3. Obesity

Several studies have shown the relation of overweight/obesity and nocturia. Obesity was associated with more than three-fold risk of nocturia in a Swedish study among middle-aged women [825], and with more than two-fold risk in the FINNO Study [826]. Confirmatory findings have been reported in numerous studies [804,827-834]. In the longitudinal TAMUS study among men aged 50 or more [835], obese men had double the risk for nocturia compared with normal weight men. The frequency of nocturia at baseline did not increase the incidence of obesity at follow-up.

7.4. Life-Style

Many studies have not found an association between nocturia and either alcohol [629,808,829,836-839] or coffee/caffeine [788,825,835,839-840] consumption. In some studies moderate alcohol consumers had less nocturia than abstainers [835,841-842]. However (as discussed earlier in 'Risk factors of overactive bladder'), these findings may be due to systematic misclassification error or residual confounding [707-710].

Many studies have not found an association between nocturia and smoking [788,805,829,835,838-839,843]. Some conflicting results have also been reported: in Swedish and Chinese studies [825,832] smoking was associated with increased nocturia but in Austrian [629] and Japanese [837] studies, with decreased nocturia.

Physical activity has been reported to be protective against LUTS in men [844.846], and against nocturia in both genders [801,825]. In an Austrian study [629], no relation was found between nocturia and physical activity. However, exercise programme has been shown to improve nocturia in non-randomised trial [847].

7.5. Race/Ethnicity And Socioeconomic Status

In several US studies, African Americans were approximately twice as likely to report nocturia as other groups [827,830,848-850]. This effect was attenuated, although remained significant [830,849], with adjustment for socioeconomic status and comorbidity. Furthermore, care-seeking black women reported also more commonly nocturia than other groups [8512-853]. Conflicting results were found in a Kaiser Permanente study [854]. In the EpiLUTS study conducted in the USA, UK and Sweden [823] and in a Kaiser Permanente study [855], Blacks and Hispanic had more nocturia when compared to White. Less is known about the relationship between ethnicity and nocturia outside the US. In small studies in Taiwan [717,856] and Scotland [857], associations of nocturia and ethnicity have been found. In the Scottish study, nocturnal polyuria was more common in the Caucasian men compared to Asian men.

7.6. Reproductive Factors And Pelvic Surgery

Nocturia is a very common symptom during pregnancy. In all studies most pregnant women report nocturia at least weekly, in many studies most women report having nocturia every night [721-725,732,858-860]. Typically the occurrence of nocturia increases during pregnancy. In an Indian study [859], nocturia (defined as more than one void per week) was reported by 51% of women before pregnancy (retrospective information), by 59% of those in the first, 72% in the second and 77% in the third trimester. In Finnish and Chinese studies [727,821], parous women reported slightly more nocturia than nulliparous women, contradicting earlier reports (conducted among perimenopausal women) of no association [729,861]. The relation of nocturia with parity has been suggested to be more likely due to pregnancy itself than trauma to the urinary tract during delivery [862] supported by finding of no difference in nocturia between primi- and multiparous women in the same Finnish study [727] and by a finding of no difference between vaginal delivery and caesarean section in a Swedish prospective study [734]. In these studies, the postpartum period was also associated with increased nocturia [727,734].

In a population-based Swedish study among young women, no difference in nocturia was found among oral contraceptive users and non-users, however, levonorgestrel-releasing intrauterine device (compared with non-contraceptive users), reported less nocturia (OR 0.53, 95% CI 0.32-0.89) [743].

Danish and Finnish population-based studies have reported more than double the risk of nocturia after menopause [727,729], consistent with other studies [738,821,861]. One study attributed this to aging rather than to menopausal transition [863]. In the Finnish and Swedish studies [727,861], there were indications of increased nocturia among women using menopausal hormone therapy, but the findings were statistically insignificant. In a small randomised trial [864], there was no difference in nocturia among those with menopausal hormone therapy or placebo. Similar findings were reported in a randomized trial of vaginal estradiol and placebo after sling surgery [865].

The relationship of nocturia and hysterectomy is unclear, with hysterectomy being protective factor [866-868], risk factor [729,855], or not associated with nocturia [727,739]. Surgery for SUI was not associated with nocturia in a population-based study [727].

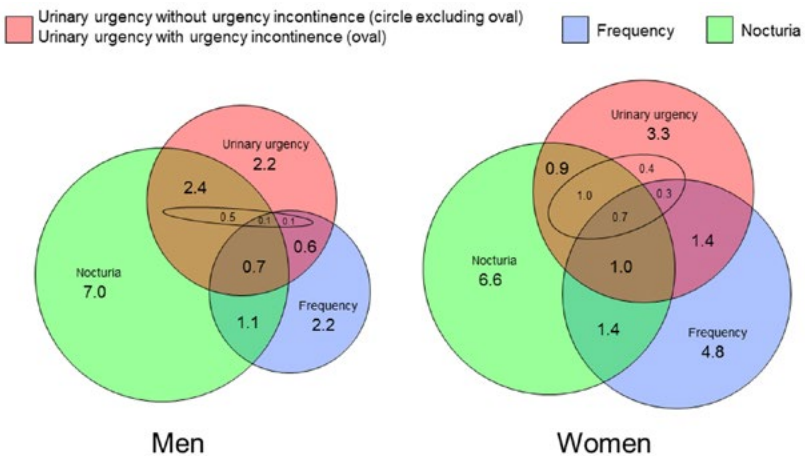

Figure 9. Age-standardized prevalence of nocturia, urinary urgency (with or without urgency incontinence) and urinary frequency among Finnish people aged 18–79 years.

The red circle represents individuals with urinary urgency (often or always in scale: never-rarely-often-always) without urgency incontinence (often or always in scale: never-rarely-often-always) excluding the area of the red oval representing individuals with urinary urgency with urgency incontinence. The blue circle represents individuals with urinary frequency (defined as more than eight voids/day) and the green circle nocturia (defined as at least two voids/night). Age-standardization performed using the age structure of Finland. Modified from "Tikkinen KA et al. Is the prevalence of overactive bladder overestimated? A population-based study in Finland. PLoS ONE 2007; Feb 7;2:e195" which is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited

7.7. Specific Conditions

BPH and prostate cancer. BPH constitutes a well-recognised risk factor for nocturia [805,839,869]. In the FINNO Study [839], half of the subjects with physician-diagnosed BPH reported at least two voids per night; however, only a third of the men with nocturia reported BPH. However, nocturia is the least specific LUTS associated with BPO and medical treatment to relieve BPO has less effect on nocturia than on other LUTS [870-871]. Furthermore, nocturia has been reported as one of the most persistent LUTS following prostate surgery [760,872], and in a study on men with bothersome LUTS, those receiving finasteride had an effect indistinguishable from placebo [873]. Many men with LUTS express a fear of prostate cancer [874], however, whether LUTS (including nocturia) are suggestive of prostate cancer is not clearly established [875]. In the large HUNT-2 study [876], LUTS severity was positively associated with the subsequent diagnosis of localised prostate cancer but not with advanced or fatal disease. More than 70% of men with physician-diagnosed prostate cancer reported at least two voids/night, while 7% of men with nocturia reported prostate cancer in the FINNO Study [839]. Whether men with nocturia are only more vulnerable to be diagnosed with prostate cancer (due to use of prostate-specific antigen), prostate cancer causes nocturia, or nocturia is a side-effect of various prostate cancer treatments remains unclear [636,877]. Impact of radical prostatectomy on nocturia has been neutral or negative (i.e. increased nocturia) [878-880].

Nocturnal polyuria. A systematic review and meta-analysis summarized the relationship between nocturia and nocturnal polyuria [881]. Authors conducted a search of PubMed and Embase databases for studies written in English, German, French or Dutch with original data on adult participants in an investigation of the relationship between nocturia and nocturnal polyuria. Fifteen studies met the inclusion criteria. Quality scores of studies were generally high for internal validity but low for external validity. Standardized mean difference of 0.6 (95% CI 0.3-0.9) for nocturnal voids between nocturnal polyuria and non-nocturnal polyuria cases was found. Risk ratio for nocturnal polyuria in individuals with nocturia was 1.41 (1.37-1.44). Authors concluded that "the association between nocturia and nocturnal polyuria is apparent and robust. However, the clinical importance of the association appears to be less obvious than previously suggested based on single studies. The observed high prevalence of nocturnal polyuria, as a result of the applied International Continence Society definition, may be responsible for this discrepancy." The ICS defines nocturnal polyuria as an increased proportion of the 24-hour output of urine volume occurring at night [645,647]. However, there is a paucity of studies providing reference values. The Krimpen study authors suggested that nocturnal urine production exceeding 90 ml/hr is abnormal [805,882] but concluded that "nocturnal urine production as an explanatory variable for nocturnal voiding frequency is of little value." Another systematic review aimed to determine population-based evidence of the diagnostic accuracy of proposed definitions of nocturnal polyuria based on data from frequency-volume charts [883]. Authors identified 13 studies which suggested that diagnostic performance characteristics for proposed nocturnal polyuria definitions show poor to modest discrimination, therefore more data is needed ffrom both women and men of all adult ages and various backgrounds. Finally, in many cases the fundamental pathogenesis of nocturnal polyuria remains largely unknown [884].

OAB. Urinary urgency was a clear risk factor for nocturia in the FINNO Study (OR 7.4, 95% CI 4.5-12 for men, and OR 4.9, 95% CI 3.2-7.7 for women) [839]. However, while half of subjects with urgency also reported at least two voids per night, only one in three with nocturia reported urgency [678]. The finding that most people with nocturia do not report frequent urinary urgency (Figure 9), has been reported also in the EPIC and EpiLUTS studies [623,676].

Diabetes. An association between diabetes and nocturia has been noted in most [792,817,823,827,832,839,842,869,885-889], but not

all reports [681,805,812]. In the BACH Survey [837] and in a Danish study at ages 60-80 years [839], nocturia was associated with double the risk of diabetes. In these surveys, however, it remained unreported whether there were gender differences. In the FINNO Study, diabetes was associated with nocturia after adjustment for other factors only in women. On the contrary, in a Chinese study, association was found for men, but not for women [801].

Hypertension. It has been suggested that essential hypertension and nocturnal polyuria are part of the same pathophysiological process [889]. In Japanese, US, Chinese and Malaysian studies [792,812,830,832,890], hypertension was associated with nocturia, although effect sizes were generally modest (ORs between 1.5 and 1.6). In another Chinese study [801], association of nocturia and hypertension was found in women, but not in men. In studies conducted in Europe [791,805,839], neither nocturnal polyuria nor nocturia were associated with hypertension. In a secondary analysis from the BACH survey, monotherapy with calcium channel blockers in women, and combination therapy with loop diuretics in men was associated with nocturia but no other associations for nocturia with any other antihypertensive was found [891]. While the treatment for hypertension may cause [620,891-892] or alleviate nocturia [893] in some cases, appropriate methods are of particular importance when trying to assess the relation between hypertension and nocturia.

Coronary disease. Earlier (male) studies [791-792,805] did not find a relation between nocturia and cardiac disease. However, in these studies, an association between cardiac symptoms/disease and nocturia was found in the preliminary analyses before multivariate modelling. In more recent studies [801,827,839,842-843,894-895] coronary disease has been shown to be associated with nocturia.

Depression. In Swedish and US population-based studies [638,896], depression and antidepressant use were both associated with increased prevalence of nocturia whereas in a Finnish study a relationship was found only among men using antidepressants after adjustment for other factors [839]. In another Finnish study (among men aged 50 or more), those with depressive symptoms at study entry were at almost triple risk for moderate or severe nocturia than those without depressive symptoms but nocturia had no effect on depressive symptoms during 5-year follow-up [897]. In a Kaiser Permanente study [855], increasing anxiety/depression scale was associated with increasing nocturia. In a longitudinal Japanese study (The Nagahama Study) of more than 9,700 individuals, authors found a clear dose-relationship between baseline nocturnal voiding frequency and new onset depressive symptoms and a weak association between baseline 5-item Mental Health Inventory and new onset nocturia [898].

Sleep apnea and snoring. In clinic-based studies [887,899-902], nocturia was associated with sleep apnea. In US studies conducted among community-dwelling older adults, subjects with increased apnea-hypopnea index had greater mean nocturia episodes, nighttime urine production and atrial natriutretic peptide excretion [903-904]. Snoring was one of the three most important nocturia population-level risk factors for both sexes in the FINNO Study [839] concurrent with a Swedish urology clinic study [294]. Overall, a systematic review and meta-analysis identified 13 studies (406 patients and 9518 controls) and found association (RR 1.41, 95% CI 1.26-1.59) between sleep apnea and nocturia [905].

Neurological diseases. Most patients with multiple sclerosis have bladder dysfunction, which may also lead to nocturia [907-908]. Nocturia was also associated with stroke and cerebrovascular disease [842,885,909]. Moreover, in a study among Parkinson´s patients, severity of disease was also associated with increased nocturia [910]. Furthermore, a relationship of nocturia with restless legs syndrome has been reported [910].

8. SUMMARY POINTS

- OAB has been defined as urinary urgency, with or without UUI, usually with increased daytime frequency and nocturia (in the absence of infection or other obvious pathology).
- Prevalence of OAB has been estimated from as low as 2% up to 53%.
- Recent population-based studies have shown that less than 10% of people have OAB with at least moderate bother, suggesting that bother measurement is essential in estimating the clinically relevant prevalence of OAB.
- Longitudinal studies have shown that OAB increases with age, and that OAB is a dynamic condition, with not only substantial progression but also remission rates.
- OAB may be associated with an increased risk of falls, fractures, and impaired quality of life.
- While age is a clear risk factor for urinary urgency and/or OAB, other risk factors have not been that well studied.
- Individuals with BPH, POP and mental health problems typically report urinary urgency more often than those without.
- Nocturia is one of – if not the - most common LUTS with similar overall prevalence in both genders.
- The prevalence of nocturia is higher among young women than young men, but the prevalence increases more strongly with age in men.
- The literature on the incidence of nocturia remains relatively sparse. The incidence of nocturia has been shown to increase with age but also remarkable fluctuation has been identified.
- Two episodes of nocturia constitute meaningful nocturia, affecting quality of life and perceived health, while a single episode does not.
- Nocturia has been associated with an increased risk of falls, fractures, and death.
- Risk factors for nocturia include conditions of the lower urinary tract, but also a range of systemic conditions, including but not limited to BPH, urinary urgency/OAB, obesity, sleep apnoea, parity, and the postmenopausal state.

9. FUTURE NEEDS

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

VII. EPIDEMIOLOGY OF PELVIC ORGAN PROLAPSE

1. GENERAL COMMENTS AND DEFINITIONS

POP refers to the loss of support for the uterus, bladder, colon or rectum leading to prolapse of one or more of these organs into the vagina. POP is thus a continuous condition when measured by visual inspection of the vaginal wall during valsalva. For clinical purposes, the degree of POP is commonly described as above the introitus, at the introitus, or beyond the introitus with or without valsalva. The International Continence Society first developed a standardised definition for the condition of POP in 1996 [911-912]. The ICS Pelvic Organ Prolapse Quantification (POPQ) examination defines prolapse by measuring the descent of specific segments of the reproductive tract during valsalva strain relative to a fixed point, the hymen. The POPQ system describes the anatomic findings of pelvic organ prolapse without consideration for symptoms and bother perceived by the woman. Validation of this system has shown it to be highly reliable [913]. The stages of prolapse severity are arbitrarily defined, and there is no clear differentiation between normal anatomic variation and mild POP. For research purposes there is consensus for use of the POPQ system until further evidence might clarify the distinction between normal variation and mild prolapse [913].

Determining POP based on self-reported symptoms is difficult because of the lack of specificity and sensitivity of most symptoms attributed to pelvic organ prolapse [914] and the fact that prolapse above the level of the hymeneal ring is usually asymptomatic [915]. The only exception appears to be a sensation of bulging into the vaginal [916] which is most strongly associated with prolapse at or below the hymeneal ring. A recent study of 110 women found that a question asking about a feeling of something bulging in or dropping out of their vagina had a sensitivity of 84% and a specificity of 94% for POP at or beyond the hymeneal ring on examination [916]. Seeing prolapse would presumably be even more specific, but is too uncommon to be useful as a definition.

2. PREVALENCE OF POP

Several studies have reported the prevalence of POP in a general population [916-924]. Reports from the Women's Health initiative (WHI) Oestrogen Plus Progestin Trial, and randomized controlled trial, have been included. While not actually population-based, the women in the trial were recruited from the community rather then from women seeking gynaecological care, and provide important information on the prevalence of POP based on pelvic examination.

The prevalence of POP based on a sensation of a mass bulging into the vagina was remarkably consistent, ranging between 5 and 10 percent. The prevalence of observed prolapse in women enrolled in the WHI trial is similar to the prevalence found in the one population-based study that also used pelvic examination [917], although the prevalence of each type of prolapse was higher in the WHI study. In both studies, prolapse occurs most frequently in the anterior compartment, next most frequently in the posterior compartment, and least in the apical compartment.

Two studies that examined POP by race found the that Black women had the lowest prevalence and Hispanic women the highest after controlling for multiple other factors in multivariate analysis [917-918]. The study reported by Rortveit et al based on symptoms found adjusted odds ratios of 0.4 (95% CI=0.2-0.8) for Black and 1.3 (95% CI=0.8-2.2) for Hispanic women, with White women as the referent group [924]. Hendrix et al reported adjusted odds ratios of 0.6 (95% CI=0.5-0.8) for Black and 1.2 (95% CI=1.0-1.5) for Hispanic women compared to White women for POP based on genital examination [918].

Table 20. Prevalence of pelvic organ prolapse (POP) defined by symptoms or observed on pelvic examination in the general population .

First author	Country	Definition of POP	Ages (years)	N	Prevalence Subgroup: %
Kumari [771]	India	a mass of flesh in the vagina or equivalent using local terminology	15+	2990	15-24: 5 25-34: 10 35-44: 8 45-54: 6 55-64: 9 65+: 3
McLennan [772]	Australia	A feeling of something coming down in the vagina	15-97	1546	8
Tegerstedt [767]	Sweden	Validated 5 item quetionnaire	30-79	5489	8
Eva [769]	Sweden	Any symptom of pelvic heaviness, genital bulge, or use of fingers in vagina or on perineum for defecation	40 60	641 663	23 28
Samuelsson [770]	Sweden	Standardized pelvic examination	20-59 (mean=39)	487	Any prolapse: 31 To introitus: 2 Cystocele: 16 Rectocele: 14 Uterocele*: 5
Rortveit [768]	USA	Feeling of bulging, pressure or protrusion or visible bulge or protrusion	40-73 (mean=56)	2109	6
Lawrence [764]	USA	Sensation of bulge in vagina or something falling out of vagina with a degree of bother of at least 33 on a 1-100 visual analogue scale (validated)	25-84 (mean= 57)	4103	6
Hendrix [762]	USA	Standardized pelvic examination	50-79 (mean=63)	27,342	Any prolapse: 40 Cystocele: 34 Rectocele: 19 Uterocele*: 14
Handa [763]	USA	Standardized pelvic examination	50-79 (mean=63)	412	Any prolapse: 32 Cystocele any: 25 Cystocele grade 1: 14 Cystocele grade 2: 10 Rectocele any: 13 Rectocele grade 1: 8 Rectocele grade 2: 5 Uterocele any: 4 Uterocele grade 1: 3 Uterocele grade 2: 1
Nygaard [766]	USA	POP-Q**	50-79 (mean=68)	270	Stage 0: 2 Stage 1: 33 Stage 2: 63 Stage 3: 2 Stage 4: 0 > hymeneal ring: 26
Bradley [765]	USA	POP-Q	50-79 (mean=68)	270	> hymeneal ring: 24

**** Denominator is women with a uterus***

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

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

3. INCIDENCE

Only two studies could be located that reported the incidence of new POP. Both studies were done on sub-groups of women enrolled in the WHI Oestrogen Plus Progestin Trial. The first study of 412 women enrolled at the University of California, Davis site, used a standardised pelvic examination repeated every 2 years over 8 years [917]. The incidence of new cystocele, rectocele and uterine prolapse was 9%, 6% and 2%, respectively. Annual rates of remission from grade 1 (prolapse to above introitus) was relatively common for each type of POP (24%, 22% and 48%, respectively) but less common from grade 2 or 3 (prolapse to or beyond introitus) (9%, 3% and 0%, respectively). In a second study of 259 women post-menopausal women with a uterus were examined using the POP-Q at baseline and annually for 3 years. POP was defined as prolapse to or beyond the hymeneal ring. The incidence of new POP was 26% at 1 year and 40% at 3 years, with remission rates of 21% at 1 year and 19% at 3 years [920].

Several studies have reported the annual incidence of surgery for POP in the US and at least one in the UK. A longitudinal study of over 17,000 women in the U K, age 25 to 39 at baseline, reported an annual rate of POP surgery of 0.16% [919]. This rate is consistent with the rate of approximately 0.2% per year reported in the US [919-920]. One US study reported an annual incidence rising with age from 0.05% in women age 30-39 to 0.5% in women age 70-79 with an estimated lifetime cumulative risk of surgery from prolapse of 7% to 11%. A recent US study reported similar surgical rates: 0.07% for women 18-39, 0.24% for women age 40-59, and 0.31% for women age 60-79 [922]. Surgical rates drop substantially after age 80 [921-922]. Estimating rates of prolapse surgery has the advantage of use of hospital discharge data on procedures, which is highly accurate for the procedure performed, but less accurate for the indications for the procedures, particularly when a procedure may have more then one indication.

4. RISK FACTORS

4.1. Bowel dysfunction and pelvic organ prolapse

Bowel dysfunction is highly prevalent among women in general and it has been estimated that up to 27% of the female population in industrialised countries is affected by constipation [926]. It is a commonly held notion that women who seek urogynecologic care report a high prevalence of bowel symptoms [927]. The overall prevalence of constipation and associated symptoms in women with POP ranges between 20-53% [928-930[. Although the definitions of dysfunction differ between studies it is widely acknowledged that bowel dysfunction is a complex condition with a multifactorial etiology. Bowel dysfunction comprises a wide variety of symptoms including constipation, rectal emptying difficulties, incomplete defecation, manually assisted defecation, fecal urgency and IBS. Neurophysiologic assessments have shown that damage to pelvic floor musculature innervation can occur as a result of chronic constipation [931]. Other predisposing factors comprise low socio-economic status, pelvic floor surgery, depressive disorders, thyroid dysfunction, physical disability and inactivity, and food habits [932].

Current epidemiological evidence on the association between bowel dysfunction and pelvic organ prolapse are at odds. A number of studies suggest that women with POP are significantly more likely to experience constipation and other symptoms of bowel dysfunction [930,933-936] whereas others show a weak or non-existent association [129, 937-939. A recent review of the literature based on 50 studies evaluating the association between POP and bowel dysfunction found that approximately 40% of women with POP have complaints of bowel symptoms but a similar frequency was reported by women without POP [940]. In a case-control study, manually assisted defecation was present in 19.7% of women with prolapse compared to 4.4% of control subjects (p<0.001) [930]. In a randomly selected population based study, IBS and constipation were both strongly associated with POP (OR 2.8 95% CI 1.7-4.6, and OR 2.5 95% CI 1.7-3.7 respectively) [935]. Varma et al. [931] suggested that among randomly selected women, having symptomatic POP more than doubled the risk for obstructed defecation (OR 2.3 95% CI 1.5-3.7). A retrospective questionnaire based survey of women with and without prolapse concluded that constipation as a young adult was an important factor in the development of POP [933]. In a case-control study, women with prolapse were at increased risk for constipation also after adjustment for dietary fiber intake (OR 2.9, 95% CI 1.1-13.5). when compared to women without POP[934]. Also in a low income setting constipation has been identified as a risk factor for symptomatic POP [941].

In the cross-sectional Women´s Health Initiative (WHI), cysto- and rectocele was only weakly associated with constipation (OR 1.1 95% CI 1.0-1.2).(10) Similar weak associations between prolapse and bowel dysfunction have been observed in other large cross-sectional studies [929,938-939]. In a clinical and ultrasonographic study of 279 patients, symptoms of obstructed defecation were significantly correlated with having a rectocele. Having a rectocele was positively correlated with straining at stool, digitation, incomplete emptying and requirement of laxatives or enema [942].

Overall severity and prevalence of bowel dysfunction has shown poor correlation with findings of POP at radiological imaging [943-945]. Also at clinical examination, increasing vaginal descensus and prolapse severity, show a generally weak (or absent) association with symptoms related to bowel dysfunction [928,946-949]. In a substudy to the WHI, no specific bowel symptom was associated with increasing loss of pelvic organ support in any vaginal compartment [930]. When considering compartment-specific pelvic floor defects, most studies suggest that increasing posterior vaginal wall prolapse and perineal descent are correlated to more symptoms of obstructive defecation [931, 945, 947]. In a cross-sectional study of 260 women with pelvic organ prolapse, women with posterior vaginal wall prolapse were more likely to incomplete emptying (41% vs 21%, P=0.003), straining at defecation (39% vs 19%, P=0.002), and splinting with defecation (36% vs 14%, P<0.001) compared with women without posterior vaginal wall prolapse. But there was no significant association bowel symptom and increasing severity of prolapse [950].

The association between bowel dysfunction other than specifically obstructive symptoms and POP is scarcely investigated. In a random population-based study of 2109 racially diverse women women with IBS (prevalence =9.7%) had higher odds of reporting symptomatic POP (OR 2.4; 95% CI, 1.4-4.1) compared to those without IBS [951]. It has also between suggested that anal sphincter dysfunction such as paradoxical anal sphincter reaction is more common in patients with rectocele as compared to women without rectocele at defecography [952].

4.2. Pelvic surgery and POP

Even though the notion that hysterectomy increases the risk for POP has wide acceptance, longitudinal studies confirming a temporal association are few and previous studies often do not differentiate between various types of hysterectomy. A number of cross-sectional and retrospective studies implicate hysterectomy as an independent risk factor for POP. However, due to a delay of

onset, large population samples and a sufficiently long duration of follow-up are required to determine an association with adequate certainty.

In a nationwide cohort study, Altman et al. [953] reported that 3.2% of women with hysterectomy had POP, compared with 2.0% in non-hysterectomized controls, corresponding to a risk of 1.7 (95% CI, 1.6-1.7). In this Swedish study, vaginal hysterectomy had the highest risk for subsequent POP surgery (HR 3.8, 95% CI, 3.1 to 4.8) in comparison to non-hysterectomised controls. These results were corroborated by Cooper et al. in a large study from Scotland showing an increased risk for POP surgery among women after hysterectomy, compared to endometrial ablation [954]. These register-based data are largely in agreement with the longitudinal Oxford Family Planning Association study by Mant et al. [955] reporting increased overall incidence rates for prolapse surgery following hysterectomy. Although not separating various hysterectomy techniques, Mant el al. determined that the risk of POP following hysterectomy was 5.5 times higher (95% CI 3.1-9.7) in women whose hysterectomy was performed for POP as opposed to other benign conditions. In a large register-based assesment from Denmark (n=154,882) it was determined that the highest cumulative incidence of subsequent POP surgery 32 years after hysterectomy was found among women where POP was the indication for hysterectomy and also that the posterior compartment was the predominant location for prolapse occurrence post-hysterectomy [956]. In a follow up study it was determined that there were only minor differences in risk of POP repair between different hysterectomy techniques [957]. A history of hysterectomy has also been identified to increase the risk for prolapse in several cross-sectional and retrospective studies [958-959].

Specific risk factors for posthysterectomy POP have been assessed in two case-control studies. Both Dällenbach et al. [960] and Forsgren et al. [961] reported that pelvic floor surgery before hysterectomy was the strongest risk factor for developing posthysterectomy POP (OR 7.9, 95% CI 1.3-48.2 and OR 2.8, 95% CI 1.0-7.7 respectively). The risk of prolapse repair was 4.7 times higher in women whose initial hysterectomy was indicated by POP [960]. Vaginal vault prolapse involves the loss of vaginal apical support and may per definition only occur after hysterectomy [962]. Marchionni et al. reported a 4.4% overall incidence of vaginal vault prolapse after hysterectomy but in women where uterine prolapse was the indication for hysterectomy the incidence was 11.6% [963]. In a register-based study Forsgren et al. showed that the greatest risks for prolapse surgery (HR 4.9, 95% CI 3.4-6.9) were observed subsequent to vaginal hysterectomy for pelvic organ prolapse but having a vaginal hysterectomy also for other indications significantly increased the risk for subsequent POP surgery compared to other modes of hysterectomy [964]. Similar observational results were shown by Cooper et al. [954]. A Danish register-based, matched cohort study focusing on nullipara entailed 809,435 person-years in risk and a 42 year observational period. 9535 nulliparous women who underwent a hysterectomy were matched individually with 47,370 nulliparous women without hysterectomy. The risk of POP surgery increased by 60% in women who underwent a hysterectomy compared with women in the reference group [965].

It has also been suggested that pelvic surgery other than hysterectomy may predispose women to subsequent genital prolapse including: rectopexy for rectal prolapse (OR 3.1; 95% CI 1.4-6.9) [966]; gynaecologic surgery in general (OR = 3.9, 95% CI 1.8-8.8) [967]; and retropubic colposuspension procedures are associated with a near 30% risk of subsequent vaginal vault and posterior vaginal prolapse at long-term evaluations [968-969]. In a prospective cohort study of 374 women, the 10-year re-operation rate was 17% after traditional POP or incontinence surgery [970]. Having undergone POP or UI surgery prior to the index operation increased the risk of re-operation to 17% compared with 12% for women who underwent a first procedure (p=.04)[970].

4.3. Obstetrical factors and POP

Observational studies will remain the main source of knowledge on the association between childbirth and POP later in life. For obvious ethical and practical reasons, randomised controlled trials to study the causal effects of vaginal and caesarean delivery on the pelvic floor will never be performed. Nonetheless it is widely accepted that childbirth is a important risk factor for POP, presumably due to overt or occult pelvic floor tissue trauma. Controversy does, however, remain with regard to the protective effect of cesarean section and if specific obstetrical events should be considered as risk modifiers. Due to a delayed onset of POP in relation to giving birth, studies on the subject need a long duration of follow-up as well as large study populations to be able to elucidate on the possible causative events. Therefore, the majority of studies on the subject are typically designed a cross-sectional surveys or retrospective cohort or case-control studies. It is, however, encouraging that long term longitudinal data are starting to emerge and in recent years several studies with follow-up periods extending beyond 10 years have been published.

Pregnancy in itself has been established as a risk factor for SUI. With regard to POP, the association is however, less well substantiated. In a clinical case-control study, all 21 nulliparous non-pregnant women had POP-Q stage 0 or 1, whereas 47.6% of 21 nulliparous pregnant women had pelvic organ descent corresponding to stage II (p<0.001) [971]. Overall POP-Q stage was higher in the third trimester than in the first (p=0.001). Also Sze et al. [972] found that in 94 nulliparous women evaluated at the 36 antepartum visit and six weeks postpartum, POP-Q staging increased.

A large number of studies identify childbirth as one of the strongest predictors for developing POP later in life [935,937,955-956,973-978. It is also a recurrent observation that number of childbirths is associated with the risk for POP although there are data to suggest the contrary [979]. In the prospective Oxford Family Planning Association study [955] childbirth was the single strongest risk factor for developing POP in women under 59 years of age and the risk increased by every childbirth. Similar findings derived from the WHI [937] where a parity of one conveyed an overall two-fold risk increase for POP compared to having no children, after which each additional childbirth added a 10-20% risk increase. In a case-control study, Tegerstedt et al. [977] found that the risk for symptomatic POP increased with number of childbirths and were 3.3-times higher among mothers of four than among mothers of one. Similarly, Rortveit et al. [935] found that the risk for prolapse increased in women with one (OR 2.8 95% CI 1.1-7.2), two (OR 4.1, 95% CI 1.8-9.5), and three or more (OR 5.3, 95% CI 2.3-12.3) vaginal deliveries compared with nulliparous women. In a questionnaire based cross-sectional study among 2,640 middle-aged women the number of vaginal deliveries was a risk factor for past or present symptomatic POP [978]. In a nationwide matched cohort survey of 14,335 women unexposed to childbirth, having had one cesarean section and one vaginal delivery the investigators found that the prevalence of symptomatic prolapse was relatively similar and below 5% across ages 40-64 years. In contrast, in women after vaginal delivery, there was an accelerating increase in the prevalence of symptomatic POP up to 65 years of age. The observed delay of onset period associated with 1 vaginal delivery seemed to be at least 20 years among women giving birth in their early 20s. At

age 64 years, the estimated probability of symptomatic POP was 12 times higher after vaginal delivery compared with caesarean delivery (13.4% [95% CI 9.4-18.9] vs 1.1% [95% CI 0.4-2.5]). The calculated reduction of symptomatic POP by cesarean delivery at 64 years of age was thus 92% [980].

Whether or not cesarean section prevents loss of pelvic organ support has been debated but today the vast majority of studies show that elective cesarean section does indeed decrease the risk for POP later in life [973-978, 981-985. In 4,458 randomly selected women, vaginal childbirth increased the risk for POP by 1.82 (95% CI 1.04-3.19).(66) In a nested case-control study, Uma et al. [986] found that cesarean section was associated with a significantly reduced risk of pelvic floor surgery compared with spontaneous vaginal delivery (OR 0.16, 95% CI 0.05-0.55). In a case-control study, Chiaffarino et al.(40) found that women who were delivered by cesarean section were at significantly lower risk for POP (OR 0.3 95% CI 0.1-1.0). In a register-based cohort study of women having their first and all subsequent deliveries by cesarean (n = 33,167), and an age-matched sample of women only having vaginal deliveries (n = 63,229) between 1973 and 1983, Leijonhufvud et al. found that women only having vaginal deliveries had a significantly increased overall risk of subsequent POP(hazard ratio, 9.2; 95% CI 7.0-12.1) compared with women only having cesarean deliveries [982]. (Figure 10). Among women with vaginal deliveries only the incidence rate for POP surgery increased steadily, reaching its peak close to three decades after first delivery. This corresponds with data from other long-term studies with more than a decade of follow-up (see below). In women with cesarean deliveries only the incidence rate for POP surgery showed very little variation over time and being notably lower compared to the vaginal delivery cohort 10 years after first birth for the duration of the observational period. There are some reports suggesting that in the long term, caesarean delivery do not provide a significant risk reduction pelvic floor morbidity compared with vaginal delivery [987-988]. These studies belong to an overwhelming minority and most long-term longitudinal studies published in recent years, with follow-up times ranging between 10 and 23 years, commonly show that cesarean section provides a significant reduction in risk for pelvic organ prolapse. Volløyhaug et al. [983] showed that caesarean delivery was associated with decreased risk of POP 15-23 years after first delivery (OR 0.42, 95% CI 0.21-0.86). Compared with women whose births were all spontaneous vaginal deliveries, women who had all births by caesarean section were the least likely to have prolapse (OR 0.11, 95% CI 0.03-0.38) 12 years after first birth according to Glazener et al. [985]. Gyhagen et al. [984] reported that 20 years after birth singleton primiparae with no further births (n = 5236) had a significantly higher prevalence of POP after vaginal delivery compared with caesarean section (14.6 versus 6.3%, OR 2.55, 95% CI 1.98-3.28) but was not increased after acute compared with elective caesarean section.

A number of specific obstetrical events and interventions have been implicated as risk factors for the development of POP. In one study, maternal age and use of epidural analgesia was associated with an increased need for POP surgery.(65) Handa et al. [989] found that operative vaginal birth significantly increased the risk for all pelvic floor disorders and POP in particular (OR 7.5, 95% CI 2.7-20.9). In a long term longitudinal study Volløyhaug et al. [983]found that operative vaginal delivery was associated with increased risk of POP (OR 1.73, 95% CI 1.21-2.48) when compared with non-instrumental vaginal delivery. There were no differences in the risk for POP when comparing forceps and vacuum delivery.

In a case-control study, Chiaffarino et al. [981] found that after forceps delivery women had an OR of 3.6 (95% CI 1.0-13.5) for developing pelvic organ prolapse, but after adjustment for vaginal delivery the odds were no longer significant (OR 1.3 95% CI 0.6-3.1). Also Moalli et al. [967] concluded that forceps delivery posed a risk for POP and a case-control study found no significant association with maternal age, instrumental delivery (forceps or vacuum), or length of delivery when comparing women with POP to randomly selected controls.(68) On the other hand, Uma et al. [976] found no significant association between POP and forceps delivery (OR 0.9, 95% CI 0.7-1.2); infant birthweight >4.0 kg (OR 0.9, 95% CI 0.5-1.7); episiotomy (OR 1.46, 95% CI 1.0-2.10); and labour prolonged >12 hours (OR 1.51, 95% CI 1.00, 2.27). Similarly both Gyhagen [984] and Glazener [985] found no significant association of increased risk between instrumental delivery and POP compared with spontaneous vaginal delivery.The inconsistency and wide variety in the magnitude of the risk estimates suggest that most studies so far lack sufficient statistical power for valid conclusions.

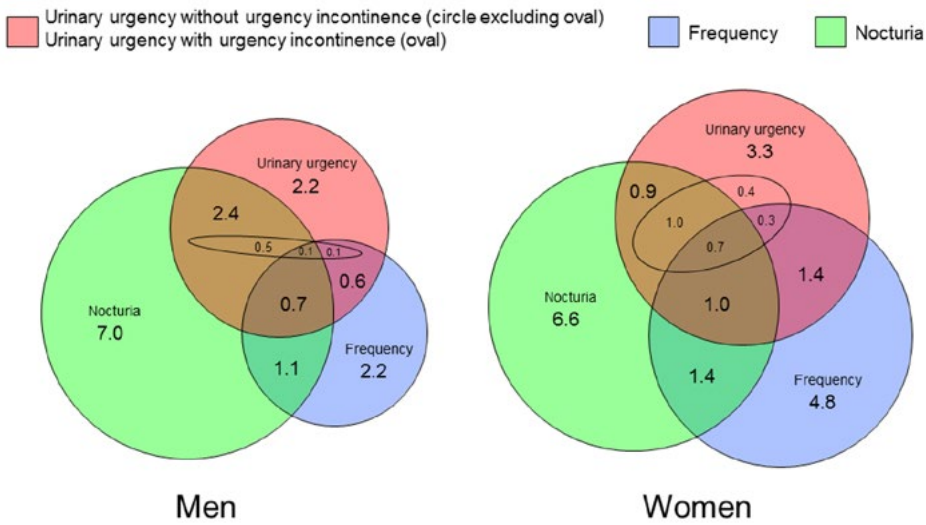

Figure 10. Rate of pelvic organ prolapse surgey in relation to mode of delivery and time from first childbirth [821].

4.4. Miscellaneous risk factors and POP

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

Several somatic risk factors for POP have been identified. Generalised connective tissue disorders such as Ehlers-Danhlos disease and Marfans syndrome [990-991] have been linked to an increased risk for POP. In a community-based study of prolapse in rural West Africa, chronic anemia was the strongest risk factor for prolapse after parity and age (OR 2.1 95% CI 1.1-3.4).(48); and chronic obstructive pulmonary disorders. Skeletal abnormalities such as thoracic kyphosis, lumbar lordosis and pelvic dimension changes have been associated with an increased risk for POP [992-993]. Women with joint hypermobility have a significantly higher prevalence of genital (and rectal) prolapse in comparison to women with normal mobility [996-997]. Weak associations have also been shown for osteoporosis and rheumatoid arthritis.(69) Obesity may be associated with increased pelvic floor symptoms and more severe symptomatic POP [978,998-999] yet increasing body mass index and obesity has not consistently been identified as risk factors for POP as compared to stress urinary incontinence [1000-1001]. Other factors that has not convincingly demonstrated any significant linkage to prolapse includes the presence of chronic obstructive pulmonary disease and diabetes mellitus [941,958,1001]. Pulmonary impairment has been shown to be more common in women with loss of pelvic organ support compared to those without [1002] whereas others suggest no association with asthma and smoking [1003]. In a study by Rogowski et al. [1004] the diagnosis of metabolic syndrome was associated with the severity of pelvic organ prolapse in urogynecological patients (OR 3.5, 95% CI 1.5-8.2) as compared to those without.

A low educational level (OR 2.16, 95% CI 1.10-4.24)[1005] and low annual income [1006] are socio-economic factors which have been associated with an increased risk for POP. Among 21,449 non-hysterectomized Italian women, higher education was a protective factor for uterine prolapse [988]. However, despite significant differences in educational level, smoking habits, alcohol consumption, and socio-economic indices, the prevalence of POPdid not differ between Croatian urban and rural women [1007]. Interestingly, risk factors for pelvic floor disorders including POP among women in developing countries were similar to those in industrialized countries (increased age and parity). In a review study across 16 low-income and lower middle-income countries the mean prevalence for POP was 19.7% (range 3.4-56.4%) but risk factors were similar to those described in studies from more affluent countries but additionally POP and other pelvic floor disorders were associated with other factors including poor nutrition and heavy physical work [1008-1009].

A physically strenuous occupation has also been shown to influence the risk for POP. In a register based study of 28,000 Danish assistant nurses exposed to repetitive heavy lifting, the risk for prolapse was higher among the nurses compared to controls (OR 1.6 95% CI 1.2-2.2) [1010]. Women who were laborers/factory workers had significantly more severe prolapse than other job categories ($p < 0.001$) in a cross-sectional study of women presenting for routine gynecological care [1006]. This notion is supported by a retrospective study of 662 women referred to a urogynecology unit for pelvic floor symptoms. Heavy lifting was associated with sonographic POP (OR 1.71, 95 % CI 1.2-2.4), confirmed on multivariable analysis and positively associated with symptoms and clinical signs of POP) on univariate analysis. It was concluded that heavy lifting may be a potential risk factor, in particular for posterior compartment POP [1003]. Also, hard physical training may increase the risk for POP as women attending paratrooper training, were more likely to present stage II prolapse compared to controls (RR=2.7 95% CI 1.4-5.4) [1011].

5. SUMMARY POINTS

- Most studies have used a cross-sectional design and there is limited longitudinal data to suggest a causal relationship between symptoms of obstructed defecation and POPor vice versa.
- Posterior vaginal wall prolapse and perineal descent are the specific pelvic defects most frequently associated with symptoms of obstructive defecation.
- Large epidemiological studies suggest that hysterectomy increases the long-term risk for subsequent pelvic organ prolapse
- Vaginal hysterectomy and hysterectomy performed for uterine prolapse are the strongest risk factors for having secondary pelvic floor surgery
- Childbirth is associated with an increased risk for POP later in life and increasing number of childbirths is positively associated with the risk.
- Long-term prospective studies data consistently show that caesarean section decreases the risk for POP and that caesarean section is associated with a decreased risk for subsequent pelvic floor morbidity in comparison to giving vaginal birth.
- Current understanding of how specific obstetrical interventions influence the risk for pelvic organ prolapse is poor but instrumental delivery may increase the risk for development of pelvic organ prolapse.
- Life style factors and socio-economic indices may be associated with the risk of POP in both industrialised and non-industrialised countries.
- A number of somatic diseases and conditions have been linked to the occurrence of POP but the cause-effect relationship is undetermined.

VIII. EPIDEMIOLOGY OF FAECAL INCONTINENCE

1. GENERAL COMMENTS AND DEFINITIONS

FI is the involuntary loss of feces – solid or liquid. AI includes these events as well as the involuntary loss of flatus, which is felt by many patients to be an equally disabling disorder. These terms will be used to a degree interchangeably throughout the chapter. A third cause of soiling or embarrassment is anal mucoid seepage, a troubling condition that cannot be deferred even by an able sphincter and intact cognition. It is most often caused by an organic colonic disease or dietary sensitivity, and more rarely by fecal impaction. This is the loss of fluid, sometimes feculent, often following a normal continent defecation. Seepage is an important condition to distinguish from other manifestations of incontinence because most authors that report very high prevalence rates of AI include leakage in their questionnaires. However in these individuals there is often no detectable sphincter abnormality [1012]. It is not treatable by any of the standard therapies for incontinence of feces: such as sphincter repair, neuromuscular re-education or even fecal diversion. It is in fact why we wear underclothes.

1.1. Ascertainment of Anal Incontinence

Older reports of AI prevalence have come from single institutions, and the patients described therein have been subject to referral bias when demographics and etiology are discussed and widely varying definitions of AI. The accuracy of AI prevalence estimates may also be diminished by difficulty in ascertaining those figures due to patients' reluctance to report symptoms or to seek treatment [1013]. It has been shown that women are more willing to report AI than men [1014]. In addition, the character (incontinence of solid feces, diarrhea, or flatus, or merely anal seepage) and frequency (daily versus episodic) and duration of reported AI varies greatly in each report. So, prevalence depends heavily on the definition of AI.

To determine accurately who has AI and who does not has resulted in the development of many scoring tools and publications that compare these tools. [1015-1020]. In an insightful tool, the authors studied adults, not excluding those in custodial care [1017]. Acknowledging the difficulty in prevalence estimation, they used three different questionnaires. The first simply asked if the participant had incontinence and if they were troubled by it, the second was a well known quantitative instrument and the third a quality of life instrument specific to fecal incontinence. In the cohort examined there were those who were totally continent, those that exceeded thresholds in all three instruments and were undeniably incontinent and those who had positive responses on only one or two of the questionnaires. The authors surmised that two out of three positive responses constituted clinical AI, though the threshold for the quality of life instrument was very high (i.e. perhaps too sensitive). The prevalence of AI varied from 12.6% to 26.8% for each individual instrument, 4.6% were positive for all three and 13.2% were positive for two of three, which was the authors' definition of AI. The remainder of the studies in this group are systematic reviews of published tools, the most thorough being Gray et al. [1018].

Two more tools are widely used or referred to: Rome IV criteria and NHANES 2010 Bowel Health Survey BHQ_F [1021-1022]. NHANES was the only publication to present data on seepage.

1.2. Data Sources and Level of Evidence

Since ICI 6, new studies were sought using a search strategy for Medline and EMBASE and the Cochrane data base of clinical trials from 1966 to April, 2021.

Because therapeutic interventions are not the subject of this chapter, the epidemiology is descriptive and in almost all cases not derived from clinical trials (aside from the pre-partum intervention described below, Cesarean delivery and surgery for anal fissure, all discussed below), the level of evidence will be at best 2 for the rest.

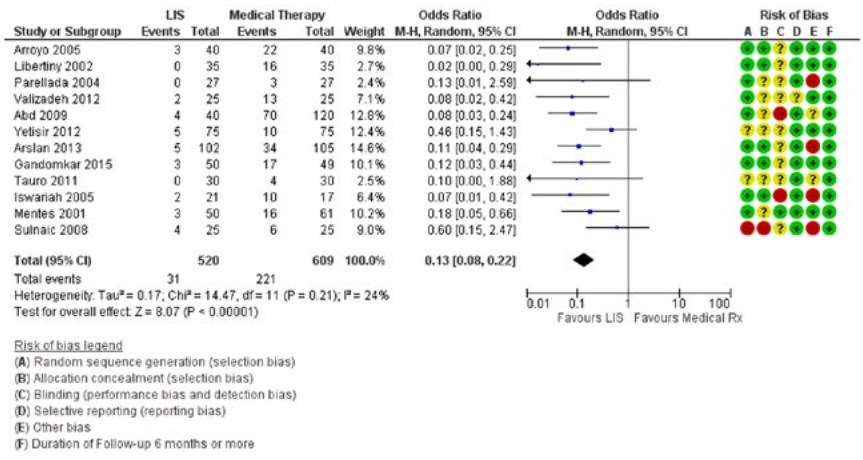

Figure 11. Forest Plot Comparing the Sustained Cure (> 6 Months Post Therapy) of Lateral Internal Sphincterotomy (LIS) With Any Medical Therapy. Medical therapy has about a 50% cure rate compared with > 90% for LIS.

2. PREVALENCE

Is FI a disease or a dysfunction? Is it reported with any accuracy, like cancer? No. Is there a broadly accepted means for assessing its prevalence? No. So reports are very idiosyncratic and very difficult to merge with other reports.

2.1. Adults

In an effort to resolve the widely varying reported prevalence figures five systematic reviews of the published frequencies have been done of community dwelling adults (Table 21) [1023-1027]. All five established a protocol for searching in advance that stressed a number of quality criteria among which the following were included: A defined search strategy. Each study presented a PRISMA statement. Quality of the included studies was assessed using variously the following variables:

1. Response rate > than 50%
2. A validated continence assessment tool.
3. A representative community based population, with selection procedures that minimize selection bias.
4. Appropriate outcome reporting.
5. Optimal data acquisition from participants

Not every included study in these five systematic reviews found a large number of reports that adhered to these criteria, but the risk of bias in each study was assessed in some of these reviews and the highest quality studies described separately. None of the five were able to find a study that did prospective cohort assembly and data collection. A summary frequency was not calculated in the second review (Table 21) [1024] because of the marked clinical heterogeneity between reports. The three reports that the authors judged most free of potential biases in this review [1024] had frequencies between 11% and 15%, though only one of these three used a validated FI assessment instrument. The degree of disability present in these 11%-15% is not known, nor even if a portion of them that had only anal seepage. These high prevalences were obtained in surveys that employed anonymous self-administered questionnaires, which may not allow objective confirmation of AI or assessment of degree of disability associated with AI.

Quality assessment was presented in Table 21 in various ways in systematic reviews 2 through 5 The authors in each systematic review were interested in estimating a prevalence that is without the massive range descriptions from individual studies in Table 21. In that regard each one was successful, with prevalences ranging from 3.5 to 7.7. Because these are systematic reviews, to varying degrees these 5 authors were assessing the same studies but had some different results.

There are two more studies that need to be mentioned regarding adult prevalence: the first is a series of publications by the Rome Society which has developed a series of assessment tools for FI among other GI disorders. The most recent is Rome IV. The criteria have changed with each iteration of this tool. A study is published of FI in 3 English speaking countries and the data pooled [1021]. 5931 participants were questioned about various aspects of FI and 957 were found to have FI, 16.1%. Using Rome III criteria, only 412 (6.9%) were categorized as having FI and with Rome IV, 196 (3.3%). Both these changes from the original 957 of Rome III and

Table 21. Systematic Reviews of Prevalence of FI

Author Search Years	Number of Studies	Children	Principal Outcomes	Prevalence	Range	?Quality?
Chiarelli 1995 - 2001	4	No	Gender Age	Men; 5.5 % Women: 5.3 %	0.5 to 56.3% 1.3 to 25%	Valid detection Instrument Heterogeneity assessed but not defined
MacMillan 1966 - 2015	14	No	Subdivision of the populations not reported		2 to 24 % w/ flatus 0.4 to 18 % w/o flatus 11 to 15 % in 3 studies with the least bias	Extension discussion of sources of bias
Ng 1966 - 2015	38	No	Gender Age	All Studies; 7.7% HQ; 11.2 % Rome ?; 6.9 %	2.0 to 20.7 % 8.3 to 13.2 % 2 to 7.8 %	5 categories of bias sources applied to each study
Pretlove 1996 - 2003	29	No	Age Gender	All FI only: 4.3% Men; 3.5% Women; 4.5%	0-15.2 3.5-5.4 95% CI 2.3 to 5.3 95% CI 3.5 to 5.9 CI all ages Significance predicting FI: Age: p= 0.007 Gender p= 0.368 High Quality p= 0.085	Meta analysis and meta-regression Uni- and Multi- variate analyses: Validity of assessment tool and Selection bias
Sharma 1996 - 2015	30	No	Methodology	5.9 %	1.4 to 19.5 % all non Rome ii studies 5.6 to 6.3 95% CI in Rome ii studies	Methodological variation and Response Rates discussed

Table 22. NHANES 2010 Report of FI Prevalence and Risk Factors

Population	Prevalence	Age	Significant Associations Odds Ratio & 95% Confidence Interval	Non Significant risk Factors of Fecal Incontinence
14,759	8.39 %	2.91 % in 20 year olds	Age > 70 2.05 (1.19-3.73)	BMI Ethnicity
NHANES 2005-2010	95% CI; 7.76 to 9.05	16.16 % in over 70s	Poor General Health 1.32 (1.02-1.71)	Marital Status Poverty
			Gender: women 1.49 (1.12-1.96) but only if the woman has UI too. Otherwise non significant	Education Physical Activity Vaginal Deliveries Pregnancies
			Urinary Incontinence 1.63 (1.27-2.14)	
			Diabetes 1.63 (1.22-2.71)	
			Stool Character 2.52 (1.79-3.56) and Frequency >21 per week 2.46 (1.41-4.29)	
			>2 Chronic Illnesses 1.74 (1.25—2.42)	

Rome IV were due principally to a change in the frequency of FI episodes. The entire 957 wrote that they had a significant reduction in their quality of life because of their FI.

Last but not least is NHANES. The National Health and Nutrition Examination Survey of the National Center for Health Statistics and the Center for Disease Control. Selection of the participants is more thorough, and results in a group more representative of the United States population than any of the heretofore mentioned and the studies. The examination of each participant is also more thorough than those studies [1028]. Examination for specific organ or disease is periodic, the most recent for FI being in the Bowel Health Survey in 2010 [1022]. Data from that survey on specific subjects and questions have been published since then, including FI [1029]. 14,759 people participated, 49% women, all over 20 years old and 8.39% had FI (95% CI; 7.76-9.05). Specific risk factors were also investigated (Table 22) and will be discussed below.

2.2. Children

The reported prevalence of AI in children can be broadly divided into two facets: those children born with congenital anomalies of the anus and rectum – either congenital aganglionosis (Hirschprung's Disease) or imperforate anus – and those children with functional disorders and without congenital anomalies. These congenital disorders are not horribly rare, occurring in 3 to 5 per 10,000 live births [1030]. The functional disorders are more common but often not referred to as incontinence, but retentive or non-retentive soiling Males are more common than females in both, 3.5 to 1, [1031]. The reported range of retentive varies from 0.5 to 19.2 % and for non-retentive, 0-1.8% [1032]

Among children without congenital defects of the anal canal, bowel control has been found to be complete in one Swiss cohort in 33% by age 1 year, 75% by age two and 97% by age three. Nevertheless in this longitudinal study, a quarter of the boys and one tenth of the girls had a major period of incomplete bowel or bladder control between the ages of 6 and 18. At least annual encopresis occurred in 2-3% of these children, boys more frequently than girls [1033].

Among those children and adults who were born with congenital anomalies, despite surgical correction of the defect, lifelong defecation difficulties are common, occurring in roughly half of affected children [1034-1035]. Problems with psychological health and development because of the defecation disorder are also common in this group, as is a generally depressed quality of life [1036-1037].

3. INCIDENCE

Characterizing new incidence of FI or AI at the time of onset and noting what preceded it gives a different perspective on causation. This has been reported in five different publications. The first included patients with new onset FI [1038-1042] and assessing risk factors at that time.

The second monitored 435 patients admitted to an acute care hospital, mean age 72 [1039]. 11% had FI. 21.1% developed AI, principally in those patients over 85. The largest number were on the orthopedic ward, were the most frail and had the longest length of stay [1042].

The third recruited a population of 1000 participants in several communities, rural and city, with equal numbers of male and females and white and African/American races , all in equal numbers [1040]. They were all examined and interviewed on day one, phoned 6 monthly thereafter and reexamined four years later, all over 65 years old. Some died, some were lost to follow up, 79 had FI at recruitment. 557 had no FI at recruitment and it is this group that was monitored for development of FI. 93 developed FI, 17% (95% CI 13.7-20.1). Table 23 shows the regression analysis of four key variables.

Table 23 Multivariable Logistic Regression Analysis Comparing Risk Factors for Incident Fecal Incontinence (FI) in Women and Men

Variable	Odds Ratio (95% Confidence Interval) for Any FI	
	Women, n =293	Men, n =259
African American	0.5 (0.2- 1.0) *	0.9 (0.5- 1.8)
Depression symptoms	3.2 (1.1 - 9.1) *	1.2 (0.2- 6.1)
Urinary incontinence	2.0 (1.0-3.9) *	2.3 (1.1-4.7) *
Chronic diarrhea	3.5 (1.0-12.5) *	0.9 (0. 1- 1.1)

Multivariable logistic regression models controlled for age, comorbidity count, and body mass index.
**** P<.05.***

Two more studies were in patients living in geriatric care facilities. Chassange followed 234 previously non-FI residents in France for 10 months, during which 20% had FI episodes, but only 7.5% developed long lasting FI [1041]. The others had acute episodes due to diarrhea or impaction. The factors associated with the development of long lasting FI were UI (2.9, 1.8-4.6), decreased mobility (1.8, 1.1-3.0), and cognitive defects: either as seen in an MMSE score <15 (2.5,1.4-4.4) of history of dementia (2.1, 1.2-3.5). Neither gender nor age were risk factors. Nelson reported, in a cohort of 18,000 nursing home residents in Wisconsin, a subgroup of 3,850 continent of both urine and feces in 1992 and were assessed one year later [1042]. 15% developed FI. Positive associations were seen for ADL loss (3.4, 2.4-4.5), trunk restraints (2.5, 1.7-3.6), dementia (1.7, 1.4-2.0), African American race (2.1,1.3-3.4) and age (1.02, 1.0-1.0). UI was not investigated as a risk factor because it was felt to be a co-morbidity.

4. RISK FACTORS

4.1. Age

Systematic reviews and NHANES have analyses of the association of age and anal incontinence and found advancing age to be the most consistent of all assessed associations [1043].

4.2. Gender

Most discussions of the etiology of AI have been based upon the assumption that women, particularly for individuals under the age of 65 years, are far more at risk for FI than men. Injury to the pudendal nerve or sphincter muscle from prior obstetric trauma is described as the primary risk factor [1044], followed by irritable bowel syndrome (a disease thought to be more prevalent in women) [1045], and other etiologies such as diabetes a distant third [1046]. Yet a population based-survey by the National Center for Health statistics of the prevalence of FI has shown a surprisingly high prevalence in males (Fig 12), [1023,1025-1026,1029]. In the most interesting finding in this review, in the NHANES list of potential risk factors for FI, in the age controlled bivariate analysis, women with urinary incontinence (UI) were significantly at risk of FI but in the multivariate analysis the risk flips to a significant risk of FI for men when UI is included in the regression model [1029]. UI is a significant risk factor for FI in women in both the bivariate and multivariate analyses, with almost identical risk in each.

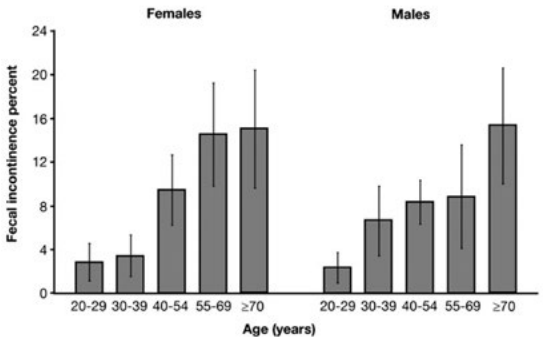

Figure 12. Prevalence of FI grouped according to age and sex

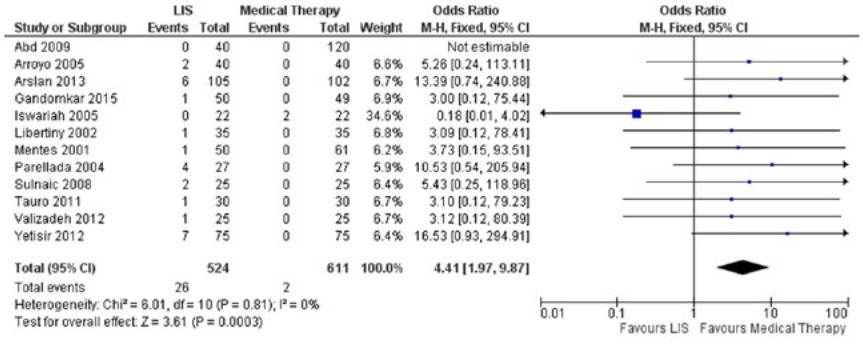

Figure 13. Forest Plot of Studies Comparing of The Risk of AI (usually to flatus alone) more than 6 Months Post Therapy of Lateral Internal Sphincterotomy versus Any Medical Therapy See Table 3

In the scoping search for this updated review, 26 publications assessed prevalence of AI, two included both genders and 24 included only women, vaginal childbirth being the risk factor of interest. Yet many women never have a vaginal delivery and of course half the population at risk are men (Figure 12). This represents a rather gross imbalance in research on this topic. Clearly, etiologies in pregnancy other than childbirth must be sought.

4.3. Obesity

Four reports have demonstrated an increased risk of AI in obese women, a Kaiser cohort, a cross sectional survey in a specialty clinic and two case control studies [1047]. One longitudinal study found a reduction in anal leakage (again not necessarily a direct correlate with incontinence) in women after bariatric surgery and weight loss, though other factors including diet and activity change may have been responsible for the improvement [1048]. A more recent SR of weight loss surgery and FI was a bit equivocal in deciding on the benefit of this surgery [1049]. However NHANES and a later Kaiser report found no significant association of FI with obesity [1029,1050].

4.4. Urinary incontinence

UI is generally regarded as a comorbidity with FI, sharing common etiologic factors [18].

4.5. Nursing home residence

The most prominent association with AI by far is nursing home residence, a post morbidity rather than comorbidity or risk factor. A very thorough discussion of this is [1051] which combines data from NHANES, The National Study of Residential Care Facilities (NSRCF), the National Home and Hospice Care Study (NHHCS) and the Minimum Data Set (MDS). Whereas the prevalence of AI is reported able to be 7-8% for community-dwelling persons, and may rise with increasing age to greater than 10%, among nursing home residents the prevalence approaches 50% [1043,1052]. This is explained by FI being one of the most common reasons for nursing home admission. In a large survey of 18,000 Wisconsin nursing home residents, risk factors for fecal incontinence (FI) were directly observed by nursing home personnel [1044]. Urinary incontinence (UI) was the greatest association with FI (OR= 12.6, 11.5-13.7), followed by the loss of ability to perform daily living activities (6.0, 4.7-7.7), tube feeding(7.6, 5.6-10.4), physical restraints (3.2, 4.7-7.7),diarrhea (3.3, 2.7-4.2), dementia (1.5, 1.4-1.7),impaired vision (1.5, 1.4-1.7), constipation (1.4, 1.3-1.6), fecal impaction (1.5, 1.1-2.1), stroke (1.3, 1.2-1.5) male gender (1.2, 1.1-1.3), age and body mass index. Inverse associations were noted with heart disease, arthritis and depression.

4.6. Diarrhea

The importance of diarrhea of liquid stool in FI cannot be overemphasized [1052-1053]. One case series noted that 51% of individuals with chronic diarrhea were incontinent [1013]. Non-infectious causes of diarrhea must also be considered, such as inflammatory bowel disease and those initiated by sports activities such as running [1051].

4.7. Constipation

Constipation may alternate with diarrhea in irritable bowel syndrome making defecation chaotic and often very urgent and result in retentive incontinence [1032,1045], seen most often in Children**.** Often retained feces lead to anal seepage that cannot be held. In the New Zealand survey, the 2 of 3 rule for categorizing an individual as incontinent when excluding constipated patients, which was also assessed in their survey [1017], the positive rate fell from 13.2% to just over 9%. This further demonstrates the frequent co-existence of constipation and AI .

4.8. Diabetes

There are two factors leading to FI in diabetics. The disease itself [1055-1057] and the medication used most commonly in its treatment [1058].

4.9. Neurological and other diseases

Several specific diseases have been associated with AI in case series, and mechanisms to explain the associations have been investigated [1059]. Examples are stroke, multiple sclerosis, Parkinson's disease, systemic sclerosis, myotonic dystrophy, amyloidosis, spinal cord injury, imperforate anus, procidentia, and any illness causing diarrhea (HIV, IBD, radiation, infection). Many of these conditions directly affect patient mobility and ability to perform daily living activities or they cause diarrhea or fecal impaction**.**

4.10. Surgery

AI originating from surgery would seem fairly insignificant in the general population, since prior anal surgery has not been an apparent risk factor in any of the larger surveys cited herein. Several operations nonetheless are thought frequently to result in AI. Examples are midline internal sphincterotomy for fissure in ano, lateral internal sphincterotomy, fistulectomy, fistulotomy, hemorrhoidectomy, and ileo-anal reservoir reconstruction, low anterior rectal resection, total abdominal colectomy, and ureterosigmoidostomy.

An example of how interventions can get a bad reputation before the definitive studies are done is the history of anal fissure [1060]. Prior to 1989, the accepted treatment for a painful chronic anal fissure was lateral internal sphincterotomy (LIS). However in 1989 everything changed. A large case series of follow-up after LIS was published in which 36% of the patients were incontinent to flatus and 5% to solid stool. In 1996 from the University of Minnesota, which had reported such low incontinence rate in 1985, in a retrospective comparison of open vs. closed LIS, it was found in a new study that 30.3% of their patients were incontinent to flatus and 11.8% to solid stool. The age of GTN (glyceryl trinitrate ointment), Botox (botulinum toxin injection) and CCBs (calcium channel blockers) as medical therapies for fissure was born. In many countries it appears that LIS had been abandoned in favor of medical therapy. Yet patient satisfaction with LIS has been reported to be high. The often crippling pain of fissure is almost immediately relieved [1059], and at surgical meetings many of us (colorectal surgeons who never encountered such a patient) wondered: "Where are all these incontinent patients?"A systematic review of all treatments for anal fissure, which included 148 randomized trials, was published in 2017 [1060]. The data in studies included in this review were reviewed by ethics committees, which are very sensitive to potential harms in clinical trials and their recording, and the trials themselves had, especially in trials with an LIS component focused on incontinence risk. The often used words permanent incontinence are particularly unfortunate, since virtually all AI is eminently treatable. Retrospective review numbers are certainly subject to selection bias, but even that doesn't seem to explain the disparity with what is described here (Figures 11) and those publications. More likely is that outcomes were measured way too early, which was found in

many studies in this systematic review, when a healing wound was perceived by patients, and or examiners as incontinence. In the patients having LIS after 2000, the risk of incontinence was 3.9% (Table 24), not radically different from what is seen after medical therapy with GTN, Botox or CCBs. The certainty for the evidence in this review in GRADE is High.

Table 24. Adverse Events After Treatment of Anal Fissure, Reported in a Systematic Review of 148 Randomized Trials. Note how close the FI rate for LIS after 2000 is to the rates of GTN, Botox and CCB (48).

Studies	Headache rate	Incontinence rate
GTN all studies	504/1801; 28%	7/634; 1.1 %
LIS all studies; both reviews	3/253; 1.2%	138/3093; 4.4%
LIS with 6-month follow-up		27/623; 4.3%
LIS in surgical studies published after 2000		31/803; 3.9%
Arginine	0/30	
"Healer Cream"	1/20; 5%	
Botox	7/138; 5.1 %	8/354; 2.3%
Oral CCB	9/24; 37.5%	
Topical CCB	27/169; 16%	4/287; 1.4%
Indoramin	7/14; 50%	
GTN patch	25/73; 34.2%	
Lidocaine	4/45; 8.9%	
Dilator; speculum 4.8 cm, balloon 3.0 cm, repeated dilation at home	0/20	0/128
Manual dilation		32/264; 12.1 %
Placebo	36/428; 8.4%	

LIS lateral internal sphincterotomy, CCB calcium channel blockers, GTN glyceryl trinitrate

The reason for this lengthy description of the systematic review of all randomized trials of anal fissure is first, the volume of publication related to surgery and FI is the greatest for fissure of all operations. Second, the best data show the concern described above is not supported by the data (Table 24) [1060]. It is important to look carefully at the quality of the data in other operations that have been associated with FI. For anal fistula, in the randomized trials, the FI rate also was in the range of 4%. There are no randomized trials of hemorrhoidectomy and FI risk. Association of hemorrhoidectomy with FI is ridiculous. No muscle is touched. Anterior resection syndrome in colorectal cancer is real, but in a very long career doing this operation, though often offered, I have had one patient ask for surgical therapy. And so on.

5. PREVENTION

5.1. Childbirth: mode of delivery

A meta-analysis of published reports that assessed anal sphincter integrity after vaginal delivery and correlated this with continence stated that 77%-83% (depending on parity) of AI in parous women was due to sphincter disruption [1044]. Another systematic review that looked only at post partum factors in prospective cohorts found that the only predictor of AI was 3rd-4th degree sphincter rupture during birth [1061]. Three things are implied by the conclusion of the first review: first, that incontinence in men, children, and in nulliparous women, or women having Caesarean delivery are not exposed to this risk factor, and so should have a lower risk of FI than parous women who have vaginal delivery. There is scant epidemiologic evidence that this is the case (Fig 14). Second, it is implied that sphincter repair would be effective treatment for anal incontinence in parous women. Yet repair of disrupted sphincter has less than a perfect track record. Even more importantly, there is a reported rapid decay in function after repair that is far too great to be explained by age alone [1062-1063]. Third, if direct trauma to the anal sphincter (and not intra-pelvic nerves) were the major cause of anal incontinence, then caesarean delivery should be effective in preventing incontinence. However an SR has shown that this is not the case [1064].

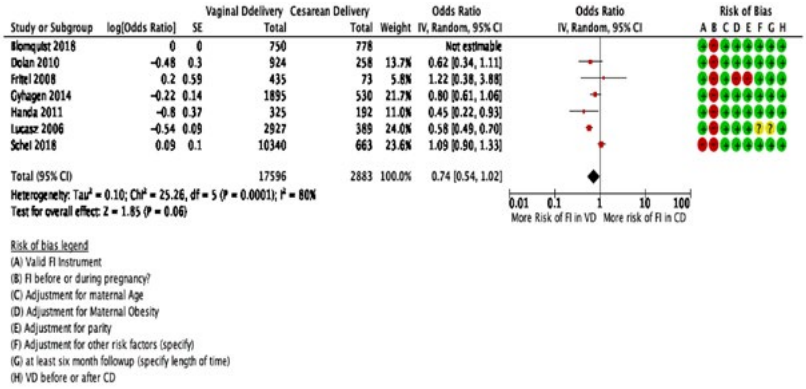

Figure 14. Forest Plot of Studies Comparing Risk of AI (Combined Fecal and Gas Incontinence) after Vaginal Delivery and Cesarean Delivery

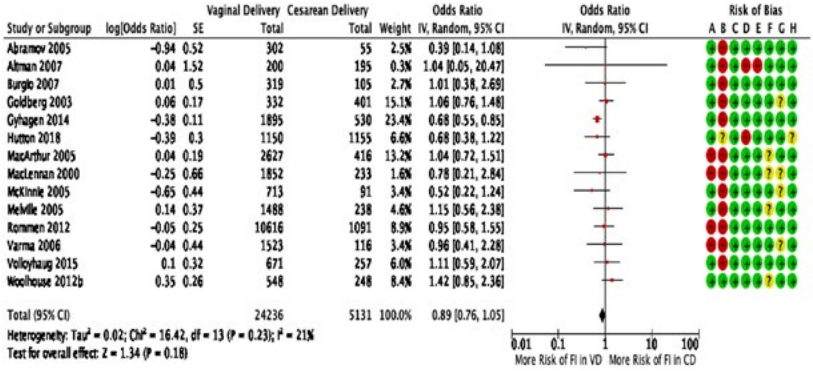

Figure 15. Forest Plot of Studies Reporting Comparison of FI alone after Vaginal Delivery and Cesarean Delivery

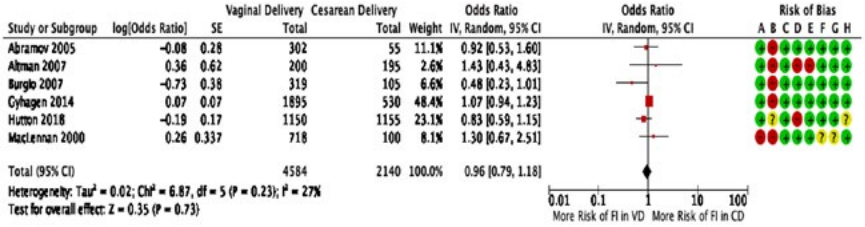

Figure 16. Forest Plot of Studies reporting Flatus Incontinence Alone after Vaginal Delivery and Cesarean Delivery

2526 titles and abstracts were found from which 24 eligible studies were analyzed that compared AI risk, vaginal delivey versus caesarean delivery. These included 39,937 vaginal delivery women and 7,484 caesarean delivery women. Forest plots of the results are in Figures 3a (combined FI and Gas I), 3b (FI), and 3c (Gas I alone). Only one of the eligible studies was a randomized trial, with significant crossover. None of the three comparisons showed a significant difference between vaginal delivery and caesaran delivery The strength of the GRADE evidence for each of these was Low for combined AI and Moderate for FI and GasI. Time Trend FI showed incontinence at three months was largely resolved after one year. As with anal fissure above, many studies measured continence too soon after delivery. This is an unresolved issue that needs clarification. Randomized trials of vaginal delivery vs. caesarean delivery of average risk pregnancies have been performed for other outcomes and need to be performed that assess continence to strengthen the evidence shown in these results.

5.2. Pelvic Muscle Training

There is another intervention that has been shown to diminish post partum incontinence: prepartum and post partum muscle training [1065]. A book on this topic was published in 2007 entitled “Prevention of Fecal Incontinence”. Not too much else other than this method was offered. A follow up Cochrane review [1066], which in 49 trials does not strongly support this intervention.

6. SUMMARY POINTS

- AI and UI commonly coexist, particularly in the elderly and in nursing home residents (2 for evidence, C for Grade).
- The prevalence of AI increases with age, but is present in all age groups in both genders varying from 1.5% in children to more than 50% in nursing home residents (2, C).
- AI is almost as common in men as in women (2, C).
- Mode of delivery does not seem to be a significant factor in the development of obstetric AI, i.e., AI develops after caesarean delivery almost as often as after vaginal delivery in non-randomized trials (2, C).
- Obesity may be the most modifiable risk factor for AI (2, C), but the data associating obesity with AI are weak.
- Prepartum pelvic floor education has been studied to determine if it can decrease the risk of subsequent development of post partum AI (2, C)
- As populations age, co-morbid disease becomes a significant component of fecal incontinence risk. Surgery, neurological diseases, and stroke are examples. (2, C)
- Cognitive and activities of daily living impairment are associated with fecal incontinence. (2, C)

7. FUTURE NEEDS

- As populations age, co-morbid disease becomes a significant component of fecal incontinence risk. Surgery, neurological diseases, and stroke are examples. (2, C)
- Prevention, and policy, are still a great distance away.
- Randomized trials are needed of AI (and UI) in average risk pregnancy comparing vaginal delivery and caesarean delivery with minimal cross over and sufficient follow-up to adequately assess FI and UI

IX. WHY DO PREVALENCE ESTIMATES DIFFER?

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

1. GENERAL PROBLEMS IN SURVEY RESEARCH

The well documented variation in prevalence estimates is thought to result at least in part from several confounders common to survey and epidemiological research. Herzog and Fultz,[1012] in a review of the prevalence and incidence of UI in community-dwelling populations, proposed that past investigations were plagued by sampling and non-response issues, by self selection and attrition, by definitional, conceptual, and measurement issues. Comprehensive reviews about measurements and methodological aspects of investigating UI are provided. It is clear that there are large methodological challenges to rigorous research in this field. In general, quality of recent large studies has undoubtedly improved, but the scientific community must continue to deal with methodological challenges in order to achieve progress.

2. DIFFERENT DEFINITIONS AND MEASUREMENT

A major problem in research on UI has been the use of different definitions and measurements, and this might contribute to the wide range of reported prevalence estimates. The former ICS definition of UI – as a condition in which involuntary loss of urine is a social or hygienic problem and is objectively demonstrable - included objective demonstration of urine loss as one critical component. This aspect limited the ICS definition for community based epidemiological investigations, because objective demonstration of UI is difficult to achieve outside of the clinical setting, and studies which were able to include this aspect in their assessment might have produced different prevalences. In addition, a social or hygienic aspect of the definition was problematic in epidemiologic studies because it added a subjective aspect to an objectively defined condition and therefore confounded the investigation of prevalence, incidence, and risk factors. In our previous report we argued for reconsideration of the definition of UI, and we emphasized that the core of the definition should be ”any involuntary loss of urine”. In accordance with this view, ICS changed its definition in 2001 to UI being ”the complaint of any involuntary leakage of urine”.

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

1. Epidemiological studies should not be based on this definition alone, and all studies should include a minimal additional data set, standard confounders, and questions specific to the aim of the study. This is discussed in the Section on Recommendations for further research.
2. The number of persons fulfilling the definition will increase. This should not be interpreted as an increase in the number potential of patients.
3. Public awareness, case finding of health care personnel, and help seeking behaviour may be affected of a new and more extensive definition.

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

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

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

One paper explored the problem of underreporting incontinence and how it can be altered with the use of an introduction to the UI

questions and probing [178]. Another paper explored the issue of selection bias in mailed surveys. The first wave had higher prevalence of UI than follow-up mailings, and thus individuals with UI tended to respond on the first wave. In an English mailed survey on UI and other LUTS, a sample of non-responders were traced, and those eligible were asked questions from the survey [1013]. Compared with the responders, the non-responders overall showed little differences in reporting of urinary symptoms. However, non-responders >70 tended to be of poorer general health, and they reported certain LUTS more frequently.

3. SUMMARY POINTS:

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

X. HELP SEEKING BEHAVIOUR

1. URINARY INCONTINENCE

A majority of people with UI have not sought help [540]. Reasons given by people for not seeking help include: not regarding UI as abnormal or serious, considering UI to be a normal part of ageing, having low expectations of treatment and thinking they should cope on their own. Some studies also confirm the notion that embarrassment may be an important reason for not seeking help. There is an association between help seeking and condition-specific factors like duration, frequency and amount, and people's perceptions of the impact of UI but other more personal characteristics like individual health care behaviour and attitudes may also play a role.

In a Norwegian study 4.4 % of all women >20 years old in a community consulted their general practitioner for UI during a 3 year period [1014]. Mentioning the symptoms to a physician may not be enough. There are reports of doctors not responding, either by ignoring the statement of symptoms or by providing a dismissive explanation, and people interpreting a lack of response from the doctor as an indication that no treatment is available. In a study of management of UI in general practice, 30% of the women who had told their doctor about their symptoms perceived that they were offered no help. It is probable that many primary health care providers lack confidence in managing UI, and that this contributes to under treatment in those seeking help.

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

It is obvious that millions of men and women suffer from their UI, and that for many of them good treatment options are available. However, for many persons with very mild or occasional UI it is probably adequate not to seek help from the health care system. Others are satisfied with just information and understanding about the causes and in many cases self care may be quite appropriate. A Danish study has shown that simple information and advice was adequate " treatment" for 23% of the women attending an open access incontinence clinic [1015]. A Swedish study found that among 136 women with UI, 36% wanted clinical evaluation, and only 24% subsequently started treatment [649].

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

2. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE

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

3. SUMMARY POINTS:

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

XI. EPIDEMIOLOGY AND CLINICAL WORK: FROM RESPONDENT TO PATIENT

We have emphasised some major and important differences between epidemiology and clinical work. These differences may have several implications. A selection process is most often accomplished first by self-selection (help seeking), then a referral system, which provides specialist physicians to a patient population with higher prevalence of disease, more severe disease, and often skewed type distribution, thus obtaining test results with fewer false positives, better diagnostic accuracy, and more efficient use of resources. However, such intended and purposeful selection bias has its drawbacks. There is growing evidence that this selection process introduces bias into research and hampers our ability to generalize hospital based research back to general or primary care

populations. Furthermore, it may result in recommendations and guidelines for diagnosis or therapy derived from tertiary care centres that are inappropriate at the primary care level. Often guidelines, review articles or teaching material do not take into account the varying prevalence and variation in clinical picture between community and hospital. They may also emphasise use of tests or equipment that are not appropriate or relevant for primary health care, thus leading to over utilisation of referrals. Data from hospitals or specialist level may also overestimate level of burden, costs and number of persons in need of treatment if such data are used for extrapolation back to community level. Therefore it is important that this Consultation uses different algorithms for initial and specialised care (see other relevant chapters).

One study provides substantial empirical evidence to support the existence of selection bias for UI [125]. The analyses were based on three populations of incontinent women: Community level (epidemiological survey), primary care level (prospective study), and secondary care level (university hospital, prospective study). The general practice patients were older and the hospital patients younger than those in the community. From community via general practice to hospital, there was an increase in duration, frequency of leakage, amount of leakage, severity and perceived impact of UI. Help-seeking at the primary care level was associated with increasing age and severity, and with urgency symptoms and impact. Referral from general practice to hospital was only associated with (lower) age and urgency symptoms.

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

1. WORLDWIDE ESTIMATES OF LOWER URINARY TRACT SYMPTOMS

In order to effectively plan health care resources it is necessary to estimate the prevalence and incidence of illnesses to know to what extent resources require to be allocated to a specific illness health care condition. This chapter has dealt with three major global problems, UI and FI as well as POP, that affect women and men throughout the world. Irwin and coworkers [539] have published data estimating the current and future worldwide prevalence of lower urinary tract symtoms.

The objective of the study was to estimate the current and future number of people with LUTS, including OAB and UI utilising the current ICS definitions. Age- and gender-specific prevalence rates from the EPIC study [417] were applied to the worldwide over 20 year old population (4.2 billion) with males and females stratified into five-year age groups (20-24 to 80+). Projected population estimates for all worldwide regions were based on the United States Census Bureau International Database (IDB).

Estimates were presented for 2008, 2013 and 2018 and are summarised in Tables 25 and 26. Table 25 summarises the estimated number of individuals with certain LUTS symptoms by year and sex in the world population and Table 26 describes the estimated number of individuals of LUTS and OAB over 10 years across the world regions.

Table 25. Estimated Number of Individuals with Certain LUTS By Year & Sex - World Population (In Millions) [539]

LUTS Symptoms	Male 2008	Male 2013	Male 2018	Female 2008	Female 2013	Female 2018
Incontinence						
Any Incontinence	98	109	120	250	275	301
UUI	22	25	27	27	30	33
MUI	11	12	14	43	47	52
SUI	10	12	13	127	140	153
Other1	55	61	66	53	58	64
Storage						
Any Storage Symptom (Noct2 ≥1)	1,050	1,151	1,250	1,249	1,363	1,474
Any Storage Symptom (Noct ≥2)	597	655	713	760	831	901
Noct ≥1	942	1,035	1,127	1,098	1,200	1,301
Noct ≥2	388	427	467	464	509	555
Urgency	205	226	247	249	273	297
Frequency	127	139	152	161	174	186
Voiding Symptoms						
Voiding Symptoms	515	563	610	402	511	473
Intermittency	164	181	198	148	176	175
Slow Stream	156	173	193	122	161	146
Straining	132	145	157	83	120	98
Term Dribble	289	315	340	210	276	245
Post Micturition Symptoms						
Post Mic3 Symptoms	332	365	396	297	350	348
Incomplete Emptying	263	288	314	257	290	302
Other Post Mic Incontinence	108	118	129	64	96	76
Any LUTS (Noct ≥1)						
Any LUTS (Noct ≥1)	1,260	1,377	1,490	1,379	1,460	1,623
Storage + Voiding Symptoms (Noct ≥1)	350	386	422	309	373	367
Storage + Post Mic Symptoms (Noct ≥1)	247	273	299	238	274	282
Voiding + Post Mic Symptoms (Noct ≥1)	205	226	247	158	205	187
Storage + Voiding + Post Mic Symptoms (Noct ≥1)	166	183	202	137	173	163
Any LUTS (Noct ≥2)						
Any LUTS (Noct ≥2)	933	1,020	1,104	994	1,068	1,170
Storage + Voiding Symptoms (Noct ≥2)	247	273	299	237	275	283
Storage + Post Mic Symptoms (Noct ≥2)	188	207	227	190	214	226
Voiding + Post Mic Symptoms (Noct ≥2)	205	226	247	158	205	187
Storage + Voiding + Post Mic Symptoms (Noct ≥2)	130	144	158	119	142	142

Table 26. Estimated Worldwide Number of Individuals with LUTS including OAB and Incontinence by Region (In Millions) [539]

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

Estimates and projections featured in this analysis were based on prevalence rates of LUTS described in the EPIC study – based primarily on a European population. The prevalence rates featured in the EPIC study are similar to other prevalence rates of LUTS that were found in others studies across other countries [284,537]

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

Prevalence of LUTS will also increase as other factors related to LUTS, such as obesity, increases. The estimated number for present and future years are not true numbers but are based on a projected population configured by the International Database (IDB). The IDB's estimates and projections are drawn by Census Bureau demographers and are based on reviewed censuses, surveys, and vital statistics provided by National Statistics Offices[9]. Data on international migration and refugee movements, public health efforts, socio-political circumstances, and historical events such as natural disasters and conflict are all considered when the IDB calculates the estimates and projections.

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

It has been shown that LUTS are burdensome to individuals [202,485] and the likely increase in the number of individuals experiencing. LUTS has implications on healthcare resources and overall health burden. This analysis is an estimate of the number of individuals with LUTS based on a conservative prevalence rate, and so the future number of those with certain LUTS may surpass those of this report.

Table 27. Summary of major findings regarding the estimated worldwide prevalence figures for lower urinary tract symptoms LUTS [539]

46% of the 4.2 billion of the adult world population (≥ 20 and over) experience any LUTS
455 million individuals or 11% of the world population estimated to experience OAB symptoms
346 million individuals or 8% of the world population estimated to experience some type of UI
SUI is the most common type of incontinence in 2008 and 2018 (Fig 1.)
136 (3%) and 164 (4%) million individuals are estimated to experience SUI in 2008 and in 2018 respectively
49 (1%) and 60 (1%) million individuals are estimated to experience UUI in 2008 and in 2018 respectively
53(1%) and 65 (1%) million individuals are estimated to experience MUI in 2008 and in 2018 respectively
108 (3%) and 131 (3%) million individuals are estimated to experience Other Incontinence in 2008 and in 2018 respectively Assuming LUTS prevalence rates remain stable for the next ten years, 2.3 billion individuals are estimated to experience LUTS by the year 2018 An increase of 18% from 2008
Storage symptoms has the highest burden in both the male and female population than other LUTS (Fig 2.)
Male: estimated 597 million in 2008, 713 million in 2018
Female: estimated 760 million in 2008, 901 million in 2018
Asia region is estimated to carry the highest burden of LUTS. Estimated 1.2 billion individuals in Asia regions may experience any LUTS

2. SUMMARY POINTS:

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

XII. RECOMMENDATIONS FOR FURTHER RESEARCH

Much biomedical research is observational and the reporting of such research is often inadequate which hampers the assessment of its strengths and weaknesses and of a study´s generalisability. The STROBE (Strengthening of the Reporting of OBservational studies in Epidemiology) statement was introduced [1016]. It is a a checklist of items that should be addressed in articles reporting on the three main study designs of analytical epidemiology: cohort, case-control, and cross sectional studies. The use of this checklist is highly recommended.

1. URINARY INCONTINENCE

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

There is still little knowledge with regard to prevalence, incidence, and other epidemiological data in developing countries. A recent review on the global prevalence of UUI clearly showed that prevalence rates are largely unknown for many countries in the world [1017]. It is recommended that fundamental research regarding prevalence, incidence and other epidemiological data in developing countries should be encouraged, and tailored to the cultural, economic and social environment of the population under study.

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

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

Primary prevention is the main goal in the management of human disease. An important strategy would thus be to identify the individuals at risk, and then take measures to reduce the risk among those individuals or in certain risk groups. A predictive modelling system based on risk factors identified in population studies has been put forward [1018]. Primary prevention studies should be encouraged, but the epidemiological basis for choosing appropriate interventions is weak.

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

Variations in definitions and measurement issues are fundamental and lead to problems with assessing the findings in epidemiological studies. We need to improve epidemiological studies by including variables that better characterise UI, so that more advanced and in-

Table 28. Elements in a minimum data set recommended for all epidemiological studies

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

formative analyses may be conducted. It is therefore recommended that all epidemiological studies include a minimum data set (Table 28), including elements of screening question, frequency measure, quantity of urine loss, duration, type, and severity. In addition, it is recommended that validated measures of bother/quality of life and LUTS other than UI should be included. We here also refer to the chapter from the committee on symptom and quality of life assessment.

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

2. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE

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

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

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CHAPTER 2

NEURAL CONTROL AND CELL BIOLOGY

Co-chairs
LA Birder (USA) and CH Fry (UK)

Members
R Chess-Williams (Australia)
B Clarkson (USA)
B Feng (USA)
GF Gebhart USA)
D Griffiths (Canada)
H Hashitani (Japan)
AJ Kanai (USA)
TA Lovick (UK)
KD McCloskey (UK)
T Mitsui (Japan)
M Takeda (Japan)

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ABBREVIATIONS

Chemical and some other specific terms used only once are not included. Please also refer to figure legends as appropriate

8-AG	8-aminoguanine
a(p)MCC	anterior(posterior) midcingulate cortex
ABC	ATP-binding cassette (transporter)
ABMA	α,β-methylene ATP
ACC	anterior cingulate cortex
ACh	acetylcholine
AHS	acidic hypertonic solution
AITC	allyl isothiocyanate
ALFF	amplitude of low frequency fluctuations
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (glutamate) receptor
ASIC	acid-sensing ion channel
AT(D)P	adenosine tri-(di-)phosphate
BAC	bacterial artificial chromosome
BK	large-conductance Ca^{2+}-activated K^+ current
BNST	bed nucleus of the stria terminalis
BPH	benign prostatic hyperplasia
BPS	bladder pain syndrome
BTX-A	botulinum toxin A
C-MiHi	mechano- and heat-insensitive ('silent') nociceptors
CaCC	Ca^{2+}-dependent Cl^- channel (Ano1)
cAMP	cyclic adenosine monophosphate
CB1,2	cannabinoid receptor 1, 2
CEN	central executive network
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
ChAT	choline acetyltransferase
ChR2	channel rhodopsin-2
CICR	Ca^{2+}-induced Ca^{2+}-release
CNG	cyclic nucleotide-gated
CNS	central nervous system
CO	carbon monoxide
CPA	cyclopiazonic acid
CPPS	chronic pelvic pain syndromes
CRF	corticotrophin releasing factor
CSF	cerebrospinal fluid
CTFG	connective tissue growth factor
CYP	cyclophosphamide
dACC	dorsal anterior cingulate cortex
DAN	dorsal attention network
DAPI	4′,6-diamidino-2-phenylindole, nuclear label
DAPR	decerebrate arterially perfused rodent
DBS	deep brain stimulation
DFV	discoidal fusion vesicle
DGN	dorsal genital nerve
DL	dorsolateral column
dlPAG	dorsolateral PAG
DMN	default mode network
DMSO	dimethyl sulphoxide
DO	detrusor overactivity
DRG	dorsal root ganglion
DTI	diffusion tensor Imaging
ECM	extracellular matrix
EFS	electrical field stimulation
EGF(R)	epidermal growth factor (receptor)
eGFP	enhanced green fluorescent protein
EJP	excitatory junction potential
EMG	electromyograph(y)
ENaC	epithelial Na^+ channels
EUS	external urethral sphincter, rhabdosphincter
FAAH	fatty acid amide hydrolase
FiMH	type-1 pilus adhesin of uropathogenic *Escherichia coli*
fMRI	functional magnetic resonance imaging
GABA	γ-amino butyric acid
GAG	glycosaminoglycan
GIT	gastro-intestinal tract
GMV	grey matter volume
GPCR	G-protein coupled receptor
GPi	globus pallidus pars interna
GRK	G-protein-coupled receptor kinase
H_2O_2	hydrogen peroxide
HCN	hyperpolarisation-activated, nucleotide-gated (channel)
HGN	hypogastric nerve
HIF-1α	hypoxia-inducible factor 1-α
IC(C)	interstitial cell (of Cajal)
IC/BPS	interstitial cystitis/bladder pain syndrome
IFG	inferior frontal gyrus
IL	interleukin
IMD	inter-mediodorsal nucleus
IMG	inferior mesenteric ganglion
IP_3	inositol trisphosphate
IPar	intra-parenchymal injection
IS	inflammatory soup
IUS	internal urethral sphincter
Ives	intravesical instillation
IVP	(bladder) intravesical pressure
KCl	potassium chloride
Kv	voltage-dependent K^+ channel
L-NA	nitro-L-arginine
LC	locus coeruleus
LP	*lamina propria*
LPS	lipopolysaccharide
LS	lumbosacral
LSN	lumbar splanchnic nerve
LUT	lower urinary tract
LUTS(D)	lower urinary tract symptoms (dysfunction)
LVDCC	L-type voltage-dependent Ca^{2+} channel
MCC	maximum cystometric capacity
MIA	mechanically insensitive afferent
MLC(P)	myosin light chain (phosphatase)
MM	*muscularis mucosae*
MMP	matrix metalloproteinase
mPFC	medial prefrontal cortex
MPO	medial preoptic area of hypothalamus
(m)RNA	(messenger) ribonucleic acid
MS	multiple sclerosis
mTOR	mechanistic (or mammalian(target of rapamycin
MVB	multivesicular bodies
N(I)DO	neuropathic (idiopathic) detrusor overactivity
NaCl	sodium chloride
NADPH	nicotinamide adenine dinucleotide phosphate
NANC	non-adrenergic, non-cholinergic
NCX	Na^+-Ca^{2+} exchange
NGF	nerve growth factor
NMDA	N-methyl-D-aspartate (glutamate) receptor
nNOS	neuronal nitric oxide synthase
NO(S)	nitric oxide (synthase)
OAB	overactive bladder
OCT	organic cationic transporter
OP	parietal operculum
P2X, P2Y	purinergic receptor classes
PAG	periaqueductal grey
(p)BOO	(partial) bladder outflow obstruction

PD Parkinson's disease
PDE5(I) phosphodiesterase type-5 (inhibitor)
PDGFR platelet-derived growth factor receptor
PFC prefrontal cortex
PFM pelvic floor muscles
PG pelvic ganglion
PHC parahippocampal area
PKA (PKG) protein kinase-A (-G)
PLC phospholipase-C
PMC pontine micturition centre
PN pelvic nerve
PoCG postcentral gyrus
PPARγ peroxisome proliferator-activated receptor-γ
PPN pedunculopontine nucleus
PRF pulsed radio-frequency (stimulation)
PuN pudendal nerve
PUV posterior urethral valves
qRT-PCR quantitative reverse transcription polymerase chain reaction
ROK Rho-associated protein *kinase*
ROS reactive oxygen species
RSFC resting state functional connectivity
RTX resiniferatoxin
RyR ryanodine receptor
SARS sacral anterior root stimulation
SCI(T) spinal cord injury (transection)
SCN suprachiasmatic nucleus
SCN10A gene that provides instructions for expression of Na^+ channels
SDAF sacral deafferentation
sGC soluble guanylate cyclase
SHH (protein) sonic hedgehog
SMA supplementary motor area
SMA(α) smooth muscle actin (type α)
SMC smooth muscle cell
SK small-conductance Ca^{2+}-activated K^+ current
SMN salience and sensorimotor network
SN salience network
SNM sacral neuromodulation
SR (ER) sarcoplasmic (endoplasmic) reticulum
STD spontaneous transient depolarisation
STO(I)C spontaneous transient outward (inward) current
SUI genuine stress incontinence
TEA tetraethylammonium chloride
TEM transmission electron microscopy
TGF-β transforming growth factor-β
TH tyrosine hydroxylase
TIMP tissue inhibitors of MMPs
TL thoracolumbar
TLR_4 toll-like receptor 4
TNBS trinitrobenzenesulphonic acid
TNP-ATP 2'(or 3')-O-(2,4,6-trinitrophenyl)-ATP
TrkA tyrosine kinase A
TRPA transient receptor potential ankyrin receptor
TRPM transient receptor potential melastatin receptor
TRPML transient receptor potential mucopilin receptor
TRPV transient receptor potential vanilloid receptor
TTX (-r) tetrodotoxin (-resistant)
TVDCC T-type voltage-dependent Ca^{2+} channel
UCP urethral closing pressure
UDIF urothelial-derived inhibitory factor
UIC urethral interstitial cells
UPEC uropathogenic *Escherichia coli*
UT(D)P uridine tri-(di-)phosphate
UTI urinary tract infection
(U)UI (urgency) urinary incontinence
VD voiding dysfunction
VIP *vasoactive intestinal (poly)peptide*
VL ventrolateral column
VNUT vesicular nucleotide transporter
VSM vascular smooth muscle
WAS water avoidance stress
WB western blot
XO xanthine oxidase

INTRODUCTION

Two chapters (Cell Biology and Neural Control) offered in previous editions of the consultation have been combined into a single compilation of fundamental research that underpins an understanding of lower urinary tract function in normal and pathological situations. Such a fusion is beneficial so that afferent and efferent nervous information can be integrated, not only within the central nervous system but also with sensory transduction processes and motor effectors in the lower urinary tract (LUT). This chapter starts with a consideration of how the nervous system integrates the functionality of the lower urinary tract: how information from the lower urinary tract is coded into afferent signalling; how sensitisation and cross-sensitisation with other organ systems occurs; to upgrade the current working model whereby the brain integrates sensory and motor nervous signalling. Efferent control of LUT activity is considered from the point of view of neuromodulation and how more effective control may be artificially achieved with a view to alleviate pain and motor disorders. A more detailed consideration is then given as to how component parts of the LUT, including the outflow tract, urothelium and detrusor muscle, act as sensory transducers and effectors of motor activity. Of importance also it to recognise that advances in experimental methods facilitate our understanding of this integrative approach and a section on the development of some novel animal models is included. Finally, such information as gained will be discussed in the context of developing better pharmaceutical therapies for managing LUT disorders.

Such a consultation cannot cover all elements of scientific activity to understand LUT function. The chosen topics have been selected to provide an upgrade of some noteworthy areas that have seen advances since the last edition and also some that have not had more detailed coverage for a longer time. There are no specific research suggestions at the end of the Chapter as individual researchers will have their own interests to pursue. However, each section highlights areas for future study that different contributors find of interest.

I. AFFERENT SIGNALLING AND PAIN IN THE LUT

Chronic pelvic pain syndromes (CPPS), including chronic prostatitis and bladder pain syndrome, are often characterised by complaints of painful bladder filling or urgency, typically in the absence of overt bladder pathology to explain the pain. CPPS are also associated with negative cognitive, behavioural, sexual, and/or emotional consequences and reduced quality of life. Typically, men with chronic pelvic pain and voiding complaints are diagnosed as having chronic (usually non-bacterial) prostatitis whereas women with chronic pelvic pain and voiding complaints are commonly diagnosed as having bladder pain syndrome (BPS). Urinary CPPS (UCPPS) is an umbrella term incorporating urinary tract symptoms (frequent urination, urgency, dysuria) with chronic pain complaints localised to lower abdominal/pelvic areas. Estimates of prevalence of chronic (non-bacterial) prostatitis range from 8.4% to 25% (1). Estimates of prevalence for BPS in women vary with diagnostic criteria, ranging from 2%-17.3% among the general population (2). Commonly, female BPS patients report that their pain is worse with bladder filling (3) and that the urge to urinate is primarily due to pressure, discomfort, or pain (4). In addition, co-morbidities such as irritable bowel syndrome, dysmenorrhoea, dyspareunia, fibromyalgia and chronic fatigue syndrome are common in UCCPS (5,6) revealing both increased pelvic visceral and widespread non-visceral somatic pain sensitivity.

Management of UCCPS is challenging in part because our understanding of the mechanisms that contribute to pain is incomplete. The physiology and mechanisms of visceral pain continue to be comprehensively reviewed (7-10). Pain is typically initiated by activation of sensory afferent endings, or “nociceptors”, in all tissues and transmitted by afferent nerves to the central nervous system, which has an obligatory role in pain perception and reaction. Whereas the role of the central nervous system (CNS) increases in complexity in chronic pain conditions (e.g., amplification of afferent input, structural alterations to the brain), the contribution of ongoing, persistent afferent input to the maintenance of chronic pain is increasingly evident (11-16), including in bladder pain conditions (17-24). Thus, blockade of bladder nociceptive input into the CNS can effectively relieve or markedly attenuate discomfort and pain. Accordingly, we focus here on the organisation, complexity, sensitivities, heterogeneity and sensitisation of bladder afferent neurons, including bladder nociceptors. What constitutes a bladder nociceptor is considered more at the end of this section. Fundamentally, bladder nociceptors are afferent endings that encode the intensity of stimulation (usually bladder filling/stretch) in the noxious range and undergo an increase in excitability after organ ‘insult’. With respect to inflammation, it is important to appreciate that the mechanism(s) by which experimentally applied inflammogens activate the innate immune system differ, thus potentially affecting interpretation and comparison of experimental outcomes.

1. THE STRUCTURAL BASIS OF BLADDER NOCICEPTION

1.1. Organisation of Bladder Afferent Innervation.

The urinary bladder is innervated by efferent autonomic sympathetic and parasympathetic (‘motor’) and afferent (‘sensory’) nerves. The dual afferent innervation of the bladder, like that of other lower abdominal and pelvic organs, originates from two independent sources with neuronal cell bodies (somata) located in spinal dorsal root ganglia associated with thoracolumbar and lumbosacral (or sacral in humans) spinal segments (25,26; see (7) for an illustration of human viscerotomes). In rats, vagal afferents extend to the urinary bladder (27), but this has not been established in humans. Because visceral afferent fibres course anatomically within the same nerve (e.g., lumbar splanchnic nerve) as efferent fibres of sympathetic (thoracolumbar) and parasympathetic (lumbosacral/sacral) nerves (28), an earlier literature described them as “sympathetic afferents” and “parasympathetic afferents - a confusing self-contradiction in terminology that unfortunately continues to be used. To avoid ambiguity in meaning and presentation, visceral afferents here are described by nerve name.

Initially, the presumed function of ‘sympathetic’ afferent fibres was transmission to the CNS of conscious sensations, including discomfort and pain. Conversely, the ‘parasympathetic’ afferent innervation was associated with autonomic control rather than sensation and perception (e.g., vagal afferent innervation of thoracic and abdominal organs). This assumed functional distinction with respect to the bladder, however, was not supported when investigated. For example, studies of the function(s) of bladder afferent nerves revealed that the pelvic (i.e., ‘parasympathetic’) nerve was important for transmission of conscious sensations (e.g., fullness, distension/urgency, discomfort, and pain). Transection or blockade of the pelvic nerve abolished bladder contractions in response to

repetitive filling and relieved pain in patients suffering bladder pain (8,29,30). This was unexpected because It was commonly held that pain arising from internal organs was transmitted in afferent nerves associated with sympathetic efferent pathways (i.e., lumbar splanchnic/hypogastric nerves for the urinary bladder). While the early proposition that 'sympathetic afferents' convey sensations of discomfort and pain to the CNS may apply generally to organs in the upper abdomen and thorax, subsequent studies in rodents as well as humans confirmed that pelvic nerve afferents were the main conveyers of painful sensations from lower abdominal and pelvic organs (e.g. 30,31). Contemporary evidence documents that the function(s) and modality-selectivity of an organ's innervation changes with organ insult and disease states. For example, lumbar splanchnic/hypogastric nerve afferents activated by mechanical and chemical stimulation of the bladder contribute to the regulation of micturition and transmission of painful sensations in the presence of bladder irritation/damage (32,33).

1.2. Complexities of Bladder Innervation and Sensation.

Three common characteristics of visceral innervation and sensation apply to the lower urinary tract: low density of afferent innervation; referral of sensations; and cross-organ sensitisation. The bladder afferent innervation is complex and broad, with bilateral input from both thoracolumbar and lumbosacral/sacral spinal nerves, but the density of innervation (i.e. the number of afferents innervating the bladder) is relatively low compared with the afferent innervation of non-visceral somatic tissues. It is estimated that only 5-15% of the total afferent input into the spinal cord arises from the viscera (e.g. 8,10). In contrast, it is estimated that up to 50% of second or higher order spinal neurons respond to visceral stimulation because visceral afferent terminals extensively arborise within the spinal cord, including to the contralateral side (34). Further, the rostro-caudal spread of accessible visceral afferent spinal terminals increases in the presence of visceral insults (e.g. 35,36).

An additional complexity of the visceral innervation is the referral of sensation to non-visceral sites (referred pain). Virtually all second order spinal neurons that receive a visceral input also receive convergent non-visceral inputs from skin and/or muscle, as well as convergent inputs from other visceral organs. Accordingly, spinal viscero-receptive neurons, located principally in Rexed's *laminae* I, V and X, and in the dorsal grey commissure of the lumbosacral spinal cord, receive multiple convergent inputs that influence responses to diverse afferent inputs. Spinal somato-visceral convergence has long been considered as the underlying basis for referral of visceral sensations to non-visceral tissues (i.e., convergence-projection, 37). Likewise, spinal viscero-visceral convergence is a factor in cross-organ sensitisation between multiple organs (38).

A third complexity of the bladder innervation that may contribute to both referred sensation and cross-organ sensitisation is that a single afferent dorsal root ganglion (DRG) soma can give rise to what has been described as dichotomising or bifurcating axons that innervate two different tissues and/or organs. Experimental evidence from anatomical, behavioural and physiological studies supports the concept of pelvic organ cross-organ innervation and sensitisation. A single DRG soma may innervate both the bladder and colon in rat and mouse (39) and the bladder and prostate in rat (40,41) and mouse (42). Anatomical evidence is generated by injection of different fluorescent retrograde tracers into the bladder wall and another organ and counting DRG neurons that contain one or both tracers (see Cross-organ Sensitisation below). The physiological or clinical relevance such dichotomised axons remains to be determined. However, with rodents' distal colon irritation increases the frequency of bladder contractions and altered micturition reflexes (43-45). Similarly, prostate inflammation leads to bladder overactivity and hypersensitivity to bladder filling (41,42) while bladder inflammation in rodents leads to hypersensitivity of colon distension (43,44).

A final complexity of bladder innervation relates to interpretation of results from different species, most clearly in recent studies of rodent bladder DRG somata. In sequential studies, mouse bladder somata in the L6 DRG (46) and rat bladder somata in L6-S1 DRG (47) were labelled and studied after intra-parenchymal (IPar) injection or intravesical (IVes) instillation of fluorescently tagged retrograde tracers. The route of tracer administration, IPar or IVes, exposed two anatomically distinct groups of lumbosacral bladder afferents. IPar labelling was distributed throughout non-urothelial layers of the rodent bladder, whereas IVes labelling was confined to the urothelium, and occasionally the submucosa. Subsequent whole-mount, *in situ* patch-clamp recordings from labelled DRG somata revealed significant differences between rat and mouse. In the mouse (46) IVes labelled, 'urothelial' DRG somata exhibited greater excitability relative to IPar labelled, non-urothelial DRG somata. These electrophysiological differences between anatomically distinct urothelial and non-urothelial bladder DRG somata, however, were not replicated in the rat, (47). The translation of findings in non-human animals to humans is considered in the closing comments.

1.3. Bladder Afferent Fibres and Receptive Endings.

Centripetal axons of DRG somata travel to the lower urinary tract in lumbar splanchnic/hypogastric and pelvic nerves (Figure 1), terminating in bladder and urethra muscle, sub-urothelium and urothelium. Pudendal afferent nerve endings, arising from sacral DRG, innervate the bladder neck and urethra. Because the urinary bladder is derived from midline structures, it has bilateral afferent inner-

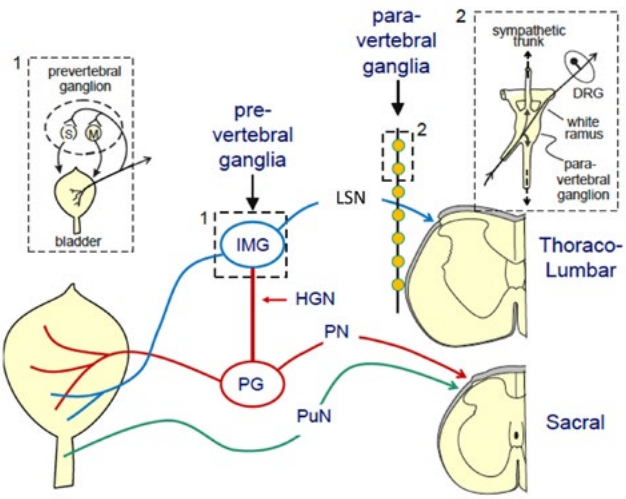

Figure 1. Afferent innervation of the urinary bladder. *Pelvic (PN, red) and pudendal (PuN, green) nerves, with afferent terminals from the bladder and urethra terminate in lumbosacral (most animals) or sacral (humans) spinal cord segments. PG, pelvic ganglion/plexus. Lumbar splanchnic nerve (LSN, blue), with many terminals at the bladder base, and hypogastric nerve (HGN, red) fibres pass through pre- (box 1) and para- (box 2) vertebral ganglia before reaching thoracolumbar spinal segments: IMG, inferior mesenteric ganglion. S,M (Box-1) represent secretory and motility functions of neurons in prevertebral ganglia. From (61,74-76).*

vation from both lumbar splanchnic/ hypogastric and pelvic nerves. Discomfort and pain often occur during voiding in individuals with urethritis (inflammation of the urethra) or urinary tract infections, but normally activation of pudendal afferents is not nociceptive.

The urinary bladder afferent innervation is comprised largely, if not exclusively, of thinly myelinated Aδ- and unmyelinated C-fibres. Unmyelinated C-fibres are slower conducting (0.5-2.0 $m.s^{-1}$), while myelinated Aδ-fibres conduct at 2.5-30 $m.s^{-1}$. Fibre myelination is related to conduction velocity and is not a reliable indicator of function, although function has been assigned to fibre type. For example, it was thought previously that Aδ-fibre endings were excited by mechanical stimuli and thus transmitted information about bladder filling, whereas C-fibre endings were excited by chemical stimuli and transmitted nociceptive information leading to discomfort and painful sensations. As discussed below, bladder Aδ- and C-fibres respond to several stimulation modalities. Receptive endings of bladder afferents in detrusor, sub-urothelium and urothelium are assumed to be unencapsulated ("free") endings - largely based on parallels with non-visceral somatic Aδ- and C-fibres. These receptive endings express multiple transducer molecules (e.g., G protein-coupled receptors, ligand- and voltage-gated ion channels, etc.) that respond to specific mechanical, chemical, and/or thermal stimulus modalities.

Bladder afferent terminals that respond to mechanical and/or chemical stimuli give rise to conscious sensations, including fullness, urgency, discomfort and pain (i.e. are *sensory* afferents). Bladder afferent terminals also respond to mechanical and chemical stimuli that are *not* consciously perceived (i.e. are not sensory), including responses to interoceptive stimuli (48). Non-sensory bladder afferents play important roles in conjunction with sympathetic and parasympathetic efferent nerves in the reflex control of urine storage and micturition. Some bladder afferent terminals are also thermosensitive (49). Thus, some are multi-modal, as are other pelvic visceral afferents that respond to thermal, chemical and/or mechanical stimuli.

Most electrophysiological studies of bladder afferents have focussed on mechano-sensation, as bladder filling is a physiologically relevant stimulus and hollow organ distension is commonly used as an experimental, noxious visceral stimulus (50-52). Bladder afferent terminals that respond to filling or distension are presumed to be in the detrusor smooth muscle, initially classified as 'in-series' tension receptors (8,53). Based on studies primarily in rats and mice, mechano-sensory bladder signalling has been assigned to several functionally distinct afferent endings, as discussed below. Until recently, detailed information about the location and morphology of bladder afferent terminals was unavailable. Spencer et al. (54,55) described morphologically distinct types of pelvic nerve afferent endings in mouse bladder. After unilateral injections of an anterograde tracer into the L5-S2 DRG, four morphologically distinct types of spinal afferent endings in urinary bladder tissue sections were distinguished: three were located in the detrusor muscle and one in the sub-urothelium and urothelium. The detrusor muscle endings comprised 81% of the total and had a "simple", "branching" or "complex" morphology; the majority (75-89%) were calcitonin gene-related peptide (CGRP)-immuno-positive, confirming their classification as 'afferent'. Sub-urothelial and urothelial endings generally had a "simple" morphology with single, fine varicose or non-varicose axons. They lacked a specialised terminal ending and were also CGRP-immuno-positive.

On a morphological basis, "complex" endings were most common (44% of labelled endings) and terminated in detrusor, with some also in the sub-urothelium. Such endings developed from a single axon that bifurcated extensively near the fibre terminal, spreading within detrusor muscle but without uniform orientation to either muscle fibres or other afferent fibres. They were distributed throughout the bladder with no preferred topography. "Simple" endings in detrusor and sub-urothelium (25% of labelled endings) terminated as single, straight axons with varicosities along terminal endings. The least common (12%) were "branching" endings, occasionally with multiple endings arising from one parent axon and typically coursed in alignment with detrusor muscle fibres. The distinctive functional properties of these four morphological types remain to be established.

2. THE FUNCTIONAL BASIS OF BLADDER NOCICEPTION

2.1. Bladder Pain, Nociceptors and Sensitisation.

Noxious stimuli that are algogenic (give rise to pain) do so only if they are "adequate" excitants of nociceptive receptive endings that are typically unencapsulated/"free" Aδ- or C-fibre nerve endings in skin, bone, joints, muscle, and internal organs. In addition, rapidly conducting Aβ-fibres have been associated with nociceptive endings (56), but they are not common in the rodent visceral innervation. Whether a nociceptive stimulus is adequate depends on the tissue to which it is applied and the modality of the applied stimulus (57,58). For example, cutting, crushing/pinching, or burning reliably excites nociceptors in skin, whereas they generally do not evoke pain or other conscious sensations when applied to hollow organs (7). Rather, stretch or distension of hollow organs, traction on intestinal mesenteries, organ hypoxia/ischemia/inflammation and chemical stimuli, such as endogenous inflammatory mediators, activate visceral nociceptors. Nociceptors are receptive endings which, when excited by an adequate stimulus, are associated with an action (a withdrawal reflex, guarding behaviour) or sensation (discomfort, pain) and thus are defined by their function. Designation of sensory neurons with slowly conducting or unmyelinated axons and small-diameter DRG somata as nociceptors, in the absence of evidence of their function, has become common but is not reliably accurate.

Nociceptors were initially thought to have high thresholds for response to applied stimuli and then to encode stimulus intensity throughout the noxious range. It is now appreciated that response threshold is not a distinguishing characteristic of nociceptors. Many skin, muscle, joint, and visceral mechano-nociceptors respond to low stimulation intensities, with respect to response threshold, are indistinguishable from non-nociceptive mechano-receptors. There are two defining properties of nociceptors: they encode stimulus intensity in the noxious range; and they sensitise (59). Most mechano-sensitive bladder endings have low response thresholds and have these properties (60-61).

Sensitisation represents an increase of nociceptor excitability and is operationally established as a leftward shift of afferent behavioural or psychophysical stimulus-response functions (Figure 2), i.e. a reduced response threshold and an increased response magnitude to a nociceptive stimulus (59,62). Note that as response threshold decreases, previously non-nociceptive intensities of stimulation or previously inadequate or subthreshold stimuli, including other modalities of stimulation, may become effective excitants; spontaneous activity may also develop. Examples of sensitisation at different levels of the neuroaxis are given in Figure 2.

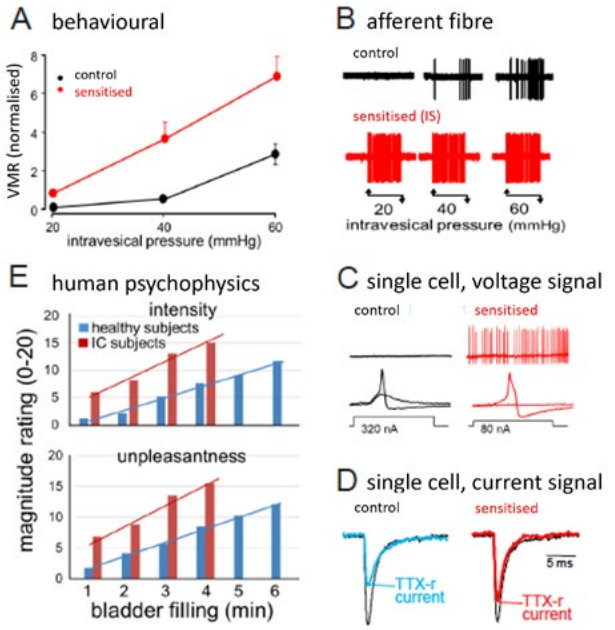

Figure 2. Examples of sensitisation. *A: behavioural; viscero-motor responses to bladder distension seven days after bladder inflammation (red). B: afferent fibres; increased responses to bladder distension of a detrusor afferent fibre after 5-min inflammatory soup exposure (red, 99). C: DRG soma responses before and after (red) cyclophosphamide exposure. D: ionic current before and after cyclophosphamide exposure – TTX-r: current resistant to tetrodotoxin. E: human psychophysics; intensity (top) and unpleasantness (bottom) scores during bladder filling in healthy subjects and IC/PBS patients. A-D from (45,61,106): E, data courtesy of TJ Ness, University of Alabama, Birmingham, AL, USA.*

*2.2. Bladder Nociception – Mechano-reception***.**

Most studies of bladder afferents focused on mechano-sensitivity and multiunit recordings of afferent fibre responses to bladder distension were first reported in the 1930s (63,64). Most afferent fibres in the pelvic and hypogastric nerves responded to bladder distension. For afferent fibres with high response thresholds, it was suggested their function was related to painful sensations. Subsequently, it was proposed that pelvic nerve bladder afferents responsive to detrusor contractions and distension were tension-sensing afferents “in series” with detrusor smooth muscle and associated primarily with regulatory reflexes (53).

Subsequent studies in cats (65-69) led to promotion of a functional distinction between Aδ- and C-fibre bladder afferents. Aδ-fibre mechano-sensitive afferents, mostly associated with the pelvic/sacral bladder innervation, responded to both bladder distension and detrusor contractions. These mechano-sensitive afferents had low response thresholds and slowly adapted to phasic increases of wall tension from either active detrusor contraction or passive bladder filling/distension. Because of their mechano-sensitivity and low thresholds for response, they were assumed to be in series with bladder detrusor muscle and associated with voiding. In contrast, C-fibre bladder afferents were mostly mechano-insensitive or chemo-sensitive (e.g. to capsaicin, 300 mM-K^+), and thus had a nociceptive function. Consistent with this, those C-fibre afferents that were mechano-sensitive tended to have higher response thresholds (25-30 mmHg) to filling.

The association of bladder function with axon myelination and conduction velocity in cats was not found in rodents. In rats, *in vivo* recordings from lumbosacral dorsal roots, from which fibre bundles were teased to record from individual bladder afferents, documented mechano-sensitive Aδ- and C-fibre pelvic nerve afferents with low or high thresholds for response to bladder distension (60,70,71). Most (70%-80%) distension-responsive afferents had response thresholds in the physiological range (<5 mmHg); the remainder had high response thresholds (~25-30 mmHg), in the noxious range (Figure 3). Bladder afferents that responded to very noxious urinary bladder distension (80 mmHg) included unmyelinated C-fibres (mean conduction velocity 1.8 $m.s^{-1}$) and thinly myelinated Aδ-fibres (mean conduction velocity 8.1 $m.s^{-1}$) (60,70). Both low and high threshold afferents, demonstrated slowly-adapting responses during phasic isotonic distension or slow bladder filling. Afferent discharge frequency increased monotonically during phasic isotonic bladder distension. During slow bladder filling, afferent activity more closely correlated with increases of intravesical pressure. Evidence of a significant proportion of stretch/distension-responsive bladder afferents with high response thresholds was proposed to confirm the existence of bladder mechano-nociceptors. This has also been documented in other visceral organs and in different species (10). However, when it was established that low-threshold mechano-sensitive afferents in the bladder and other visceral organs (stomach, colon) sensitised (see below), the notion that high threshold afferents are “the” bladder/visceral nociceptors was reassessed.

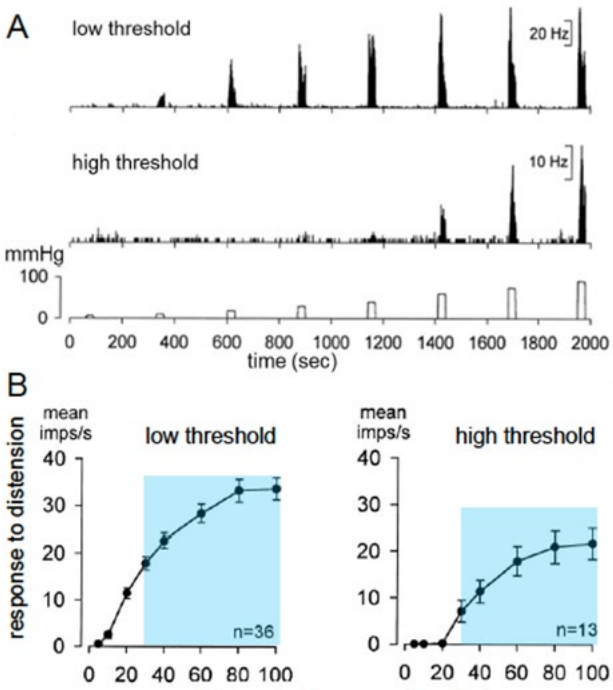

Figure 3. Responses of mechano-sensitive rat bladder pelvic nerve afferents. *A: examples of a low threshold and high threshold afferents to bladder distention (5-100 mmHg, 30 s each at 4-min intervals). B: mean stimulus-response functions of low- and high-threshold afferents with mean extrapolated response thresholds of 6.0±0.5 mmHg and 31.1±1.2 mmHg. Shaded areas represent the range of noxious intensities of bladder distension: note the greater magnitude responses of low- relative to high threshold afferents. Adapted from (70).*

Studies in mice and guinea pigs subsequently characterised mechano-sensitive classes of bladder afferents and clarified their ability to sensitise. With an *ex vivo* flat-sheet urinary bladder preparation with nerves attached, fine filaments can be teased to record from single afferent fibres. Four functionally distinct mechano-sensitive afferent types have been characterised. In the guinea pig, bladder afferent fibre recordings distal to the pelvic ganglia (thus including afferents in both the lumbar splanchnic/hypogastric and pelvic nerve innervations) were classed as: i) muscle mechano-receptors responding to bladder stretch, with low or high response thresholds; ii) tension-mucosal afferents responding to both stretch and mucosal stroking with monofilaments; iii) mucosal mechano-receptors responding only to mucosal stroking; iv) chemoreceptors responding mucosal application of acid (pH 4), high-K (50 mM), or in about 25% of fibres to capsaicin (3 μM) (72,73).

With a similar mouse preparation, four functionally distinct mechano-sensitive afferent types were also characterised in the lumbar splanchnic/hypogastric nerve (LSN) and in pelvic nerve (PN) bladder innervations (61). Here, with the urothelial side facing up, all afferents responded to probing with monofilaments. In the LSN bladder innervation, fibre types were classed as muscular/urothelial, muscular, or serosal; in the PN innervation, the same fibre types were found, as well as endings that responded to urothelial stroking (Figure 4). Of interest, there were significant differences between

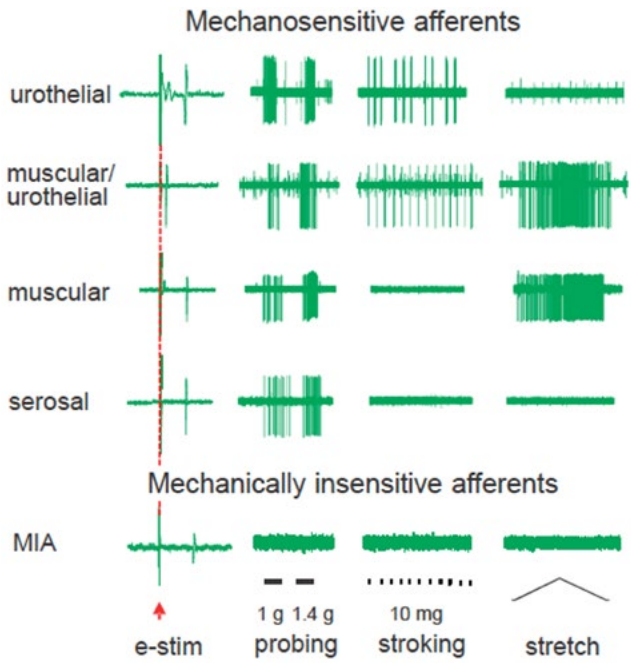

Figure 4. Classes of afferent endings in the mouse bladder. *Endings located by electrical stimulation of a bladder sheet, urothelial side up (e-stim; left column; red arrow, vertical line stimulus artifacts). Classes based on responses to different mechanical stimuli. All mechano-sensitive endings responded to blunt vertical probing by 0.4-1.4 g monofilaments. Urothelial endings also activated by stroking the urothelial surface (10 mg). Muscular/urothelial endings additionally activated by stroking and circumferential stretch (0-170 mN, 35 s). Muscular endings also activated by circumferential stretch. Serosal endings activated only by blunt probing. MIA (mechanically insensitive afferents) endings did not respond to any mechanical stimuli. From Feng B and Gebhart GF, unpublished.*

the two innervation pathways of the mouse bladder with respect to the topographical distribution of receptive fields on the bladder sheet and in the proportions of afferents that responded to these different stimuli.

LSN afferent endings typically had a single, small (typically 0.5 mm) punctate receptive field, clustered at the base of the bladder, from which responses could be reliably evoked. Muscular afferents, which comprised 30% of the LSN mechano-sensitive fibre types, responded to probing and to stretch but not to urothelial stroking. A small (3%) proportion of LSN afferent endings were designated muscular/urothelial because they responded to stroking of the urothelium, and also to graded bladder stretch. No 'urothelial' afferent endings were found in the bladder LSN innervation. The largest proportion (67%) of LSN afferent endings were designated as serosal; they had receptive fields that were reproducibly activated in a graded fashion only by perpendicular, blunt monofilament probing of the bladder sheet and not by bladder stretch or urothelial stroking.

With the PN bladder innervation the four types of afferents from their receptive fields (urothelial, muscular/urothelial, muscular and serosal: Figure 4) also had single, punctate fields. Muscular afferents (63% of fibres) that responded to graded bladder stretch, but not urothelial stroking, were the most common fibre type. Muscular/urothelial PN afferents (14%) responded to both urothelial stroking and graded bladder stretch. A similar proportion of PN afferents (14%) responded only to probing of their receptive field and were classed as serosal afferents. The fourth class of PN afferents (9%) were classed as urothelial afferents as they were responsive only to stroking of their receptive fields. Unlike LSN afferents, PN afferent receptive fields were distributed throughout the bladder (Figure 5). However, none of the PN urothelial afferents had receptive fields at the base of the bladder, where most LSN mechano-sensitive receptive fields were located. These differences in the topographical distribution of LSN and PN receptive endings in the mouse bladder are consistent with the anatomical distribution of LSN and PN terminals in the cat bladder. In the cat bladder it was found that PN/sacral axons were distributed equally to all areas of the bladder whereas LSN/lumbar axons were most numerous in the trigone (74-76). With respect to response thresholds to bladder stretch, 64% of PN mus-

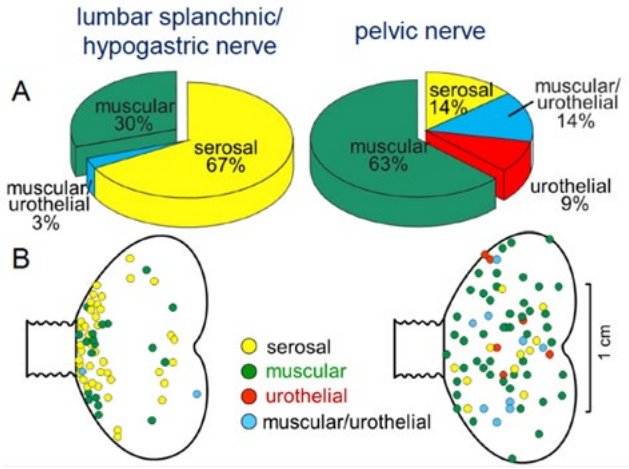

Figure 5. Mechano-sensitive lumbar splanchnic/hypogastric and pelvic nerve bladder mouse afferents. *A: Proportions of different classes. B: Topographical distribution of receptive endings. Adapted from (61).*

cular afferents had low response thresholds, two-thirds of which encoded stretch over the range of applied loads (61). The residual one third were 'non-encoding'; i.e., response magnitude to stretch did not increase as the applied load was augmented. PN muscular afferents with high response thresholds to stretch (36% of the sample) encoded stretch throughout the range of applied loads. There was no differential topographical distribution of receptive endings on the bladder sheet between low and high threshold muscular PN afferents.

An underlying assumption about the dual innervation of internal organs is that different innervation pathways communicate unique aspects of afferent transmission, both sensory and non-sensory. The foregoing comparisons between afferent responses to identical stimuli in LSN and PN pathways innervating the bladder reveals that there is some overlap, as well as distinct differences in functionality between these pathways - see also with the mouse colon (77). It is apparent that all afferent types in both pathways encoded the intensity of stimulation. The bladder PN pathway is primarily comprised of stretch responsive low and high threshold muscular and muscular/urothelial endings distributed throughout the bladder (77% of all afferents, 61). By contrast, the bladder LSN pathway is primarily comprised of 'serosal' endings (67%) that respond only to blunt probing; with receptive endings clustered mostly near the bladder base. The designation "serosal" is not a histological assignment; it simply denotes a mechano-sensitive ending for which a potential function is not apparent. About 10% of the PN innervation were classed as urothelial; no urothelial afferent endings were found in the LSN innervation.

PN afferent endings were detected using a search strategy of focal electrical stimulation and their receptive fields noted (77). These were subsequently tested for mechano-sensitivity using probing, stretch and stroking stimuli. The proportions of muscular/urothelial (20%) and urothelial (9%) afferent endings (Feng B, Gebhart GF, unpublished data) were comparable to proportions where mechanical probing was the search stimulus (61). The proportion of muscular afferents (37%) was less and of serosal afferents (30%) was greater than previously reported (61). Endings that did not respond to these mechanical stimuli were called mechanically insensitive afferent (MIA) endings (Figure 4). MIAs constituted 5% of the total, 37.5% of which were Aδ-fibres; this is smaller than the proportion (~25%) in the LSN and PN innervations of the mouse colorectum (77).

2.3. Bladder Nociception - Chemoreception.

Fewer studies have examined chemical activation of bladder afferents. Additionally, these studies have often been models of bladder inflammation without attention to nociception. Bladder afferent endings contain neuropeptides, including substance P and CGRP, and also express a wide variety of voltage-gated and ligand-gated receptors, including the capsaicin activated transient receptor potential vanilloid receptor 1 ($TRPV_1$), the mustard oil activated transient receptor potential ankyrin 1 receptor ($TRPA_1$), the nerve growth factor receptor tyrosine kinase A (TrkA), and adenosine triphosphate (ATP) activated purinergic receptors (P2X, P2Y). Accordingly, these and other substances have been used to interrogate bladder afferent chemosensitivity.

With *in vivo* cat studies, low and high threshold mechano-sensitive afferents in the pelvic/sacral innervation of the bladder are also responsive to intravesical instillation of mustard oil or turpentine oil, which also led to spontaneous activity and a change in mechano-sensitive properties (78,79). In a succeeding study, it was shown that mechano-sensitive pelvic/sacral bladder afferents were activated at short latency by intravesical instillation of mustard oil or turpentine oil. Thus, a large proportion of mechano-sensitive pelvic/sacral bladder afferents are also chemo-sensitive (80). Subsequently, in a rat study, whereas bladder filling with isotonic NaCl increased multiunit afferent hypogastric nerve activity two-fold, there was a five-fold increase with isotonic KCl infusion (32). In contrast, pelvic nerve bladder afferents exhibited no chemosensitivity as responses to NaCl and KCl bladder infusions did not differ.

With a guinea pig preparation, the chemo- and thermo-sensitivity of two classes of low-threshold mechano-receptors (stretch-responsive muscular/urothelial afferents; and stretch-insensitive urothelial afferents), as well as high-threshold, stretch-responsive afferents were compared (81,82). With low threshold stretch-responsive afferents serotonin (100 μM) and bradykinin (10 μM) and a high concentration of the $TRPA_1$ receptor agonist, allyl isothiocyanate (AITC, 100–300 μM) activated sub-populations of afferents. However, capsaicin (3 μM), substance P (100 μM), prostaglandin E2 (10 μM), H_2O_2 (300–1000 μM), or low pH solution (pH 4) were without effect. Heated Krebs (46-65°C) activated about 50% of afferents tested. With low threshold stretch-insensitive afferents virtually all (95%) responded to heated Krebs, capsaicin and bradykinin, but were unresponsive to serotonin, substance P, and prostaglandin E2 at the same concentrations as above. With high-threshold, stretch-responsive afferents capsaicin (3 μM) excited 86% of fibres, of which most were also activated by H_2O_2, or AITC. H_2O_2-induced activation was significantly attenuated by the $TRPA_1$ receptor antagonist HC-030031, but not by a $TRPV_1$ receptor antagonist.

Purinergic signalling in the bladder has long been a topic of interest. Exogenously applied or endogenously released ATP, acting on P2X ligand-gated ion channels is excitatory and mediates non-cholinergic bladder contractions (83). During bladder distension, ATP is released from urothelial cells to act on P2X-expressing bladder afferent endings below the urothelium where ATP is thought to signal changes in fullness, as well as pain (84). In an *in vitro* mouse bladder PN preparation, intravesical application of the P2X receptor agonist α,β-methylene ATP (ABMA; 0.03–1 μM) increased multifibre discharges and both low and high threshold PN afferent fibre responses to bladder distension in a receptor-selective manner; the effects of ABMA were antagonised by the $P2X_3$-$P2X_{2/3}$ receptor antagonist 2'(or 3')-O-(2,4,6-trinitrophenyl)-ATP (TNP-ATP; 85).

Responses of bladder thoracolumbar (TL) and lumbosacral (LS) afferent DRG somata to purinergic agonists, low pH and capsaicin were compared (86). The majority of LS neurons (93%) but only 50% of TL neurons responded to ABMA; most LS and TL bladder neurons also responded to low pH (>75%) and capsaicin (>90%). Most TL (85%) and LS (61%) DRG somata bound isolectin B4 (IB4) - a marker for neurons associated with unmyelinated C-fibre axons - consistent with reports that >90% of LSN bladder afferents and 50-70% of PN bladder afferents conduct in the C-fibre range (26,60,87). Although purinergic signalling in the bladder has been well-documented in rodents, its contribution in humans, particularly with respect to nociception, has yet to be confirmed. However, it may play a role in those with pathological bladder conditions (e.g., detrusor overactivity, interstitial cystitis; 83). It is noteworthy that mRNA for the $P2X_3$ receptor is expressed in ~70% of mouse bladder DRG somata (88) and its expression is highly correlated between human and mouse DRG somata (89). This suggests that the $P2X_3$ receptor is a reasonable target for drug development (see also below).

Importantly, these studies of bladder mechano-sensitive afferents reveal a variety and mixture of sensitivities with respect to mechan-

ical, chemical and thermal modes of activation. Low- and high-threshold stretch/distension-sensitive bladder afferents exhibit mixed chemical and/or thermal sensitivities, revealing significant heterogeneity with important clinical implications. It is important also to realise that afferent sensitisation to mechanical activation also leads to sensitisation by other modalities. Thus, modest acidification of urine, for example, may stimulate sensitised low-threshold mechano-sensitive afferents when such a chemical intervention would otherwise have no effect.

2.4. "Silent", Mechanically Insensitive Endings.

Silent (or sleeping) afferents more accurately designated as mechanically-insensitive afferents (MIAs, 90), constitute a significant proportion of the afferent innervation in many tissues. MIAs acquire mechano-sensitivity after tissue insult and are important contributors to the development and maintenance of hypersensitive states (e.g., UCPPS) and were first characterised in the knee joint of the cat (91). These endings are electrically excitable but insensitive to mechanical stimulation. After experimental inflammation of the knee joint, however, they became spontaneously active and acquire mechano-sensitivity. MIAs have been reported in the visceral innervation, but because mechanical search stimuli were employed in these studies, the designation MIA was inferred p*ost hoc* by their appearance in electrophysiological recordings following an inflammatory or chemical insult to the tissue (92-95). In the cat, following *in vivo* bladder filling with irritants, the estimated proportion of bladder MIAs ranged greatly, between 6 and 97% (78,79,80). An unbiased electrical stimulation search strategy to locate receptive endings in the mouse colorectum found that that MIAs comprised 23-33% of the PN and LSN innervations (77). An unpublished study of the mouse urinary bladder, also using an unbiased electrical search strategy, found a much smaller proportion of MIAs in the PN bladder innervation (5%). For reference, the proportion of C-fibre MIAs in human skin is ~24% (96). The differences in estimated proportions of bladder MIAs summarised here may reflect how bladder afferents were studied (e.g., *in vivo* bladder filling with irritants), species differences (cat *vs* rodents), or that the urinary bladder simply differs from other organs/tissues.

The chemosensitivity of MIAs is usually associated with irritant chemicals or tissue inflammation related to MIA sensitisation, and thus acquisition of mechano-sensitivity. A recent study, using an optogenetic strategy to examine the contribution of action potential initiation to afferent encoding, described two distinct chemo-sensitive populations of PN MIAs in the mouse colo-rectum (97,98). MIA endings were stimulated and then tested for activation/sensitisation by application to the receptive ending of an inflammatory soup (IS, containing bradykinin, serotonin, histamine and prostaglandin E2 in pH 6.0 Krebs solution, 99) and/or an osmotic stimulus (acidic hypertonic solution (AHS); pH 6.0, 800 mOsm.l^{-1}). Both interventions activated and sensitised MIAs. The optogenetic strategy revealed that IS-sensitive and AHS-sensitive MIAs represent two discrete afferent groups: one group was inflammation-sensitive and the other osmo-sensitive.

A different approach was used to characterise in mouse DRG a subset of peptidergic MIA somata. Specifically, retrogradely labelled bladder DRG somata that expressed the nicotinic acetylcholine receptor alpha-3 subunit (nAChRα3) were sensitised by the inflammatory mediator nerve growth factor (NGF) and mechanically-activated currents recorded by whole-cell patch-clamp (100). The underlying reasoning in this study was that mechanical stimuli applied incrementally to the cell soma by the patch pipette was equivalent to mechanical stimuli applied to receptive endings in the bladder and thus sufficient to classify DRG somata as "mechano-insensitive 'silent' nociceptors". nAChRα3-expressing DRG somata accounted for up to 40% of the CGRP-immuno-positive somata population in T12-L1 and L6- S1 DRG, from which the lumbar splanchnic/hypogastric and pelvic nerves that innervate the bladder are derived, respectively. It was concluded that mechano-insensitive nAChRα3-expressing afferents account for ~50% of all peptidergic somata innervating the bladder (and colon) and after sensitisation, the mechanically-gated ion channel Piezo2 mediates NGF-induced mechano-sensitivity.

2.5. Contemporary Research Approaches.

Newer optogenetic and molecular profiling strategies have been applied to study urinary bladder afferents and their function. An optogenetic approach bypasses the process of transduction of stimulus energy (mechanical, thermal, chemical) and focuses on the process of action potential initiation at the receptive ending. Archaerhodopsin (Arch), a light-activated proton pump, hyperpolarises neurons in which it is expressed when activated by a specific wavelength of green light to an extent sufficient to suppress neuronal firing. This optogenetic approach was employed to target bladder afferent neurons by expressing Arch in a sensory neuron-specific Cre BAC transgenic mouse line, where Cre is under the regulation of SCN10A (Na^+ channel Nav1.8) promoter elements. Optogenetic Arch-induced inhibition of mouse bladder afferents suppressed the bladder distension-provoked visceromotor response (a nociceptive guarding response) and significantly increased detrusor inter-contraction intervals (101). Light activation of Arch also reduced both ongoing nociceptive behaviour, as well as referred cutaneous hypersensitivity in mice with experimentally induced cystitis. In a related study, light-activated excitatory channel rhodopsin-2 (ChR2) was expressed in two distinct populations of afferent neurons: Nav1.8-positive neurons (as above) and $TRPV_1$-lineage neurons (102). Excitatory stimulation of ChR2-expressing bladder afferent terminals by blue light significantly increased viscero-motor responses to bladder distension in both transgenic mouse lines and produced phasic detrusor contractions in the Nav1.8/ChR2 mouse line. However, it must be appreciated that nociceptors are not selectively targeted by this approach (102) and not all mouse bladder C-fibre afferents express the Nav1.8 sodium channel. In addition, nearly one-third of sensory neuron specific-Cre lineage neurons express a neurofilament protein (NF200) present in myelinated Aδ-fibres (103) and are not targeted by Nav1.8 or $TRPV_1$ promoters. Thus, interpretation of results with respect to nociception *per se* requires additional validation.

With a different approach, a recent study examined 32 selected genes expressed in thoracolumbar and lumbosacral mouse bladder DRG somata to assess their potential role in bladder function and bladder nociception (88). The genes chosen for study were based on their previously-validated roles in stimulus detection (e.g., TRP receptors, mechano-sensors, purinergic receptors, acid-sensing ion channels, cytokine receptors) or neuronal excitability (opioid receptors, neuropeptides, Na^+ channels). The objective was to correlate the molecular phenotype of individual neurons, or clusters of neurons, with the physiological properties of their afferent endings (responses to mechanical and/or thermal stimuli, nociceptive signalling). From retrogradely labelled bladder DRG somata and single-cell qRT-PCR, bladder DRG somata were sorted into distinct clusters (peptide, non-peptide, neurofilament expressing thoracolumbar [TL], lumbosacral [LS] or mixed TL/LS clusters). The principal conclusion was that bladder afferents from different portions of the neuraxis have overlapping functions, consistent with the earlier literature.

Currently, such contemporary research approaches, all using mouse models, do not provide coherent results with respect to targets and nociception. Because of the large number of genes expressed in DRG bladder somata, as well as genes not included for evaluation, it is unclear at present if afferent function based on molecular characteristics of the cell soma can be reliably defined, but improvements in bioinformatic analysis may improve this situation.

3. BLADDER SENSITISATION

Virtually all chronic pain conditions are associated with increased sensitivity to multiple modalities of natural and applied stimuli. In such visceral pain states, sites to which sensation is referred exhibit characteristic hypersensitivity; reduced thresholds to applied stimuli, often with complaints of discomfort to normally non-painful palpation; referred sensation areas are increased in size. More broadly, patients suffering from chronic pelvic pain conditions (bladder pain syndrome, primary dysmenorrhea, non-bacterial prostatitis) experience generalised somatic hypersensitivity and enhanced negative perception of both innocuous and noxious stimuli. Underlying bladder hypersensitivity is increased neuron excitability (sensitisation), initially localised to afferent endings in the bladder but rapidly including spinal and then supra-spinal neuronal excitability. There is considerable evidence that ongoing, persistent afferent input often contributes to maintenance of chronic visceral pain states.

3.1. Afferent/Cellular Sensitisation.

As indicated above, sensitisation represents a change in neuronal excitability that is expressed and evident at both the cell soma and afferent ending. Mechano-sensitive bladder afferent sensitisation has been documented in cat, rat, and mouse. In the cat, intravesical instillation of 2.5% mustard oil initially (30 min) sensitised pelvic/sacral mechano-sensitive afferents to bladder distension, after which (120 min) afferent responses were desensitised (80). In studies with rats, responses to bladder distension of pelvic nerve afferents from the L6 and S1 dorsal roots were recorded before, 30 min after intravesical exposure to 10% DMSO, and then again after filling the bladder with a solution of human recombinant NGF in DMSO (104). Nearly all myelinated Aδ-fibre afferents and ~50% of unmyelinated C-fibre afferents were mechano-sensitive, responding to graded distension of the bladder (0-60 cm H_2O) at low pressure thresholds in the innocuous range and encoding responses into the noxious range. Within 30 min after NGF instillation, most mechano-sensitive Aδ- and C fibre afferents were sensitised (response threshold was reduced, and response magnitude increased) that persisted up to 3 hr. Furthermore, some afferents, initially unresponsive to bladder filling, developed mechano-sensitivity. Similarly, intravesical instillation of xylene or mustard oil into the rat bladder sensitised responses of pelvic nerve afferents in the L6 dorsal root to bladder distension with isotonic fluids (70).

In addition to establishing purinergic chemo-sensitivity of mouse bladder mechano-sensitive pelvic nerve afferents (85), responses to bladder distension of almost all high threshold afferents and most low threshold afferents were sensitised after intravesical instillation of 1mM ABMA. As noted above (11), afferents that did not respond initially to bladder distension did so after exposure to ABMA. In a study of muscle, stretch-sensitive PN mouse bladder afferents (61), sensitisation to bladder stretch was tested by applying directly an inflammatory soup (IS, 99) to the receptive ending. The response magnitude to stretch of both low (encoding) and high threshold PN muscle afferents increased significantly when tested five minutes after washout of the IS, and the response threshold of high threshold muscle afferents decreased (see examples in Figure 6). Sensitisation to stretch was selective in that responses to monofilament probing of the same afferent endings were not sensitised by application of IS. In addition, about 60% of muscle PN afferents tested responded directly to application of IS, revealing chemosensitivity to one or more component chemicals.

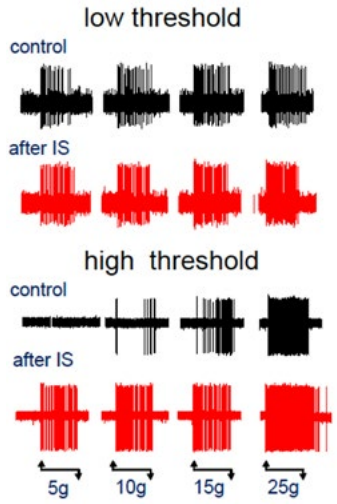

Figure 6. Sensitisation of mouse low- and high-threshold pelvic nerve bladder afferents. *Sensitisation (red) after 5-min exposure to an inflammatory soup (99) applied directly to the receptive ending. Adapted from (61).*

An alternative approach to bladder sensitisation showed afferent sensitisation in the absence of bladder inflammation (105). Bladder permeability was increased by *in vivo* instillation of protamine sulphate (100 µl, 1 $mg.ml^{-1}$) and PN multiunit responses to bladder filling were examined 1, 7, and 28 days after treatment. One day after treatment, mechano-sensitive PN bladder afferents were sensitised to bladder filling, the activation threshold of afferents was decreased and afferent peak firing rates increased. In particular, only low-threshold afferents were sensitised, and sensitisation was no longer apparent 7 or 28 days after instillation. It was further concluded that MIAs were not recruited by protamine sulphate treatment, leading to the hypothesis that such bladder afferent sensitisation is functionally distinct from inflammation-induced bladder sensitisation.

In studies of rat bladder DRG somata, identified by retrograde tracer injection, cellular properties and P2X receptor involvement were examined after bladder inflammation, induced by cyclophosphamide (CYP) (106). Neuronal excitability, spike frequency during current injection and current density, were all significantly increased in both thoracolumbar (TL) and lumbosacral (LS) bladder DRG somata after CYP treatment. Peak inward current, as well as the proportion of TL neurons (>80%) activated by purinergic receptor agonists, were also increased. In addition to sensitising bladder neurons, bladder inflammation also led to a selective increase in the functional expression of heteromeric $P2X_{2/3}$ and homomeric $P2X_3$ receptors in LS and TL bladder neurons, respectively (Table 1).

In a related study with mouse bladder DRG somata (107), CYP-induced bladder inflammation also significantly increased mouse LS and TL bladder neuron excitability. However, in contrast to the rat study, no bladder DRG somata from CYP-treated mice exhibited spontaneous activity. Moreover, whilst inward currents generated by purinergic agonists are changed in both rat and mouse bladder

Table 1. ABMA-evoked currents and P2X transcripts in bladder DRG somata

	current type	Saline-treated	CYP-treated
Rat LS somata (n=52 sal, 56 CYP)	slow	87%	100%
	fast	6%	0%
Rat TL somata (n=27 sal, 44 CYP)	slow	15%	9%
	fast	22%	43%
Mouse LS somata (n=28 sal, 24 CYP)	slow	100%	100%
	fast	0%	0%
Mouse TL somata (n=22 sal, 29 CYP)	slow	73%	79%
	fast	27%	21%
Mouse P2X transcripts			
	LS P2X2 only	6.7 ± 3.8%	14.0 ± 7.3
	LS P2X2/3	82.2 ± 2.2%	76.8 ±9.8
	LS P2X3 only	4.5 ± 2.2%	4.6 ± 2.3%
	TL P2X2 only	0	0
	TL P2X2/3	51.2 ± 8.0	73.3 ± 6.7
	TL P2X3 only	49.8 ± 8.0	26.7 ± 6.7

Proportions of bladder DRG somata with slowly (slow) and rapidly desensitising (fast) inward currents on ABMA exposure. Slow currents associated with heteromeric P2X2/3 receptors; fast currents with homomeric P2X3 receptors. "n" is number of DRG somata in lumbosacral (LS) and thoracolumbar (TL) DRG from saline (sal)- and cyclophosphamide (CYP)-treated rats and mice. The bottom part of the table presents the proportions of P2X receptor transcripts in mouse bladder DRG somata. Each group consisted of 45 bladder LS and TL DRG somata. Adapted from (106,107). The vertical connector in the top of the table indicates the difference of slow currents in rats and mice. Note the significant increase in the proportion of rat TL DRG somata exhibiting a fast current with CYP treatment (red arrow) and the absence of change in mice TL counterparts (black arrow). The vertical connector in the bottom part of the table shows the difference in P2X3 transcripts between LS and TL mouse DRG somata.

DRG somata after CYP-induced bladder inflammation, they are associated with different P2X receptor subunits and also different bladder afferent pathways.

The differences between rat and mouse bladder neurons with respect to P2X receptor gene transcripts and purinergic-evoked inward currents reinforces differences between rats and mice with respect to electrophysiological properties of urothelial and non-urothelial L6-S1 DRG somata (46,47). This raises questions about which, if either, rodent species best represents bladder physiology and pharmacology in humans. As previously stated, the contribution of purinergic signalling in humans with respect to the lower urinary tract is uncertain at present. The broader issue about translation of research data obtained in non-human animals to humans is discussed further at the end of this section.

3.2. Cross-organ Sensitisation.

Cross-organ sensitisation represents a different, indirect mode of sensitisation (i.e. the bladder is not the primary afferent sensitiser) and has significant implications for understanding and managing chronic pelvic pain conditions. Potential mechanisms underlying cross-organ sensitisation have been considered elsewhere (38,108,109) and will not be discussed at length here. Rather, the focus will be on sensitisation of bladder afferents initiated by events in other pelvic organs (e.g., colon to bladder, prostate to bladder, and uterus to bladder cross-sensitisation).

Colon-to-bladder. It has been appreciated for some time that patients with irritable bowel syndrome (in the absence of a diagnosis of endometriosis) complain of genitourinary problems and exhibit signs of bladder overactivity, including nocturia, frequency and urgency (110-112). Experimentally, colorectal irritation in rodents (43-45) induces increased contraction frequencies, reduced inter-contraction intervals and altered micturition reflexes.

In the rat, colorectal inflammation sensitises bladder function and bladder afferents. One hour after intracolonic instillation of trinitrobenzenesulphonic acid (TNBS), responses of PN C-fibre bladder afferents were significantly enhanced at distending pressures ≥30 mmHg, as were responses to administration of intravesical capsaicin, bradykinin, and substance P (113). In a subsequent study of rat PN bladder afferents three days after intracolonic instillation

of TNBS, enhanced afferent fibre responses to bladder distension were accompanied by mast cell infiltration and raised neuropeptides in the bladder, a further implication of colon-to-bladder sensitisation (114). In a behavioural study of rats 10 days after intracolonic instillation of TNBS, nociceptive behaviours attributed to the lower urinary tract were significantly increased, consistent with colon-to-bladder and colon-to-urethra cross-sensitisation by C-fibre afferent pathways (115). Similarly, in the mouse, the micturition reflex was significantly altered (increased voiding frequency) seven days after intracolonic instillation of TNBS (45). Non-visceral somatic hypersensitivity was also evident as responses to mechanical and thermal stimulation of both hind paws were sensitised. In a study of retrogradely labelled rat bladder afferent somata in lumbosacral DRG, colonic inflammation enhanced both the peak amplitude of a tetrodotoxin-resistant Na^+ current (see example Figure 2D) as well as neuronal responses to capsaicin, revealing increased excitability of bladder somata (116).

Prostate-to-bladder. Bladder sensitisation is also associated with other pelvic organs but has not been studied as extensively. For example, chronic non-bacterial prostatitis is characterised by genitourinary pain in the pelvic region. Greater than 90% of such patients report urological pain or discomfort associated with urinary symptoms and/or sexual dysfunction, revealing that the bladder is the main organ affected by prostatitis (117). A peripheral, afferent component associated with prostate-to-bladder sensitisation has been documented in rodents. In the mouse, prostate inflammation induced significant up-regulation in the bladder of pro-inflammatory and anti-inflammatory cytokines, NGF (nerve growth factor), as well as T-lymphocyte markers FoxP3, CD4 and CD8 (42). Prostatitis also produced significant functional changes and sensitisation of bladder afferents. After injection of zymosan into the dorsal lobe of the mouse prostate to generate inflammation, bladder function and PN afferent responses to bladder distension were measured after 7-28 days. Cystometry revealed increased bladder contraction frequency that persisted for the 28 days of testing. Similarly, visceromotor responses to bladder distension were significantly enhanced after prostate inflammation (Figure 7C) as were responses of PN afferents (Figure 7A), characterised by an increased response magnitude and a decreased response threshold. Normally, 20-25% of mechano-sensitive PN bladder afferents have high thresholds for response to stretch, but this proportion progressively decreased after generation of prostatitis (with a phenotypic switch from high to low threshold afferents; Figure 7B). In a rat model of non-bacterial prostatitis, produced by 5% formalin injection into each ventral lobe, prostate-to-bladder sensitisation was assessed by examining bladder activity and the functional properties of L6-S1 retrogradely labelled afferent bladder DRG somata (41). Bladder inter-contraction intervals were significantly decreased and the number of non-voiding contractions during the storage phase were increased. Whole-cell patch-clamp recordings confirmed hyperexcitability of bladder and dichotomised afferent somata (prostate and bladder double-labelled somata; see example in Figure 8) after prostate inflammation. Sensitisation was more robust in double-labelled DRG somata than in somata labelled only from the bladder, ascribed to be related to "direct" *vs* "indirect" sensitisation mechanisms.

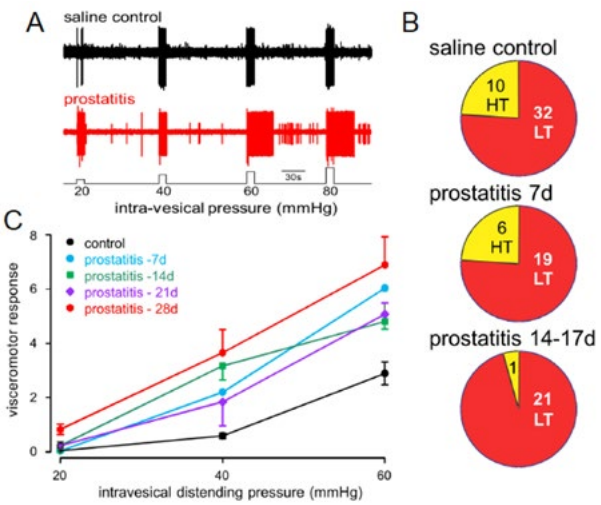

Figure 7. Prostatitis: sensitisation of bladder afferents and visceromotor responses after experimentally-induced prostatitis in the mouse. *A: representative pelvic nerve bladder afferent responses to bladder distension 7-10 days after intra-prostate saline or inflamogen (zymosan) injection. B: Numbers of low-threshold and high-threshold stretch-sensitive pelvic nerve bladder afferents from control and prostatitis (zymosan-treated for 7- or 14-days) mice. C: bladder visceromotor responses (normalised to control) at three distending pressures during zymosan-induced prostatitis. Adapted from (42).*

Uterus-to-bladder. Uterus-to-bladder cross-sensitisation is evident from the coexistence of UCPPS in women with dysmenorrhoea. Even in the absence of overt bladder pain syndrome, women with dysmenorrhoea experience bladder pain hypersensitivity (118). About 25% of women with dysmenorrhoea, when challenged by a non-invasive oral water ingestion test (118), reported bladder pain nearly as severe as those diagnosed with bladder pain syndrome (119); they also reported widespread non-visceral somatic hypersensitivity. The self-stated severity of their menstrual pain was predictive of the bladder pain evoked by water ingestion. They also reported more non-menstrual pain, including reduced vaginal pressure thresholds, dysuria, and dyspareunia. These findings of unappreciated bladder hypersensitivity in women with dysmenorrhoea suggest that an easy-to-administer water ingestion test may identify those at greater risk for development of UCPPS, and this provides an opportunity to examine whether early intervention could modify that risk (6,120,121). There is relatively little non-human experimental evidence at present regarding uterus-to-bladder afferent cross-sensitisation. It has been reported that two hours after administration of mustard oil into the rostral part of the right uterine horn, plasma extravasation in the bladder was significantly increased (108). Of interest, uterine horn-to-bladder cross-organ sensitisation occurred only in proestrus, not metoestrus, and sensitisation was absent with hypogastric nerve transection.

Dichotomising afferents. The potential contribution of so-called dichotomising afferents to cross-organ sensitisation is an appealing, but indeterminate underlying mechanism at present. The concept that dichotomising neurons (afferent endings of one DRG soma innervating two different tissues) contribute to referred visceral pain is not new (7,38). The concept re-gained currency with evidence from the primary afferent innervation of the rodent colon and bladder (122-124) and rodent prostate and bladder (Figure 8; 41,42,125). The reported proportions of double-labelled DRG somata range between 14-21% for colon and bladder and 7.5-18% for prostate and bladder. Given that the visceral innervation generally represents a relatively small proportion of all spinal afferents (5-10%; 10), and the proportion of dichotomising axons arising from DRG somata innervating the viscera comprise no more than a fifth of this fraction, only a limited role can be ascribed at present for dichotomising afferents in cross-organ sensitisation.

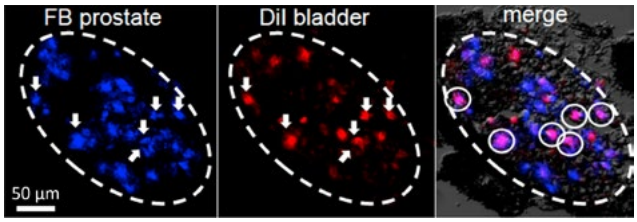

Figure 8. Dichotomising afferents. *Retrogradely-labelled somata in the same mouse L6 dorsal root ganglion (dashed line boundary). Left, fast blue label; middle, DiI label; right, merged image. Arrows in the left and middle panels identify somata that were labelled from both the prostate and bladder, circled in the right panel. From E Schwartz E, J-H La and GF Gebhart, unpublished.*

4. ADDITIONAL CONSIDERATIONS

4.1. What Constitutes a Visceral/Bladder Nociceptor?

Implied or explicitly stated in much of the literature on bladder afferents is that nociceptors are a component if not the focus of study. The conception and classification of an afferent receptive ending as a nociceptor derives from Sherrington's studies of stimuli that he described as "nocuous" (noxious) because they damaged or threatened damage to tissue and thus were "adequate" for the sense of pain (57,58). Specified as a receptive ending that responds to a noxious stimulus, the nociceptor was thus defined in a functional context (and not by axon myelination/conduction velocity, size of neuron somata, etc., although contemporary transcriptomic research approaches are clarifying the 'barcodes' of human nociceptors – see below). Two points of clarification are important: firstly, the tissue upon which Sherrington worked was skin; and secondly, Sherrington fully appreciated the distinction between pain (a conscious perception) and nociception (the neural process of encoding noxious stimuli). As the study of nociceptors grew, largely based on studies of skin, reconsideration of nociceptor properties, particularly visceral nociceptors, generated continuing discussion and debate, in part because the viscera had long been regarded as insensate (7,9,10). Subsequent clinical and experimental evidence documented the sensibility of the viscera and efforts continue to clarify the structural and functional basis of visceral sensation and pain.

Our view of what constitutes a visceral/bladder nociceptor has been informed by affirmation that afferent endings in the viscera/bladder possess two important, obligatory properties of nociceptors: 1; the ability to encode stimulus intensity into the noxious range and 2; to sensitise. Firstly, bladder afferents with low response thresholds to distension encode stimulus intensity well into the noxious range (Figure 3) and similar findings have been made in other tissues: e.g. group III (Aδ-fibres) and IV (C-fibres) skeletal muscle afferents (126); joint afferents (127), and C-fibre mechano-sensitive cutaneous afferents (128). Accordingly, despite existing definitions of nociceptors as high threshold sensory receptors, growing evidence establishes that the property of encoding into the noxious range is not limited to afferent endings with high response thresholds. Importantly, cutaneous, muscle, joint, and visceral mechano-nociceptors with low response thresholds are indistinguishable from non-nociceptor mechano-receptors, which do not encode stimulus intensity into the noxious range (61). Moreover, the slope of hollow organ visceral/bladder afferent encoding functions to organ distension is generally greater for low threshold afferents than for high threshold afferents. Similarly, the response magnitude to noxious intensities of bladder distension is greater for low threshold than for high threshold afferents (Figure 3B). Secondly, both low and high threshold visceral/bladder mechano-sensitive endings sensitise (Figure 6). In addition, spontaneous activity and previously ineffective stimuli may become effective (i.e. "adequate"), including other modalities of stimulation (chemical, thermal, etc.) as most visceral/bladder afferent endings are multi-modal in character. Collectively, these findings document that visceral/bladder nociceptors include those with thresholds for response in the physiological range. This is clinically relevant in patients with organ insult or inflammation as well as those diagnosed with so-called 'functional' disorders that exist in the absence of documentable organ pathology.

4.2. Translation of Research to Humans.

The broad issue about translation of research data obtained from non-human animals to humans requires consideration with respect to the relevance of what has been presented above. Regarding bladder afferents and nociception, the translation of results to humans requires consideration of the component parts of afferents: neuronal somata in DRG and receptive endings/afferent fibres.

Neuronal somata in the DRG. The use of dissociated DRG cell cultures to study nociceptive processing is based on two fundamental assumptions. The first assumption is that what is expressed and contained in the neuron soma is faithfully represented in the receptive ending, and this is generally accepted. The second assumption is that a dissociated cell culture represents *in vivo* conditions, and this is known to be incorrect. Moreover, the extent to which it is incorrect depends on many factors (culture medium, time in culture, presence of other cell types in the culture) that requires evaluation.

Furthermore, the above differences between rat and mouse bladder afferent DRG somata with respect to purinergic signalling and to the electrophysiological properties of urothelial and non-urothelial L6-S1 DRG somata raise concerns about which, if either, species better represents bladder physiology and pharmacology in humans. This is of considerable importance, given their widespread reliance as experimental animals. Initial studies suggested that gene expression of potential targets for development of analgesics was not dissimilar between mouse and human DRG somata. As noted above with respect to the $P2X_3$ receptor, the P2rx3gene is expressed in ~70% of mouse bladder DRG ganglion somata (88) and its expression correlates reasonably well in human and mouse DRG somata (89). This recent RNA-sequencing study of mouse and human DRG somata (89), found conserved enrichment of most transcription factors in mouse and human DRG somata, suggesting similarities between mouse and human. Accordingly, it was tentatively concluded that the mouse DRG was a reasonable model system for studying human DRG.

To return to the use of dissociated DRG cell cultures as model systems. It is appreciated that DRG somata removed and cultured acquire an injury-like transcriptomic phenotype. This is evident from the increased expression of genes associated with nerve injury or inflammation in cultured mouse and human DRG somata and has implications for use of DRG cultures to model sensory neuron physiology and pharmacology (129). In addition, when comparing expression profiles of putative pain-relevant genes in human and mouse DRG, the expression of G-protein-coupled receptor and ion channel gene families specifically expressed in neurons were markedly lower in culture, and also not all genes detected in intact DRG were expressed in culture.

In a study when RNAscope *in situ* hybridisation compared parallel neuron populations in mouse and human DRG, interspecies differences were apparent (130). Based largely on mRNA-expression studies of mouse DRG somata, putative nociceptor populations have been identified: peptidergic nociceptors (CGRP-expressing somata), non-peptidergic nociceptors and larger diameter somata that express NF200 and classed as mechano-nociceptors. This template, however, is not representative of human DRG somata, in which a large, overlapping subpopulation of CGRP and $P2X_3$ receptor co-expressing DRG somata is apparent (130). In addition, there were also significant differences between mouse and human DRG somata in the expression of mRNAs for $TRPV_1$ and $TRPA_1$ receptors, nicotinic cholinergic receptors, as well as Na^+ and K^+ channels. Although mRNA expression does not always reliably project protein expression, these findings challenged the translatability of findings in the mouse DRG to the human DRG.

The above findings were based on bulk sequencing approaches. More recently, a near-single DRG neuron spatial transcriptomic study of human lumbar cells has uncovered additional significant differences between mouse and human gene expression in DRG somata (131). At least ten clusters of human DRG somata, exhibiting distinct expression profiles were identified: six were classed as C-fibre nociceptors, one as an Aβ-fibre nociceptor, one as an Aδ-low threshold mechano-receptor and two as Aβ-low threshold mechano-receptors. Clusters of putative nociceptors included those classed as cold, itch or silent nociceptors. This granular analysis also evaluated sex differences, noting several that may be relevant for therapeutic drug development. Of interest, although many of the same G-protein-coupled receptors are expressed in both human and mouse DRGs, their cellular expression and distribution within DRG somata differ. Moreover, the distinction in mouse DRG somata between peptidergic and non-peptidergic nociceptors, upon which considerable weight rests relative to drug development, is non-existent in human DRG equivalents. Most human DRG somata classed as nociceptors express neuropeptide, $TRPV_1$ and $NTRK_1$ (NGF receptor), exposing a combination of several markers in the human that distinguish in the mouse putative peptidergic from non-peptidergic nociceptors. Collectively, these recent studies, employing increasingly advanced tools, reveal that the general translatability of findings in mouse DRG somata to human DRG somata is low, leaving open the question whether another animal species is a better model.

The studies performed to date in human DRG somata have used lumbar DRG which contain few, if any, visceral afferent somata. Thus, it is not known if visceral afferent somata are the same or in some way distinguishable from the results described above. One could imagine, given that stretch/distension is a common, natural noxious visceral stimulus, that mechano-sensitive channels/receptors might be expressed at a higher level in visceral afferent DRG somata. Alternatively, genes not included in the studies cited above may be important for visceral nociception. Future studies will clarify whether there are tissue-specific nociceptors whose 'adequate' stimulus is represented by a distinctive pattern of gene expression.

Receptive endings/afferent fibres. Electrophysiological studies of visceral afferents have a substantial history from which to draw inferences about translation to human afferents. Bladder afferent recordings in cats documented early-on that mechano-sensitive endings responded to bladder filling. Subsequent studies in rats, guinea pigs and mice described subsets of mechano-sensitive endings with low or high thresholds for response to bladder filling/distension/stretch. In rats and mice, C-fibre and Aδ-fibre axons were associated with both low and high threshold afferent endings. Moreover, when tested, many mechano-sensitive bladder afferent endings also exhibited chemo- and/or thermo-sensitivity and were thus revealed to be multi-modal. Finally, mechanically insensitive, silent afferent endings have been documented in the bladder. The studies on afferent endings from different species reviewed above suggest that findings in non-human animals translate well to human afferent physiology.

Although there have been no reported electrophysiological recordings of bladder afferents in humans, relevant information about mechano-sensation and nociception is available in the human microneurographic literature. Developed in the mid-1960s by Swedish investigators in Uppsala, microneurography is the technique of recording nerve action potentials in resting, fully awake humans using a metal microelectrode inserted percutaneously into a nerve (a personal history of microneurography has been published recently, 132). The great advantage of microneurography is the ability to easily switch between intraneural nerve recording and stimulation modes and thus incorporate psychophysical detection into the study. Accordingly, microneurography has successfully revealed functional properties of afferents subserving touch and pain (in addition to its application to the study of sympathetic efferent fibres). For example, intraneural stimulation of rapidly adapting low threshold mechano-sensitive afferents is associated with sensations of tapping, tickle and vibration, depending on the frequency of stimulation, and linked to Meissner's and Pacinian corpuscle end organs. Slowly-adapting low threshold afferents are associated with the sensation of pressure and linked to Merkel's disk (e.g. 133-135). Intraneural stimulation of Aδ-fibre mechano-nociceptors produce a sensation of sharp pain, whereas stimulation of C-fibre nociceptors produce sensations of itch or dull/burning pain (associated with C-mechano-sensitive endings or C-mechano-heat [C-MH] endings, commonly referred to as polymodal nociceptors, 136). C-MiHi (mechano- and heat-insensitive, or "silent' nociceptors) are also present in human cutaneous tissue (137). Importantly, there is close correlation between the number of action potentials evoked from human C-fibre nociceptors by intraneural stimulation and the temporal pattern of discharge with psychophysical estimates of stimulus intensity and perceived sensation, respectively. Similarly, intraneural stimulation of group IV (C-fibre) mechano-sensitive (deep pressure) skeletal muscle afferents produce a sensation of cramping pain (138,139). Microneurography has also documented the presence of C-fibre tactile receptors that respond vigorously to gentle skin stroking and, when stimulated intraneurally, produced hedonic ratings that subjects reported as pleasant at higher firing rates (140). Recently, A-fibre high-threshold mechano-receptors that encoded noxious skin indentations, but were unresponsive to gentle touch, were described in human skin (141). Of interest, the pain produced by intraneural stimulation was associated with thickly myelinated axons (i.e. Aβ-fibres) and described as an "ultrafast system for signalling mechanical pain", consistent with the presence of Aβ-fibre nociceptors in many non-human animal species (56).

The foregoing is the result of microneurographic studies of superficial nerves innervating the skin, typically the peroneal or superficial radial nerve, and knowledge about human visceral afferents in general or bladder afferents in particular is not available. However, what is known from human microneurographic studies and the study of visceral/bladder afferents in non-human animals suggests reasonable translation of studies of afferents in non-humans to humans. Rodent bladder afferents exhibit mechano-sensitivity, chemosensitivity, thermo-sensitivity, and multi-modality as well as mechanical insensitivity, as do human skin afferents. In an evolutionary context, one might consider innervation of human skin as highly developed with respect to sensibility and interaction with its

environment in comparison to the innervation of internal organs in non-human species. However, the same fundamental sensibilities are represented in both tissues, although the breadth of sensitivities and proportions of afferent types are certainly different.

The functions of human DRG somata classed as 'nociceptors' remains to be determined independently of expression profiles of receptors and channels, peptide content, etc. However, contemporary research approaches applied to human DRG somata and afferent fibre recordings in human tissue samples will contribute to and clarify our appreciation of the visceral/bladder innervation. Recent electrophysiological recordings of colon afferents from human tissue samples have already opened this avenue of research (142-144) for translation of findings from studies in non-human animals. It is anticipated that a similar approach could be applied to the study of human bladder afferents.

II. INTEGRATIVE FUNCTIONS OF THE BRAIN IN LUT CONTROL

1. BACKGROUND AND OVERVIEW OF THE CONTROL NETWORK

Loss of bladder control (urgency urinary incontinence, UUI) is a common and morbid condition that is often refractory to treatment by drugs, conservative measures, or electrical stimulation at spinal, peripheral, or brain sites. Regarding UUI, the neural control committee of the previous International Consultation on Incontinence (ICI-6) concluded that "The fact that voiding and continence are under forebrain control is now well established (145)." The elements of this control were summarised in a 'working model' showing the regions of the brain believed to be most important for bladder control, and their interconnections (Figure 9; 146,147). This section will concentrate on bringing the working model up-to-date by incorporating newly published knowledge. Furthermore, measurement of connectivity in the brain will be considered and will include sections on the effect of neurological disease (in particular, multiple sclerosis; MS) on brain maps and connectivity. Finally, there will be a consideration of what can be learned about UUI from deep brain stimulation (DBS) of patients with Parkinson's disease (PD), many of whom have concomitant UUI.

1.1. Neural Control.

The basis of control is a long-loop, spino-bulbo-spinal reflex (the voiding reflex) that acts as a switch between the two phases of micturition (148) - urine storage (or bladder filling) and voiding (bladder emptying). The rostral terminus of the reflex comprises two brainstem or midbrain nuclei: the pontine micturition centre (PMC) and the periaqueductal grey (PAG). The PAG has numerous forebrain and limbic projections, some of which enable bladder afferents to be relayed to regions of the forebrain where sensations such as desire to void or urgency are generated. Moreover, signals descending from cortical or limbic regions act on the PAG and modulate firing of the voiding reflex, thus maintaining continence or promoting voiding as appropriate. According to the current version of the working model, as the bladder fills signalling from bladder afferents increases, so progressively exciting the PAG. When PAG activity attains a critical trigger level, it excites the PMC, which is believed to send a descending signal to the sacral spinal cord and, *via* spinal circuitry, make the urethral sphincter relax and the bladder contract

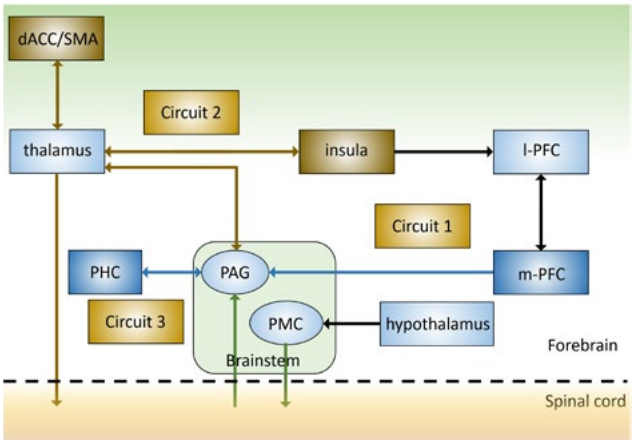

Figure 9. The bladder control network, working model of the forebrain. *The PAG and PMC form the rostral terminus of the voiding reflex and together act as a switch between the two phases of the reflex. The PAG receives ascending afferents from bladder. It also propagates into and receives signals from circuits-1, -2 and -3, to allow forebrain modulation of the switching action. Key - PHC: parahippocampal area; dACC/SMA: dorsal anterior cingulate cortex/supplementary motor area; PAG: periaqueductal grey; PMC: pontine micturition centre; l-PFC: lateral pre-frontal cortex; m-PFC: medial pre-frontal cortex.*

and empty, i.e. the reflex switches to the voiding phase. This basic automatic reflex behaviour is modulated by input to the PAG from cortical and limbic circuits, so enabling generation of sensations such as desire to void or urgency as well as voluntary control of voiding (148). Thus, according to this model the PAG is activated during bladder filling, and the PMC is quiescent, while the PMC is active during voiding and passive during filling.

1.2. The Working Model of Forebrain Control.

The working model described above relies to a considerable extent on the results obtained by a few research groups (149,150). Data have typically been generated by recording a functional magnetic resonance imaging blood-oxygen-level-dependent (fMRI BOLD, henceforth fMRI) signal during performance of a 'task' such as repeated infusion and withdrawal of fluid into and out of the bladder. Since ICI-6, other publications dealing with this topic have used a variety of methods or tasks (e.g. functional connectivity, regional homogeneity, resting-state fMRI, and diffusion-tensor imaging). Although this variety hinders direct comparison with the working model, the use of several different methods may disclose important complementary facts that otherwise would remain hidden. This section will examine whether and how the working model needs to be revised in the light of the continued development of methods that examine brain function and anatomy.

1.3. Midbrain Involvement

Periaqueductal grey matter (PAG). As explained above, the PAG modulates autonomic functions such as micturition, serving as a bridge between higher decision-making brain centres and lower centres responsible for reflex voiding. It may be affected in many disorders, including multiple sclerosis (MS), stroke, idiopathic normal pressure hydrocephalus, Parkinson's disease and multiple-system atrophy. It is critical for the basic understanding of voiding and storage disorders and is a potential candidate for diagnostic and therapeutic interventions. For example, deep brain stimulation in humans (DBS; section II.4.1) that targets the PAG increases bladder capacity. PAG involvement is discussed further in section I.2.2.

A review of PAG function (151) has provided more detail about how signals ascending from the bladder are processed in the PAG with the help of the PMC (Figure 10). The afferent bladder-distension signal first reaches the ventrolateral column of the PAG (vl-PAG), from where it may trigger excitation of the PMC and thereby induce bladder contraction without requiring any modulation from higher brain centres. In the rat the vl-PAG projects to a nucleus of the thalamus, and thence to the insula. The signal ultimately reaches the medial prefrontal cortex (mPFC) where, in humans, conscious, voluntary control can be exerted (Figure 10). The return projections from the medial prefrontal area reach predominantly the dorsolateral PAG (dl-PAG). Part of this pathway has been mapped out in the mouse (152). The medial preoptic area of the hypothalamus may provide additional signalling, ensuring a safe start to voiding. This network of connections provides continuous monitoring of incoming signals regarding the level of the bladder fullness and the state of the environment, and ultimately enables a decision about the feasibility of voiding (152). A recent study, using 7T-fMRI with human subjects, demonstrated a parcellation technique which showed the presence of within-PAG connectivity related to state of bladder fullness (153), setting the stage for future detailed investigations of this integral component of the model.

Thalamus, basal ganglia and limbic brain structures.
It has been suggested that electrical stimulation of the subthalamic nucleus and PAG inhibits micturition and improves urinary incontinence, whilst stimulation of the ventral intermediate and ventral posterolateral nuclei of the thalamus induced micturition (154). Other subcortical targets in the basal ganglia for modulating micturition and urodynamic parameters include the globus pallidus, where deep brain stimulation can ameliorate detrusor overactivity in some patients but can also worsen maximum flow rate and post-void residual volume. In patients with neuropathic pain, deep brain stimulation of the PAG dramatically increases maximum cystometric capacity (MCC; 155) - the volume at which patients ask for an artificial saline infusion to be stopped (urgency) - but it does not affect the volumes at which voiding is desired and where there are strong and very strong desires to void.

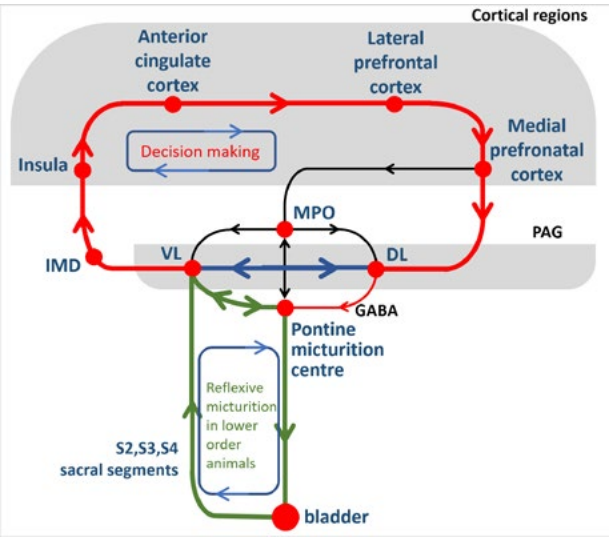

Figure 10. Schematic diagram of the organisation of the PAG. *Two loops, the decision-making and reflexive micturition feedback loops, are active in higher- and lower-order animals, respectively. Key – VL: ventrolateral column; DL: dorsolateral column; IMD: intermediodorsal nucleus of the rat thalamus (analogous to mediodorsal nuclei of the human thalamus); MPO: medial preoptic area of hypothalamus.*

The pedunculopontine nucleus (PPN).
The PPN is a brainstem nucleus in the rostral pons that differs from either the PMC or the PAG described in the working model. It may be identical to the "L-region" introduced by neurophysiological experiments in the cat (156,157) and is believed to be a "pontine continence centre". Stimulation of the PPN acts on the bladder in an inhibitory manner but does not appear to be a clinically useful as a target for treatment (158).

The L-region. The L-region first described neuroanatomically and later by its response to electrical stimulation, has an inhibitory effect on the bladder, probably mediated by stimulation of the urethral sphincter mechanism (156,157).

The bed nucleus of the stria terminalis (BNST).
The BNST is emerging as a critical region in disorders such as anxiety, post-traumatic stress disorder, panic disorder, as well as alcohol and substance misuse (159). It is also a region within which viscero-motor and viscero-sensory signals converge (160). Animal and human studies have examined connections of the BNST and their impact on BNST function. Structural connections between the BNST and insula (part of circuit-2, Figure 9) have been described in rodents, and recently by Pang et al (161), who found evidence of a BNST-insula structural connection in humans. It would be interesting to examine whether the BNST also mediates urinary tract disorders such as urgency urinary incontinence.

2. CONTINENT ADULTS: HUMAN STUDIES OF BLADDER STORAGE, FILLING AND VOIDING

2.1. Overview.
Since ICI-6 several papers have been published which have a bearing on the validity of the working model. Whether for historical reasons or for reasons of convenience, the filling phase has been more commonly investigated in females and the voiding phase in males. Studies generally require use of a 'task' that defines what is actually measured; for example, repeated bladder filling is a commonly used task. Alternatively, in some studies 'imagined voiding' has been used (150), whereby the subject imagines initiating voiding without actually doing so. Differences in these tasks, while hindering direct comparison of studies, may reveal subtle differences in the control mechanism related to different parts of the micturition cycle.

2.2. The Voiding Phase
Relatively few groups have investigated real voluntary voiding, most likely due to practicality. One group (150) investigated the central regulatory mechanisms activated during micturition in 22 healthy males. They used as the 'task' an alternating sequence of micturition phases: imaginary voiding, initiation of voiding (divided into early and late), and actual voiding. Despite the best of intentions, not all subjects were able to void in the scanner. Those who could (voiders) showed prominent supraspinal activity during the late phase of initiation, particularly in the brainstem (PAG, pons), insula, thalamus, prefrontal cortex, parietal operculum and cingulate cortex; with significant functional connectivity between the forebrain and parietal operculum (Figure 11). Subjects unable to void in the scanner (non-voiders) showed less activation during initiation of attempted micturition, particularly in the forebrain and brainstem. It

was deduced that micturition is controlled by a specific supraspinal network which is used for voluntary initiation. Once the network has been triggered, micturition normally continues automatically without further supraspinal input until the bladder is empty. This suggests that the micturition cycle may best be described not just by two phases (storage and voiding) but a more complicated switching action of storage, initiation of voiding and then maintenance of voiding. The network involved includes not only the brainstem (PAG, pons) but also the insula (the seat of interoception - or perception of sensations from inside the body, 162); the thalamus (a way-station); the prefrontal cortex (executive decision-making); and the cingulate cortex (functional connectivity between prefrontal regions and parietal operculum). Within the reflex pathway, projections from S2, the sensorimotor area in the parietal operculum, enter the temporal lobe and limbic structure via the insula (Figure 11). S2 is thought to be important in recognising the nature of a more-or-less painful stimulus such as 'urgency'. Most of the regions identified in this network are near to similar regions in the working model, thus providing some support for this revised model. Moreover, once voiding has been initiated by a barrage of descending bladder neurons, maintenance seems to require little or no further neural activity, but only myogenic elasticity or 'tone'.

Figure 12 shows that the difference between voiders and non-voiders is in fact real and significant. This suggests that the cortical sensorimotor area (in particular the parietal operculum) is part of the mechanism of voiding. Furthermore, brainstem regions such as PAG and pons (PMC) are more strongly activated in voiders than non-voiders.

2.3. The Storage Phase

Given the constraints of fMRI scanning, it is simplest to investigate brain control of the bladder in a steady state. As such, resting state fMRI analysis at discrete bladder volumes can give some insight into fundamental functional differences based on continence status, thereby establishing foundational knowledge of relevant mechanisms. While this technique lacks the ability to measure acute changes occurring with dynamic bladder stimulation, it might suggest regions of interest for further interrogation with additional techniques.

fMRI analysis in a single bladder state.

'Resting state' analysis has become popular and offers the opportunity to identify subtle differences between subgroups of individuals without the addition of a complex task, i.e. at rest. Additionally,

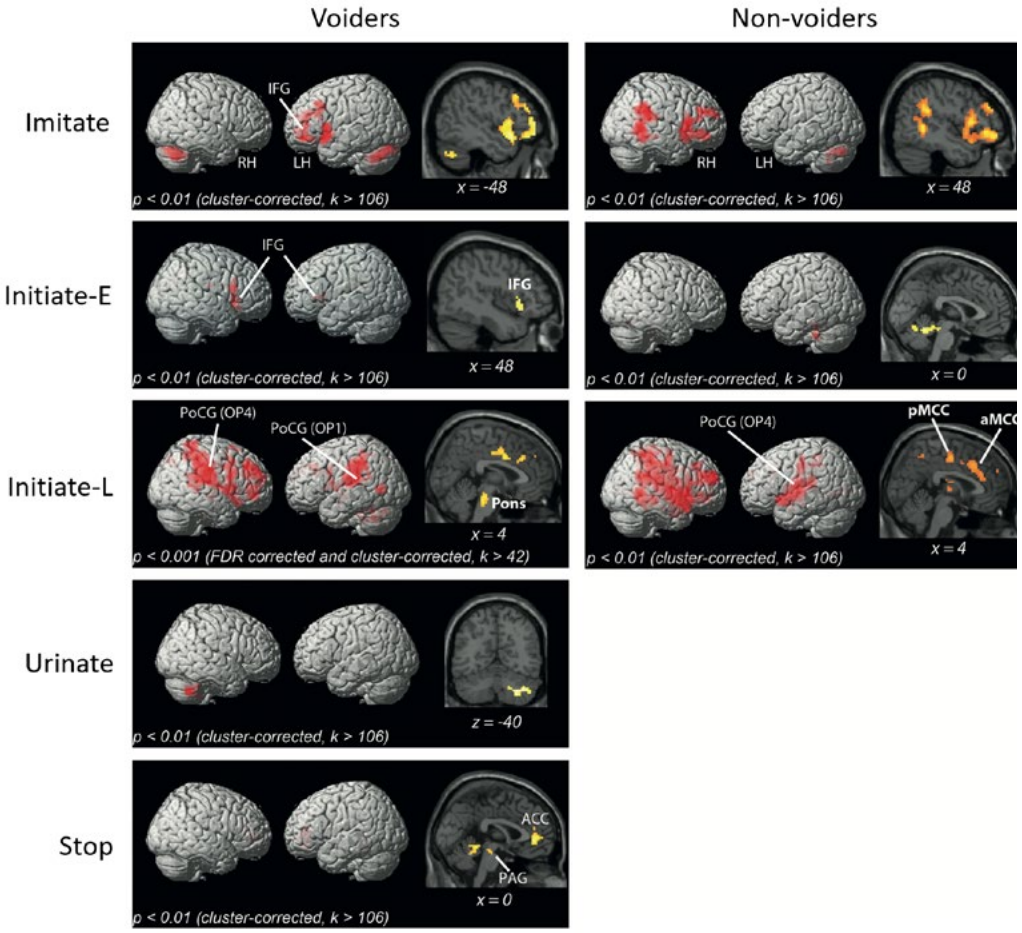

Figure 11. Bladder control in normal males during the voiding cycle. *Voiders (left, n=14) and non-voiders (right, n=7). Imagined voiding (Imitate) activates modestly parts of the forebrain in both voiders and non-voiders. During initiation of voiding there is at first (Initiate-E) minimal excitation, followed by (Initiate-L) strong excitation in cortex and pons in both voiders and non-voiders. Finally, during actual voiding (Urinate) there is very little excitation: voiding continues automatically, normally until the bladder is empty (Stop). Key – LH/RH; left/right hemisphere: IFG, inferior frontal gyrus: PoCG, postcentral gyrus: OP, parietal operculum: aMCC/pMCC, anterior/posterior midcingulate cortex: ACC, anterior cingulate cortex: PAG, periaqueductal grey. From (150) with permission.*

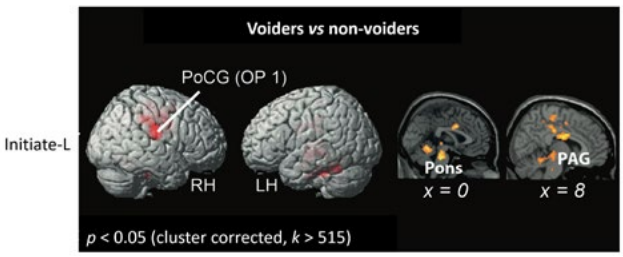

Figure 12. Bladder control in normal males, voiders and non-voiders. *Difference between voiders and non-voiders. During the late initiation phase (Initiate-L), there are significant differences between voiders and non-voiders in the parietal operculum, pons and PAG. The parietal operculum includes the secondary sensorimotor area S2 and is thought to be important in helping to recognise the nature of a potentially painful stimulus, possibly such as urgency. Key – LH/RH; left/right hemisphere: PoCG, postcentral gyrus: OP, parietal operculum: PAG, periaqueductal grey. From (150) with permission.*

evaluation of functional connectivity between identified regions or within established brain networks aligns with an increasingly network-focussed view of brain control mechanisms. Connectivity measures can be evaluated at rest and during stimulus tasks (such as filling) using generalised psychophysiological interaction analysis (section II.3.1 - *connectivity*). Connectivity is a measure of brain activity which evaluates the temporal connections between regions and has given rise to an understanding of networks such as the Default Mode Network (DMN), typically engaged at rest. Resting state functional connectivity (RSFC) is a measure of this connectivity at rest. In bladder studies this is typically performed with a full and/or empty bladder. One might evaluate the RSFC of seed regions known to regulate the bladder to identify baseline differences according to continence status: RSFC strength may be a predictor of the potential to activate the appropriate circuitry when necessary. Alternatively, connectivity measured during a bladder 'task', might highlight circuitry which fails or may be augmented with successful therapy.

Resting state and functional connectivity in continent adults.
Resting-state fMRI (rs-fMRI) has been used to identify brain areas related to bladder sensation in several studies of continent participants. Gao et al. (163) measured regional homogeneity (ReHo) in 30 participants at rest, with both an empty bladder and at 'strong desire to void'. ReHo is a voxel-based measure of brain activity which evaluates the similarity or synchronisation between the time-series of a given voxel and its nearest neighbours (164). In general, homogeneity was greater when there was strong desire to void, especially in the prefrontal cortex (PFC), anterior cingulate cortex (ACC), hypothalamus, temporal lobes and left caudate nucleus, indicating that these regions might play an active role in attending to the full bladder. The cortical areas (ACC and PFC) are similar to those in the working model, lending support to their involvement in the cerebral control of bladder storage.

The use of graph analysis found topological changes in the brains of continent women between empty and partially filled (after infusion of 100 ml fluid) bladder states (165). Specifically, reduced global efficiency in the Salience Network (SN), Dorsal Attention Network (DAN), Default Mode Network (DMN) and Central Executive Network (CEN) was found, as well as changes to local efficiency in the Salience and Sensorimotor (SMN) networks in a fuller bladder. This suggests a shift in focus to attend to bladder-associated networks. Similarly, Pang et al. (166) found decreased global efficiency in the full *vs* empty bladder state, with increased functional connectivity in the DMN, medial frontal cortex, inferior and superior frontal gyri, and the cingulate gyrus, known to be important regions of the continence mechanism.

Mawla *et al*. (167) evaluated changes in amplitude of low frequency fluctuations (ALFF) between an empty and 'fuller' (after ingestion of 350 ml) bladder state in 62 continent men and women. ALFF is a measure of regional spontaneous neuronal activity which may reflect pre-disposition to certain conditions. Anterior cingulate cortex, supplementary motor area and pre-frontal cortex showed ALFF decreases with increasing urinary urge. Additionally, PAG connectivity with the cingulate cortex, motor area, prefrontal cortex and right insula was associated with increasing urinary urge and bladder volume. Further linear regression of the brain networks revealed increased SN, SMN and DMN connectivity with bladder volume as seen by Pang *et al.* (166). Zhao *et al*. (168) used ALFF analysis to identify seed regions which changed between the empty and 'fuller' (200 ml infusion) bladder state to examine changes in connectivity. Their analysis confirmed that the connectivity between the pre-frontal cortex, insula, and cingulate gyrus, components of circuits-1 and -2 of the working model, plays a role in continence control of healthy bladders.

These resting state analyses suggest that throughout all stages of bladder filling in continent adults, from infusion of 100 ml to 'strong desire to void', the brain focus diverts from the default resting networks, which are active with an empty bladder, to regions and networks known to be involved in continence control and highlighted in the working model.

2.4. The Filling Phase.
Regular clinical studies allow for inter-subject variation, but not for variation between different trials, because they are performed in different centres, or use slightly different protocols. Meta-analyses can take into account this source of variation.

A meta-analysis based on 14 different studies of 181 healthy adults between 1997-2015, examined brain activation in response to experimental bladder filling (169). It revealed significant activation of the fMRI signal in brain regions that includes thalamus, right insula, cerebellum, brainstem and right PAG (Figure 13). These regions (apart from those in the cerebellum) belong to, or are located close to, circuit-2 of the working model. Among the six areas shown in Figure 13; the insula, thalamus, and PAG appear in similar locations in the working model, supporting the idea that they are activated during bladder filling (the storage phase). The case of the thalamus deserves special mention: it not only gives and receives signals to and from the PAG but may also have direct access to the spinal cord, as suggested in Figure 1. Of interest, of the cortical regions most important in the working model, the anterior cingulate cortex (ACC) was only seen in men and the medial prefrontal cortex (mPFC) was not replicated in this analysis of healthy subjects. This may reflect the type and variety of bladder filling tasks included. PFC activity may only occur when there is a desire to void that is less likely to be reached in those with good bladder control.

Comparison of bladder filling with rectal distension.
Adults with pelvic floor disorders commonly present with overlapping bladder and bowel symptoms. To further investigate this phenomenon a meta-analysis of responses to rectal distension has been carried out (170). It showed that different areas of the brain were activated by rectal distension and by bladder filling, apart from the right insula, which was activated by both. The insula is involved in interoception and sensory processing in general (162) and so it

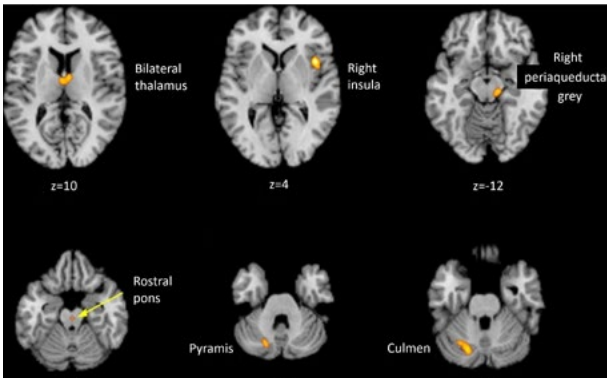

Figure 13. Areas of the brain activated during bladder filling in healthy adults. *Meta-analysis of 14 neuroimaging studies with 181 subjects showing regions activated during bladder filling: bilateral thalamus (4,-4,10; -2,-6,10); right insula (42,22,4); right periaqueductal grey (12,22, -12); rostral pons (0,-22,-20); pyramis (posterior lobe of cerebellum; -20,-72,-28); culmen (anterior lobe of cerebellum -28,-64,-26). Adapted from (169) with permission.*

is not surprising that it registers urgency of both bladder and rectum. Overlapping of activations in the insula may enable interaction between rectal and urinary function, in both motor and sensory aspects.

3. NON-NEUROGENIC LUTD: HUMAN STUDIES OF BLADDER STORAGE, FILLING AND VOIDING

3.1. The filling phase.

Several imaging studies of bladder filling have been published. A trial of biofeedback-assisted pelvic floor muscle training for urgency urinary incontinence in 62 older women (171) used a common 'infusion-withdrawal' bladder filling task. A small control arm (*n*=11) showed only weak activations of questionable significance. Of 62 women with UUI, 28 subjects responded to training (responders) and showed a reduction of dorsal ACC (dACC) activation after treatment, potentially a reduction of circuit-2 involvement upon reduction in symptoms. The remaining non-responders showed marked deactivation of the medial prefrontal cortex (mPFC) during rapid filling of the bladder. It was suggested that this unexpected observation might signify that the mPFC was the origin of a cortico-pontine pathway conveying executive control to the PAG - a part of circuit-1 that was revealed in a mouse model by optogenetic methods (172).

Nardos (173) and Ketai (149) used similar bladder filling tasks (multiple infusion/withdrawal cycles to induce a strong desire to void or urgency) to identify key brain areas involved in continence control. These regions were subsequently used as seed regions for resting state connectivity analysis (Section II.3.2). Differences in activation between those with UUI and continent controls were investigated (149). According to the working model this manoeuvre should activate typical regions of circuit-2, the interoceptive network. As anticipated, brain responses to infusion were greater in those with UUI than controls. In both, changes were greater when infusion was greatest and with a large amount in the bladder. Figure 14 shows differences in activation between UUI patients and controls during an infusion phase with a high fill rate. Infusion is associated with activation in the region labelled dACC in Figure 14, slightly anterior to the region with the same name in the working model. Similarly, infusion corresponds to activation in the anterior and posterior insula and ventrolateral PFC, which correspond to the insula in the working model. Thus, there is reasonable correspondence with circuit-2.

A main-effects analysis of UUI *vs* continent controls (173) identified 28 regions of interest that had significant differences in activity over an infusion-withdrawal cycle. These regions included the ACC and insula, also corresponding to circuit-2. Specifically, the ACC showed significant differences in how activity changed over the infusion-withdrawal cycle between different bladder volumes and continence status groups. The ACC may be the driver of, or main responder to, urgency within circuit-2.

Connectivity (the filling task).

An evaluation of functional connectivity between seed regions of interest (174) identified in previous studies (171) was carried out. Here, a small control group was compared with a larger study of pelvic floor muscle therapy. Significant connectivity changes between seed regions identified from the working model between groups were seen, but these did not survive multiple-comparison correction. Connectivity differences were seen at baseline (pre-therapy) and tended towards 'normal' in successfully treated UUI subjects, specifically there were connections between: the insula and primary motor cortex; insula/dACC and primary visual cortex; and prefrontal cortex and midcingulate. The reported changes in functional connectivity reveal a potential 're-training' effect in treatment responders, whereby brain activity becomes more like that of continent individuals. Conversely, the connectivity patterns in the non-responder group were either already similar to the continent group pre-treatment ('re-training' unnecessary) or did not change 'toward' the continent group after therapy ('re-training' unsuccessful). This led to the proposal that these changes may reflect therapeutic mechanisms associated with behavioural retraining of PFMT. The subgroup dif-

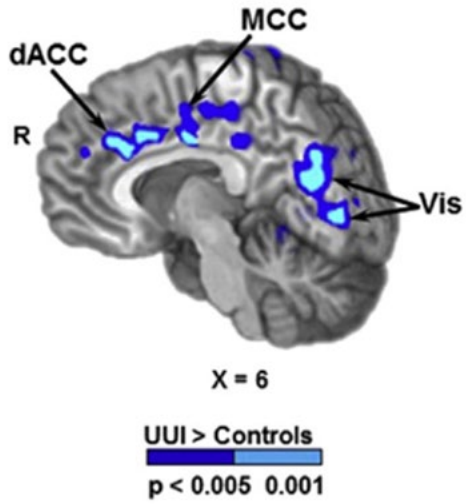

Figure 14. Bladder filling in patients with urgency urinary incontinence (UUI). *Differences in activation between controls and UUI patients during high fill rates. Magnitude of p-values denoted using dark blue (p<0.005) and light blue (p<0.001). Sagittal (X) slice locations according to the Talairach atlas. Key – dACC, dorsal anterior cingulate cortex: MCC, middle cingulate cortex: Vis, visual cortex. Adapted from (149) with permission.*

ferences in the changes may reflect the effect of underlying phenotypes of UUI which require different treatment approaches - e.g. brain re-training *vs* bladder-targeted approaches.

3.2. The Storage Phase. Resting state functional connectivity (RSFC).
RSFC has been evaluated in women with OAB/UUI, using a graph theory technique (175), or by studies that used seed regions identified from task-based studies (149,173): all compared OAB/UUI to continent controls. Changes in functional connectivity strength between OAB/UUI and continent patients in the superior frontal gyrus, middle frontal gyrus, anterior cingulate and precentral gyrus with an empty bladder (175) were also found to be predictive of UUI; using a Support Vector Machine (SVM) analysis (173) of connectivity differences between full and empty bladder states. A comparison of RSFC was carried out between responders and non-responders to pelvic floor muscle therapy, all with an empty bladder (174). The caudate, putamen and cerebellum/culmen had both significant differences in connectivity according to therapeutic success in this study and exhibited differing connectivity according to continence status in another study (173). By contrast another study (149) found differences in connectivity, dependent on continence state, between the mid cingulate cortex and dorsolateral and ventrolateral prefrontal cortices with an empty bladder. Methodological and analytical differences in these studies, such as selection of connectivity seeds and quantitation method, preclude making robust claims about their concurrence, but there is significant qualitative overlap in regions with connectivity differences dependent on continence state and treatment outcome. These regions could give insight into successful compensatory control mechanisms or mechanisms of treatment that would allow prediction of success.

4. NEUROLOGICAL TREATMENT OF URGENCY URINARY INCONTINENCE (UUI)

4.1. Deep Brain Stimulation (DBS).
The nuclei of the basal ganglia and their connections are often targetted by deep brain stimulation (DBS, 176). DBS is an emerging therapy for neurological diseases, especially Parkinson's disease, where it improves the motor symptoms found in severe disease. Specifically, stimulation of the subthalamic nucleus or the globus pallidus internus – parts of the basal ganglia – can improve urinary symptoms such as OAB or voiding difficulty. During the past few years, DBS has gained acceptance as an experimental treatment for intractable incontinence in patients with neurological diseases such as Parkinson's or multiple sclerosis (MS: 177,178) and animal models have also been developed (179).

DBS can improve conditions such as intractable incontinence, and the site of stimulation may indicate particular elements of the brain/bladder control system with possible lesions. However, the subject population exposed to DBS is biased towards patients with conditions such as Parkinson's, so that little can be discovered about normal function. Additionally, such invasive treatment may not be appropriate for those without concurrent neurological disease. DBS is typically performed using stimulation by electrical pulses delivered via a multi-lead electrode (180) implanted in defined regions of the basal ganglia – usually the subthalamic nucleus or the globus pallidus internus (178). The parameters of the stimulating pulses may continue to be adjusted for some months after implantation. This enables the clinical response to be optimised (176) but makes comparisons between studies more difficult, as standardised protocols cannot always be established.

The effect of DBS on urinary symptoms.
A review of the effect of DBS on autonomic function (154) emphasised that, depending on the specific target in the brain, DBS can raise or lower blood pressure, normalise the baroreceptor reflex, alter the calibre of bronchioles and eliminate abnormal excessive sweating – all through modulation of the sympathetic nervous system. In particular, DBS improves cortical control of the bladder and directly induces or inhibits the micturition reflex (178).

The effects of DBS on urinary function during voiding and storage in 416 patients with advanced Parkinson's disease (307 males and 109 females) were evaluated (178). With the use of standard symptom scales, the aim was to determine if DBS of the globus pallidus pars interna (GPi) or the subthalamic nucleus (STN) could improve lower urinary tract symptoms. Scores on LUTS items at baseline and after 12 months for the GPi DBS and STN DBS groups were separately evaluated, and any potential gender-associated differences were also sought. Significant improvement of urinary incontinence and frequency scores occurred in the STN DBS group, and in both men and women. Thus, it seems that the STN could be an important part of the working model. However, the role of GPi DBS is less convincing in this context.

A further clinical study of the effects of DBS on urinary dysfunction in patients with Parkinson's Disease was carried out (177) where the location of DBS was not specified but was presumably optimised at the time of, and in the period following, surgery. Symptoms such as urinary frequency, urgency, and incontinence were notably relieved by DBS treatment. Compared to male patients, DBS surgery significantly improved the AUA-SI (American Urological Association, Symptom Index) scores for urinary symptom and quality-of-life scores, as well as maximum urinary flow rate, detrusor pressure at peak flow, and residual urine volume. It was concluded that DBS surgery is effective in improving urinary function in Parkinson's Disease patients, as primarily reflected by the alleviation of symptoms such as urinary frequency, urgency, and incontinence.

A rat model was used to assess the feasibility of regulating bladder activity by DBS (179). Four potential targets were evaluated: the PAG, the locus coeruleus (LC), the rostral pontine reticular nucleus, and the pedunculopontine tegmental nucleus. DBS of the PAG region inhibited detrusor overactivity, whereas targetting the pedunculopontine tegmental nucleus slightly increased maximum bladder capacity measured during urodynamics. These observations are consistent with human investigations (158).

4.2. Sacral Neuromodulation (SNM).
Two studies have recently investigated the effect on brain function of sacral neuromodulation for treatment of urinary symptoms. Gill *et al*. (181) investigated the immediate effect by cycling a Medtronic Interstim II device on and off *during* fMRI signal acquisition at three different stimulation intensities (sub-, supra-, and at sensory threshold) in six participants. There were functional differences between on-stimulation and off-stimulation cycles at all three sensory levels. Sub-sensory stimulation predominantly generated deactivation throughout the brain, though specifically in the PAG and may suggest a role for SNM in suppression of the voiding reflex. Supra-sensory and at-sensory threshold stimulation predominantly produced activation in the insula and thalamus (Figure 15). While the implications of such results are speculatory, this data provides some evidence that neuromodulation has immediate effects on brain function.

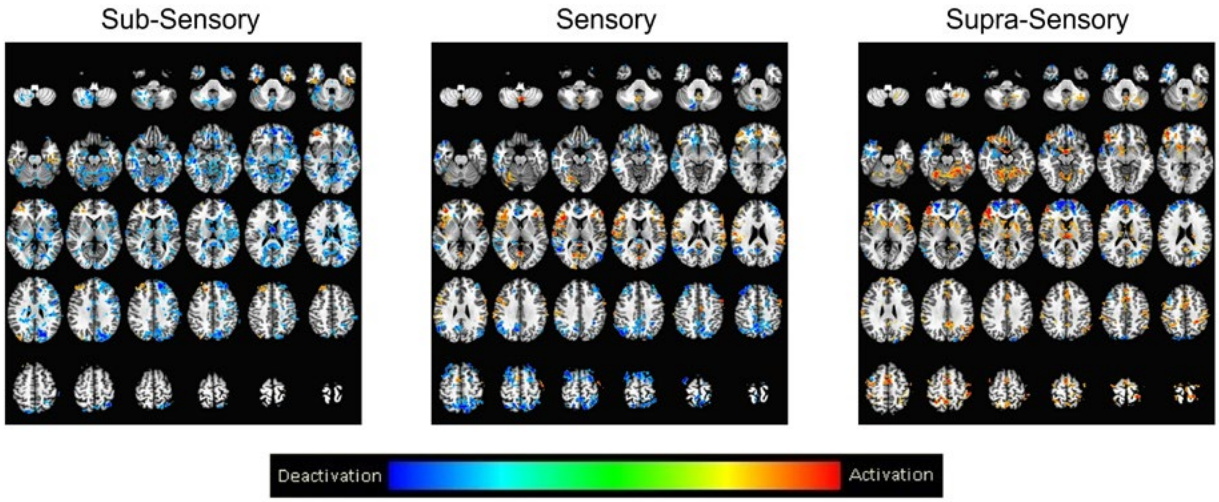

Figure 15. Changes in brain activity during sacral neuromodulation. *Stimuli are set at subsensory, sensory and suprasensory levels. Red areas indicate maximal activation, blue areas indicate maximal deactivation. Adapted from (181) with permission.*

Weissbart *et al*. (182) investigated the therapeutic effect of SNM on the brain by comparing functional brain changes during bladder filling associated before and after six weeks of SNM treatment. Data was compared between those who had successful responses to lead implantation (responders) with those who failed the SNM trial (non-responders). In post-implantation measurements the neurostimulator was 'off' when subjects were in the scanner. Pre-treatment, responders had significantly different activation patterns with bladder filling compared to non-responders; there was greater dACC, right insula, dorsolateral prefrontal cortex, orbitofrontal cortex and right supplementary motor area (SMA) activity. In those who responded, these areas (except the SMA) reduced in activity post-treatment. Because effects of SNM persist for a short time after sustained stimulation, this is a good indicator of a change in brain activity due to SNM itself. These observations are potentially suggestive of activation patterns which might be 'abnormal' and are returned to 'normal' after successful therapy. This is similar to that seen with biofeedback-assisted pelvic floor muscle therapy, where a reduction in dACC and PFC activity was seen in responders to therapy (171). This study did not identify any pontine activity changes. However, the overall reduction in brain activity with successful SNM treatment is consistent with a proposal that its mode of action is related to reduction in brain activity in key continence-related areas and that sub-sensory (the clinical therapeutic level) stimulation produces generalised deactivation (181). It is also consistent with a similar reduction of activity in the prefrontal cortex, cingulate gyrus, cerebellum after SNM (183). The mechanism of action of SNM remains unclear, but these studies suggest avenues for further exploration.

5. STUDIES OF NEUROGENIC LUTD

5.1. Multiple Sclerosis (MS): Structural and Functional Considerations.

Evaluation of urinary symptoms in multiple sclerosis may be a useful tool in addressing the relationship of brain lesion location and extent of the severity of urinary symptoms. Studies have assessed the location of brain lesions in MS patients with incontinence to understand which are more likely to induce deficits in the continence control mechanism. Comparison of the urinary symptoms of MS patients with and without pontine lesions showed no difference, despite the those with MS-related pontine lesions to those without, despite the importance of the pontine micturition centre plays in the voiding reflex (184). There was a weak statistical association between pontine lesion size and both a weak stream and urinary incontinence, but no effect of presence or absence of lesion, which may suggest a threshold size of lesion that might affect continence. A voxel-based lesion mapping system (185) was used to reveal those potentially related to UI symptoms. Lesions tended to affect the frontal and temporo-occiptal white matter, and included para-hippocampal areas, the posterior cingulate cortex, precuneus and cerebellum. A further study showed that specific locations of white matter plaques had an association with urinary symptom severity (186), whereby there was an increased volume of plaques in the cingulate gyrus in those with severe urinary symptoms.

Functional differences of continence control have also been assessed in those with MS compared to healthy controls during strong desire and initiation of voiding (187). MS patients showed increased activation of areas related to: executive function (frontal gyri); motor tone (lentiform nucleus); emotional recognition and attention (cingulate, insula, parietal lobules and precuneus); and anxiety and depression (subcallosal gyrus) at both strong desire and initiation of voiding. In general, there was more activation in those with MS during strong desire to void than healthy controls, and less activation during initiation of voiding. Those with neurogenic detrusor overactivity had increased activation in areas associated with executive function, as did those with detrusor sphincter dyssynergia, who also had increased activation in the cingulate gyrus, caudate and brainstem.

A further study (188) of MS patients compared those with and without voiding dysfunction (VD and non-VD). Multiple areas had reduced activation in those with VD, but of greater importance some regions, such as the PMC, right PAG, left thalamus and left cingulate gyrus, showed deactivation in those with VD and activation in the non-VD group. Overall, the non-VD group resembled healthy controls in activation pattern, though with reduced activity, whilst those with VD showed a distinctly different pattern of activity. A study of the effect of onabotulinumtoxin A therapy on LUTS in MS (189) showed increased activity in areas related to sensation (cin-

gulate, insula and pontine micturition centre) after therapy, but not a level seen in healthy controls.

Overall, MS patients exhibited lesions in brain areas associated with continence control, with different brain activation patterns to controls during voiding initiation and desire. The current literature does not allow us to assess the direct effects of structural damage on function, but further study of brain lesions and concurrent voiding dysfunction may shed light on this relationship.

6. STRUCTURAL CONSIDERATIONS FOR LUTD

6.1. Overview.
It is known that white matter damage causes incontinence by disruption of pathways critical to the continence mechanism as discussed above. Structural abnormalities occur in the forms of white matter hyperintensities (overt white matter damage); reduced structural integrity of white matter tracts (quantified by Diffusion Tensor Imaging, DTI; analysis of water diffusion along and perpendicular to white matter tracts – lower fractional anisotropy denotes poorer structural integrity); and hypertrophy or atrophy of grey matter (volume differences assessed by Voxel Based Morphometry, VBM). These differences may be caused by ageing or disease, and may be causal of, or contributory to, lower urinary tract dysfunction. Many fundamental studies of the relationship between structural brain damage and incontinence have been in those with neurological conditions such as multiple sclerosis (section II.5.1), where lesion mapping may provide insight into loss of function. Here we cover more recent non-neurological UUI-focused work assessing structural differences in those without overt neurological disease and which may provide insight into structural abnormalities that directly relate to bladder dysfunction.

6.2. White Matter.
In an attempt to relate white matter damage to urinary symptoms in non-neurological UUI, the Pittsburgh group (190) found that in women with UUI, after age adjustment, there is a significantly greater white matter hyperintensity burden compared with continent controls. This is true in the whole brain and specifically in the cingulate and superior longitudinal fasciculus. The cingulum itself, the nerve tract that forms the white matter core of the cingulate gyrus and connects components of the limbic system, exhibits lower fractional anisotropy, representing poorer structural integrity, in those with UUI compared to continent controls. Because the cingulum projects between the ventromedial pre-frontal cortex and the parahippocampal areas, this may be an integral structural connection within 'circuit-1' of the working model. Thus, the association between damage in this location and reduction in bladder control is plausible.

Of interest, in the same study (190), the burden of white matter damage was higher in those who responded well to behavioural therapy than those who did not. It was suggested that 'responders' may belong to a phenotype of incontinence caused by disruption of brain control of the bladder; successful re-learning of bladder and pelvic floor control may be associated with strengthening or re-routing of these pathways, specifically the superior longitudinal fasciculus.

6.3. Brain volume.
Assessment of grey matter volume (GMV) may provide an estimate of altered cellular structures (e.g. neuron number or dendritic complexity), potentially indicating reduced traffic to certain brain areas (atrophy), or increased usage of a particular area (hypertrophy). Comparison of GMV via voxel-based morphometry (190) showed relative atrophy of hippocampal and parahippocampal areas in those with UUI, compared to continent controls. Responders to pelvic floor muscle therapy showed hypertrophy pre-treatment in the mid-cingulate area compared to non-responders, potentially related to the poorer integrity of the white matter pathways. A similar grey matter volume comparison of those with OAB symptoms and those without (191) showed decreased volume in the anterior cingulate, hippocampus, left insula (plus caudate, middle frontal gyrus, superior temporal gyrus and cerebellum) in OAB patients compared to continent controls.

A pilot *post-hoc* analysis (192) of responders *vs* non-responders to anticholinergic therapy, assessed pre-treatment, showed non-responders had significantly smaller white matter volume in the anterior cingulate gyrus and parahippocampal areas. Thus, brain areas identified in the working model continue to show significant structural differences when stratified by continence status, and further, by potential continence phenotype.

6.4. Summary.
It is worth noting that structural differences between those with UUI/OAB and continent controls appear in biologically plausible brain areas, consistent with the working model. Incontinent subjects have more white matter damage and potentially related grey matter volume changes within 'circuit-1'. Since UUI and OAB are symptom-based diagnoses, the cause is generally unknown, and whether structural brain changes are causal or coincidental with a common cause cannot be ascertained by these studies. Future studies that evaluate structural and functional brain changes in responders and non-responders to brain (e.g. behavioural therapy) and bladder (e.g. anticholinergic medication) targeted therapies can offer valuable insight into potential causes of UUI and may allow for identification of disease phenotypes.

7. CONCLUSION

7.1. The Working Model.
The body of evidence presented here is largely in line with the working model of bladder control presented in 2.1.2. Variation between study designs, brain coordinate systems, spatial resolution limitations, and the image manipulation techniques required to facilitate group analyses of fMRI studies limits expectation of exact positional concordance in identification of brain regions. However, by incorporating established knowledge of brain function and fundamental science studies, the consensus is that of broad agreement. It is also clear that the identification of brain regions not presented in the working model and an increased focus on the 'network' model of brain control suggests that this working model is a simplification of a complex process, especially when considering the failure of LUT control. Despite this acknowledgement, many regions identified as significant in those with some level of LUT control failure are those outlined in this model; it still represents the integral components of the mechanism.

7.2. Future Work.
Studies thus far have concentrated on the voiding and storage/filling phases of the micturition cycle. It is likely that there are more complex processes regarding initiation and continuation of voiding and the role of sensation and psychological factors related to voiding. These should be considered in future work.

Further, UUI incidence increases with age, as do structural brain changes. It is difficult to identify those changes that may be causal of bladder symptoms, versus those that are coincidental. Careful study and subsequent consideration of the differences associated with UUI in younger people, in specific neurological disease and changes associated with successful and unsuccessful treatment, of different types, will help to parse out these subtleties.

In addition, evaluation of the basal ganglia and other midbrain components are largely missing from our current knowledge-base in humans. These should also be considered in further study of this process.

7.3. Summary.
Evaluation of LUT control is largely symptom-based; it is representative of a highly variable system which is affected by lifestyle factors and often driven by sensation, perception and socially conditioned processes. There are no objective, slow-changing measures that can be monitored to correlate with brain processes. As such, trying to understand the association of UUI with brain control is difficult and requires a careful, iterative process, considering all aspects of bladder function to map out the control mechanism and its associated failures. Here is presented a diverse array of studies which have provided robust foundational knowledge; this foundation should be used to plan confirmatory studies and those which seek to fill in the gaps in knowledge highlighted in this chapter.

III. EFFERENT NERVOUS CONTROL OF THE LUT – A TARGET FOR NEUROMODULATION

1. INTRODUCTION

The motor nerves supplying the detrusor and external urethral sphincter muscles act as a functional unit whose activity is co-ordinated at spinal and supraspinal levels to promote the storage and periodic release of urine. In the event that such control is lost, due to disease or traumatic injury, the ability to manipulate activity of the efferent nerves by electrical means (neuromodulation) presents a therapeutic target for restoring coordinated bladder function. Peripheral nerve stimulation to modulate voiding dysfunction has emerged as an effective alternative to help voiding dysfunction in patients who are refractory to drug treatment. Here the innervation of the lower urinary tract is considered, with a focus on how stimulation of peripheral nerves can be used to restore bladder control following disease or injury to the urinary voiding circuitry.

2. EFFERENT INNERVATION OF THE LOWER URINARY TRACT

The innervation the pelvic viscera has been the subject of several excellent comprehensive reviews (193-195). With subtle species-specific and strain-specific differences (196,197), innervation of the lower urinary tract (LUT) – comprising the bladder and the urethra - follows a basic pattern. Essentially, efferent axons are carried in three sets of peripheral nerves that exit the spinal cord at lower lumbar and upper sacral levels: sacral parasympathetic (pelvic nerves) and thoracolumbar sympathetic nerves (hypogastric nerves) which supply smooth muscle of the bladder and urethra, and sacral somatic nerves (primarily the pudendal nerves) that innervate external urethral sphincter (EUS) or the rhabdosphincter, which as the latter name implies is composed of skeletal muscle fibres (Figure 16). In each component of this circuit, the efferent fibres (sympathetic and parasympathetic) involved in bladder control are intermingled with other nerve types innervating both the LUT and other pelvic organs. Approximately one-third of all pelvic nerve axons are sensory, most of which are unmyelinated (198), with those innervating the bladder body, bladder trigone and urethra being completely segregated from those innervating the rectum (199). There is some evidence for sexual dimorphism: the pelvic ganglion of males contains more than twice the number of cell bodies of spinal preganglionic parasympathetic efferent nerves compared to males (200).

With the exception of the somatic motor neurones innervating the striated muscle of the EUS, which originate in Onuf's nucleus in the sacral cord, preganglionic axons (sympathetic and parasympathetic) carrying information from the spinal cord synapse with autonomic ganglion cells in the pelvic plexus, prevertebral sympathetic ganglia (inferior mesenteric ganglia), paravertebral sympathetic chain ganglia or ganglia on the serosal surface and in the wall (intramural ganglia) of the organs. As befits controlled synchronised contraction of the smooth muscle wall of hollow organs, the postganglionic efferent nerves distribute widely over the bladder surface (201).

Various neurotransmitters, including acetylcholine, noradrenaline, dopamine, serotonin, excitatory and inhibitory amino acids, adenosine triphosphate, nitric oxide and neuropeptides, have been implicated in the neural regulation of the lower urinary tract (194,202,203).

Current understanding of the detailed anatomy and transmitters utilised at the neuroeffector junctions has opened the way for development of pharmacotherapies to normalise bladder and voiding dysfunction. However, despite considerable success in pharmaco-

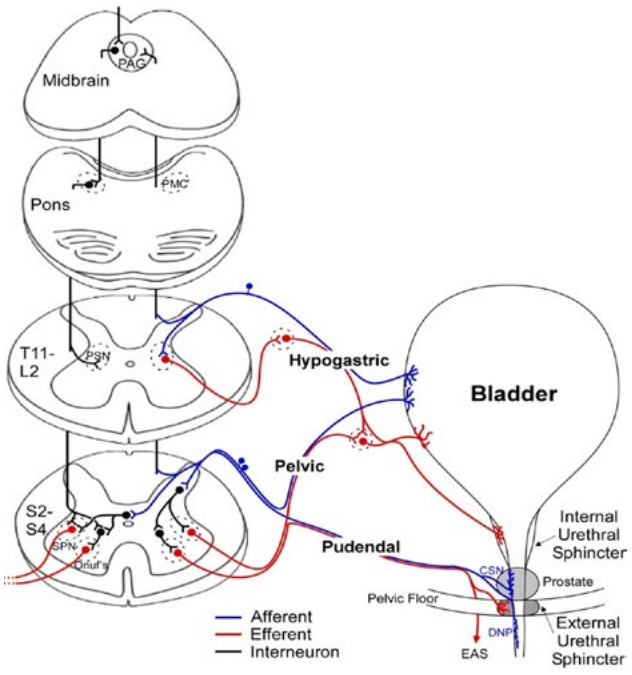

Figure 16. Innervation of the lower urinary tract in males. *Modified from (206) with permission.*

logical management of some disorders, there remains a significant number of patients who are refractory to drug treatment. Even in patients who are responsive, adverse side-effects, often due to actions at other organs, limit drug usage and necessitate a search for alternative therapies that could be tailored to target more specifically patient needs.

3. NEUROMODULATION OF PERIPHERAL NERVE ACTIVITY

3.1. Sacral Nerve Activity to Elicit Voiding.

Electrical stimulation of nerves offers the opportunity to influence storage and voiding by modulating the efferent supply to the bladder. One of the earliest targets for neuromodulation was the efferent outflow to the bladder as it exits the upper sacral cord. Studies in baboons with areflexive bladders following complete supra-sacral spinal cord injuries showed that stimulation of the anterior (ventral) sacral root, which contains efferent nerves supplying bladder and sphincter muscles (S1-S4 depending on species), could elicit emptying of the bladder (204). For efficient voiding to take place, and to avoid bladder sphincter dyssynergia, the urethra and sphincter muscles must relax whilst the detrusor contracts. Whilst sacral anterior root stimulation (Figure 17) activates efferent nerves to detrusor and EUS muscles, its functional effectiveness relies on the differential responsiveness of striated and smooth muscles to stimulation of their efferent nerve supply. A short period of stimulation of motor axons supplying the striated muscle of the EUS elicits a rapid contraction, followed by rapid relaxation once stimulation stops. In contrast, the response of the smooth muscle of the bladder follows a much slower time course so that contraction is still ongoing after the sphincter has relaxed, thereby allowing urine to flow. In this manner, repeated short bursts of stimulation can evoke coordinated voids. In the early stages following spinal cord injury the bladder is typically areflexive but later becomes hyper-reflexive (neurogenic bladder), leading to incontinence. A modification of the technique to include dorsal (posterior) root rhizotomy (Figure 17) to sever afferent inputs and reduce spontaneous reflex contractions of the bladder can improve continence (205).

Recent evaluations of sacral anterior root stimulation with sacral deafferentation (SARS-SDAF) in male and female users have concluded the procedure to be beneficial, with a high level of patient satisfaction, a decline in the need for intermittent catheterisation and fewer cases of involuntary urine leakage; importantly the treatment can remain effective for many years (206-208).

3.2. Sacral Nerve Stimulation to Inhibit Voiding.

Whilst early neuromodulation therapy focussed on efferent nerve stimulation to promote bladder contractions, the development of sophisticated stimulation paradigms now offers the potential to inhibit as well as activate different nerve types by electrical stimulation. In particular, the realisation that efferent nerve activity could be modified reflexly by activation of afferent nerve fibres has broadened the field of neuromodulation to restore control to patients with overactive bladder and urinary urge incontinence. Rather than evoking micturition, continuous stimulation targetting afferents running in dorsal (posterior) roots (Figure 17) is able to reduce bladder excitability and improve continence by reflexly influencing efferent activity (205). Preclinical studies in cats demonstrated that sacral neuromodulation-evoked inhibition of reflex bladder hyperactivity by activation of afferent nerves occurs primarily in the central nervous system, to inhibit the ascending or descending pathways of the spino-bulbo-spinal micturition reflex (209,210). Several recent

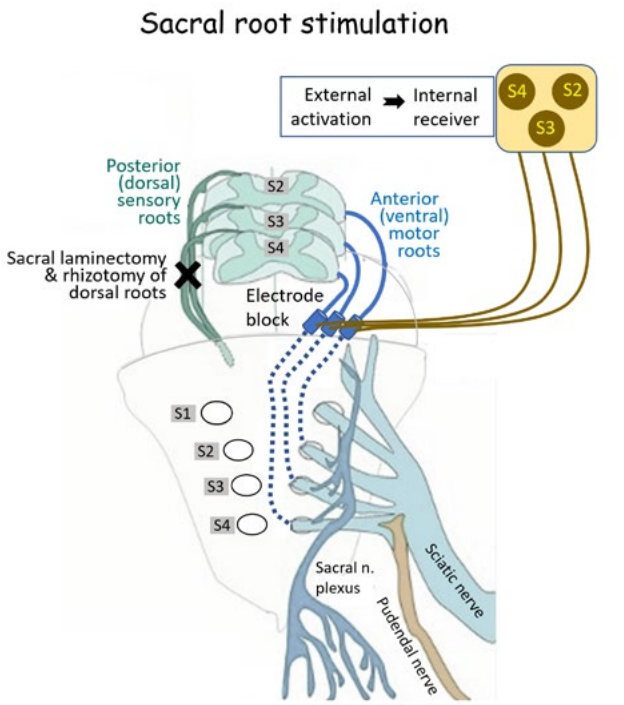

Figure 17. Anatomical arrangement of the sacral nerves. *Shown is the location of a stimulator for anterior root sacral neuromodulation. Adapted from (205).*

meta-analyses confirm the efficacy of sacral neuromodulation in patients with overactive bladder (211-213).

Notwithstanding the success of sacral root neuromodulation, there is still room for improvement. There is ongoing debate over the importance of stimulation parameter selection to optimise functional effectiveness: whether intermittent as opposed to continuous stimulation, or bilateral versus unilateral (214-216). Several recent innovations developed using animal models, may further improve clinical practice. For example, recent experimental work using a spinal injury model in minipigs (217) indicates that very early intervention after spinal cord injury may prevent the development of bladder sphincter dyssynergia without the need for dorsal rhizotomy. Transcutaneous Electrical Spinal Stimulation for LUT functional Augmentation (TESSLA) is a less invasive procedure that can be utilised in patients with spinal injury to either evoke voiding (218,219) or to improve symptoms of overactive bladder (220). The use of epidural stimulation, developed in spinal cord injured rats to elicit voiding, represents another promising minimally invasive procedure (219). Contemporary wireless-powered stimulation technology (221,222) is another innovation that obviates the need for repeated surgical interventions to replace batteries.

4. DISTAL STIMULATION SITES

Despite the considerable technological and surgical advances made since the introduction of the Brindley procedure, one major drawback associated with stimulating large mixed nerve trunks such as the sacral roots is the incidence of non-specific unwanted side effects due to activation of afferent and efferent axons supplying organs outside the LUT. By moving the stimulation site distally towards nerves supplying the target organ (pelvic, hypogastric and

pudendal nerves), the risk of unwanted side-effects should be reduced. It is worth remembering however, that even these peripheral nerves are mixed, at least in rats (198).

4.1. Pudendal Nerve Stimulation.

The pudendal nerve has proved to be one such effective target. This mixed nerve contains afferent and efferent fibres innervating the external urethral sphincter, although a branch to the urethra and external genitalia (the dorsal penile nerve in males) contains only afferent fibres. In humans, pudendal afferent fibres can be activated by stimulating the dorsal genital nerve (DGN) and the procedure has been adopted into clinical practice with some success. Importantly, it can be applied on-demand by the patient outside of the clinical environment. DGN stimulation has proved an effective means to engage and enhance bladder emptying in patients with retention and/or detrusor sphincter dyssynergia, or to normalise bladder function in patients with overactive bladder (OAB) (211,223-225). Although the primary action of DGN stimulation is activation of somatic afferent fibres, the functional outcome is suppression of bladder efferent activity and improvement in urodynamic outcomes in patients with overactive bladder following spinal cord injury (226,227). Indeed, there are indications that DGN stimulation may be superior to sacral neuromodulation for treatment of OAB (227-229). Limited evidence also reports excitatory bladder contraction can be evoked by pudendal nerve stimulation in patients with spinal cord injury (230).

In the cat and rat, electrical stimulation of the pudendal nerve trunk or the DGN at low frequency (5-10 Hz) promotes continence by suppressing bladder excitability, thus reducing spontaneous isovolumetric contractions, and by increasing bladder capacity. Of importance, this effect outlasts the initial stimulation period and also persists after spinal cord transection (231-234). Stimulating peroneal skin, which activates pudendal nerve afferents, inhibits isovolumetric bladder contractions in rats (235).

The effectiveness of pudendal nerve stimulation appears to be both intensity and frequency specific. Due to the electrical characteristics of different fibre types, it is possible to activate selectively different functional classes of axons. For example, low intensities of stimulation (twice the threshold for evoking the pudendal-anal reflex) were optimal to induce inhibitory effects, whereas stimulation at higher intensities facilitated voiding (236,237). In a similar way, low frequency stimulation (5-15 Hz) is optimal to inhibit micturition, whereas voiding can be facilitated in cats and rats by stimulation at higher frequencies (>20Hz), particularly when intermittent stimulation (33 Hz, duty cycle 1-s on, 0.2–0.3-s off) is delivered (231,232,238,239). Low-frequency effects are mediated via a supraspinal pathway whereas high-frequency effects are spinally-mediated (240). Analysis of the fibre types involved revealed that Aβ-fibre activation evoked a long latency, delayed onset effect over several minutes, whereas stimulation of Aδ-fibres evoked responses at short latency (235).

The pattern of activation is another variable which determines the functional effectiveness of stimulation. In humans, micturition is normally characterised by relaxation of the EUS (241) in order to permit urine to be expelled in a stream. In the rat the EUS undergoes a burst of contractions and relaxations during micturition, so urine is expelled in spurts. The pudendal efferent nerves have a median burst frequency of 40 Hz with 3-4 action potentials per burst in rats (242). By adjusting the pattern of pudendal nerve stimulation to evoke burst firing of the EUS, rather than sustained tonic firing, voiding efficiency was enhanced in cats which, like humans, expel their urine in a stream, as well as rats (239,240). The effect was mediated through activation of pudendal sensory pathways (243-244). Presumably the high resistance generated as the bladder contracts against the intermittently closed EUS would lead to a higher rate of pulsatile flow in the urethra during the periods of intermittent relaxation of the sphincter, rather than releasing urine in a continuous stream. Urethral flow at high bladder volumes relaxes the EUS by engaging the spinally-mediated augmenting reflex (245), which further facilitates urine flow.

The early studies of pudendal nerve effects were performed on animals with normal bladder function. However, stimulation has also been shown to be effective in rat and cat models of overactive bladder (234,246). In rats with reduced bladder capacity due to acetic acid-induced irritation of the bladder, pudendal nerve stimulation increased bladder capacity via a β-adrenergic mechanism involving the hypogastric nerves (246). Stimulation of pudendal afferents can also improve bladder emptying in rats with urinary retention following spinal cord transection (231,247), as well as improving voiding efficiency in diabetic rats (243). These studies in animal models provide insight into to the translational potential of amplifying the sensory feedback from pudendal urethral afferents to modulate efferent activity to the bladder and EUS.

4.2. Hypogastric Nerve Stimulation.

Whilst predominantly a sympathetic nerve, the hypogastric nerve also contains sensory afferent fibres which detect bladder distension at normal physiological pressures, as well as a population of nociceptor fibres that become sensitive after chemical irritation of the bladder and likely play a role in the facilitation of the nociceptive bladder activity induced by bladder irritation (248,249). In healthy individuals, activation of sympathetic efferent fibres in the hypogastric nerve evokes a β3 receptor-mediated relaxation of the detrusor in response to distension of the bladder – the guarding reflex (250). Of interest, reflex activation of these fibres by sensory pudendal nerve stimulation increased bladder capacity in rats and cats with irritated bladders, but not in normal animals (246,251). This intriguing finding suggests that the presence of bladder irritation may in some way unmask suppressed sympathetic reflexes, opening new avenues for therapeutic options to treat overactive bladder.

4.3. Pelvic Nerve Stimulation.

The pelvic nerve has recently been re-examined as a potential target for neuromodulation therapy. The nerve constitutes the major efferent supply to the bladder although a significant minority of its fibres are afferent (252). The postganglionic nerve bundles on each side distribute to the entire bladder musculature (201), which ensures that efficient voiding can take place even after unilateral denervation (253). There appears to be sexual dimorphism with respect to the pelvic nerve, at least in the rat where in males the preganglionic pelvic nerve ganglia contain approximately 2.5-times the number of cells compared to females (200). The functional significance of this sex difference is not clear. There is no evidence that ganglion cells modulate transmission of the efferent signal to the detrusor, at least in rats and pigs (254), but local reflex pathways exist between the bladder and the pelvic ganglia, which regulate non-voiding contractile activity (255) and may be involved in bladder fullness perception during urine storage (256).

Early studies using animal models with underactive or areflexic bladders were carried out to examine the potential of pelvic nerve stimulation to enhance bladder contraction and restore voiding function. This goal was thwarted by simultaneous activation of the external urethral sphincter (257). However, by incorporating a sophisticated stimulation paradigm, which permits efferent stimulation whilst blocking afferent activity, bladder-sphincter dyssynergia was

overcome and more than 75% voiding efficiency has been achieved in rats (258).

Stimulation of the pelvic nerve also has potential to normalise overactive bladder. In both rat and cat models of chronic overactive bladder, continuous pelvic nerve stimulation increased bladder capacity measured during single fill cystometry, effectively normalising urodynamic function (259,260). The stimulation was effective within only a very narrow range of parameters. In rats, stimulation at 10 Hz was effective, whereas 1 Hz was ineffective, but only when the intensity was raised to the threshold for evoking reflex activation of the EUS (259). On the other hand, in cats, stimulation at 1 Hz and twice threshold was required to produce a similar effect (259,260).

Promising effects have also been produced by adopting low voltage, pulsed radiofrequency (PRF) stimulation of the pelvic nerve in an acute acetic acid model of OAB (261). Pre-treatment with 5-minutes of nerve stimulation produced an increase of bladder capacity that persisted for at least 3.5-hours. The effective PRF stimulation parameters were 80 ms biphasic pulses at 2 Hz frequency; each pulse comprising 500 kHz sinusoid radiofrequency waves, intensity ±3 V. It has been proposed that PRF stimulation produces extremely high electric fields (E = 45-200 kV.m^{-1}, 37-44°C) that may disturb the neuronal membranes and function, inhibiting abnormal bladder contractions by blocking afferent signals from the bladder to the spinal cord (261). Of interest, in this study the effect could not be reproduced by PRF stimulation of the pudendal nerve, even though conventional low frequency stimulation at this site has been shown to be effective in inhibiting bladder excitability (see above).

A further development in rats is the use of high-frequency stimulation (in the kHz range) of the pelvic nerve to suppress voiding on-demand. In anaesthetised animals 30-s of high frequency (1-3 kHz) stimulation instigated at the onset of an imminent void, suppressed the void by aborting the detrusor contraction and increasing tonic activity in the EUS. Importantly, the effect was rapidly reversible so that voiding resumed within minutes of ceasing stimulation (253,262). The stimulation regimen was similarly effective in conscious rats (263). There were no signs of discomfort to the animal during stimulation or any evidence that long-term implantation compromised normal nerve functionality (263,264). It is not clear how such high frequency stimulation produces functional blockade of the voiding circuitry. Efferent fibres within the nerve seem not to be engaged since stimulation at this frequency range did not evoke bladder contractions (253). A modelling study of the effects of kHz stimulation in small, myelinated nerves predicts that transmission occurs, but the stimulation likely evokes a non-physiological pattern of firing (265). This might lead to transmission failure of efferent activity through the pelvic ganglion as well as functional blockade of afferent transmission through the micturition reflex circuitry at spinal or brainstem level, so that the neural network is prevented from generating a co-ordinated void (253).

Although still at an early stage, pelvic nerve stimulation may have translational potential for management of OAB. In cases of urinary urge incontinence, the ability to suppress rapidly an unwanted imminent void on demand could restore volitional control. However, in humans the pelvic nerve is diffuse and does not lend itself to easy surgical access, unlike the rat where the pelvic nerve is a discrete entity. Advances in laparoscopic techniques and robotic-assisted surgery (the LION procedure, (266-267)) may however, overcome these limitations in humans.

4.4. Tibial Nerve Stimulation.

Activation of somatic afferents in the tibial nerve to therapeutic advantage has emerged as another means to indirectly influence the efferent supply to the bladder. Tibial nerve stimulation has the advantage of ease of access and a lower incidence of side effects and complications compared to sacral nerve modulation (268,269). Patients with refractive overactive bladder and/or pelvic floor dysfunction report a decrease in daytime and night-time voiding frequencies and a reduction in the incidence of urge incontinence following tibial nerve stimulation (270). Tibial nerve stimulation has also undergone limited trials for non-obstructive urinary retention, but results obtained so far are not compelling (271).

Tibial nerve stimulation normally requires visits to the medical practitioner in an out-patient setting to allow percutaneous insertion of a needle above the medial malleolus in order to activate afferent fibres in the tibial nerve. Unlike other neuromodulation therapies, the effects of tibial nerve stimulation persist after the stimulation session (272) but even so, treatment with percutaneous tibial nerve stimulation (PTNS) typically involves 12 weekly treatment sessions followed up with a monthly maintenance programme (81). However, a new generation of minimally invasive implantable stimulators is evolving which employ wireless power transfer (273). By offering non-invasive transcutaneous stimulation with associated cost and safety benefits and allowing patients the ability to stimulate at home and on a daily basis if required, this procedure shows considerable promise in terms of improved outcomes compared with traditional office-based PTNS (274-275).

How activation of somatic afferents produces significant effects on bladder function is still not fully understood; the effect is exceptionally dependent on stimulation frequency. In cats with healthy bladders tibial nerve stimulation at 5-6 Hz, but not at 15 or 30 Hz, induced bladder underactivity by significantly increasing bladder capacity and reducing contraction amplitude (276-278). Studies using rat models also report frequency specificity of effective tibial nerve stimulation, but the optimal frequency ranges differ between different centres (279,280). Both tibial and pudendal nerve stimulation at 5 Hz reduced the frequency of firing induced by bladder distension in spinal cord neurons (281) but only tibial nerve-evoked effects persisted following termination of the stimulation suggesting that the underlying mechanisms are not identical (280,281). Indeed, tibial nerve stimulation is known to engage supraspinal brainstem pathways, in contrast to pudendal nerve-evoked effects, which are spinally-mediated (282).

Of interest, the effectiveness of tibial nerve stimulation may actually depend on activation of fibres in the saphenous nerve (283), which is probably co-activated when electrodes are positioned for tibial nerve therapy (284). In fact, selective saphenous nerve stimulation evoked frequency-dependent inhibition of bladder function in anaesthetised cats (279,285). A pilot study in humans indicates that the procedure offers a promising new intervention for treating overactive bladder (286).

5. NOVEL STIMULATION PARADIGMS

Studies with animal models have considered not only alternative targets for neuromodulation of bladder function but also the optimisation of stimulation parameters. Within a mixed nerve adjusting intensity, frequency, pulse duration, pulse waveform, pattern of stimulation (continuous of intermittent) can lead to selective ac-

tivation of different fibre types and different functional outcomes. Optimal stimulation parameters to evoke the same functional outcome may differ depending on the site of stimulation. Thus, bladder contractions evoked reflexly by stimulating the dorsal nerve of the penis (pudendal nerve afferents) in cats were optimal in response to trains of single pulses or doublets at 33Hz (233). However, bladder contractions evoked by direct stimulation of the spinal outflow to the bladder (pelvic nerve efferent fibres) were optimal in response to lower (5Hz) frequency stimulation (287,288).

At present, stimulators available for clinical use offer only a limited range of stimulation parameters and there is relatively little information available about the impact of programming changes on clinical effectiveness (289). However, investigations in preclinical models suggest that the efficacy of such devices could be improved by increasing the range of available stimulation parameters**.** A more in-depth understanding of the neurophysiological effects produced by different stimulation parameters also has the potential to allow tailoring of stimulation paradigms for specific patient needs and to optimise therapeutic outcome.

Another property of peripheral nerve electrical stimulation, which deserves more attention, is its ability to inhibit rather than excite nerve axons. High frequency stimulation in the kHz range blocks conduction in mammalian nerves, including pudendal nerve efferent fibre supplying the EUS (290-292). Combinations of low frequency (multiples of 10 Hz) stimulation and kHz frequency stimulation can activate some fibre types whilst inhibiting others. Low frequency stimulation of the S2 sacral roots combined with high frequency-induced block of transmission in the pudendal nerve enabled co-ordinated micturition in cats (293). Another elegant study (258) showed it was possible to prevent the development of bladder-sphincter dyssynergia in rats by combining distal low frequency (10 or 20 Hz) pelvic nerve stimulation to evoke detrusor contraction, with high frequency (20 kHz) stimulation at a more proximal site along the pelvic nerves to block afferent fibre-induced activation of the EUS. A similarly imaginative strategy to promote continence in cats with complete spinal cord injury utilised continuous bilateral 5 Hz stimulation of the pudendal nerve to excite afferents and reflexly inhibit bladder overactivity during storage to promote continence. This was combined with periodic 20-30 Hz stimulation to induce reflex bladder contraction and 10 kHz stimulation to block conduction in efferent nerves to the sphincter, thereby enabling low pressure voiding to empty the bladder (294).

Until recently, a major limitation of all implantable stimulation devices has been the finite lifespan of the batteries, with the requirement of surgical intervention for battery replacement. This problem may soon be overcome by the new generation of stimulators driven by wireless-powering (30), or which can be recharged by wireless power transfer (295). The use of time-interfering current technology for non-invasive stimulation, which delivers higher penetration efficiency than transcutaneous methods (296) is another potential refinement. The development of optogenetic technology, which can excite or inhibit the bladder nerve supply (297), and transcutaneous ultrasound technologies for stimulation (298) represent further developments that are paving the way towards a new era of clinically effective neuromodulation devices.

A recent development of great interest is ‘on demand’ or ‘conditional’ stimulation. Sensory feedback-based closed-loop stimulation may offer greater clinical benefit by driving bladder relaxation to increase bladder capacity or inhibit imminent unwanted voids only when bladder contractions are detected. In rats, dorsal penile nerve stimulation, triggered automatically by an increased frequency of bladder non-voiding activity, resulted in bladder inhibition, and a consequential increase in bladder capacity (299). This study demonstrates the feasibility of using the frequency of non-voiding contractions as a trigger event for conditional inhibition of detrusor contractions. In a similar vein, the application of stretchable electronics technology to detect bladder fullness (297) and drive optogenetic stimulation to inhibit bladder excitability and suppress voids is another exciting development.

In the past decade advances in understanding the neurophysiological mechanisms underlying neural control of the bladder, combined with technological advances in stimulation technology mean that therapeutic manipulation of activity in peripheral nerves of lower urinary tract by non-invasive means is becoming an attainable goal for management of LUT dysfunction. This is set to revolutionise neuromodulation therapy to normalise dysfunctional bladder storage and voiding control mechanisms.

IV. THE TISSUES OF THE URETHRA

1. INTRODUCTION (STRUCTURE & FUNCTION)

The muscular tissues of the urethra are composed of an inner longitudinally arranged and an outer circularly-arranged layers of smooth muscle and an outermost striated muscle layer. Inside this muscular tube is the mucosa, that contains a dense distribution of blood vessels, containing vascular smooth muscle cells (SMCs) as well as scattered SMCs in the *lamina propria* (SMC-LP). The contractility of these smooth muscles is enhanced by noradrenaline released from sympathetic nerves supplied via the hypogastric nerves, while smooth muscle relaxation is predominantly mediated by nitric oxide (NO) released by the action of parasympathetic nerves that are conveyed by pelvic nerves (300). In contrast to these autonomic innervations of the urethral smooth muscle, contractions of the striated muscle fibres are mediated by acetylcholine (ACh) released from somatic motor neurons via pudendal nerves (Figure 18).

During the bladder storage phase of the micturition cycle a sustained urethral closing pressure (UCP), that is greater than bladder intravesical pressure (IVP), is generated to maintain urinary continence. The highest closing pressure of 100–120 cmH_2O occurs approximately 3 cm from the bladder neck in the female urethra and approximately 5 cm from the bladder neck in the membranous region of the male urethra (301). Upon sudden rises in IVP due, say, to an increase of abdominal pressure, reflex increases in the UCP known as the ‘guarding reflex’ are developed to prevent urine leakage (250). Prior to the voiding phase, UCP starts to decline so that the bladder can void urine, with a minimal rise in the IVP (Figure 19). Such active opening of the urethral lumen preceding the bladder contractions is nicely visualised using transrectal or transvaginal ultrasound scanning (see supporting information in (302). Such urethral opening results not only from a decline of striated muscle tone, associated with a cessation of bursts in external urethral sphincter (EUS) electromyography (EMG) signals, but also the active relaxation of the smooth muscles.

All muscular components contribute to the closure of the urethral lumen. Animal studies report that the relative contribution of the striated muscle to the UCP is one-third or even less of the smooth muscle (303,304), suggesting a predominant role of the smooth muscle

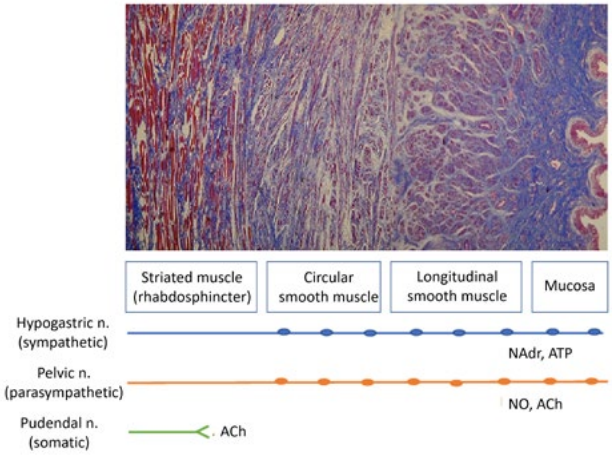

Figure 18. Muscular layers in the urethral wall. *The urethral wall has four major layers. Innermost (right) is the mucosal layer, made up of epithelial cells (urothelial cells in the proximal urethra) and lamina propria. The muscular layer consists of inner longitudinal and an outer circular smooth muscle layers and outermost striated muscle layer. The mucosa and smooth muscle layers receive efferent innervation from sympathetic hypogastric nerves, releasing noradrenaline (NAdr) and ATP, and parasympathetic pelvic nerves releasing NO or ACh. Striated muscle receives innervation from somatic, pudendal nerves releasing ACh. With acknowledgement to the late Prof. Alison Brading, University of Oxford, UK*

layers in developing UCP. This includes the mucosal smooth muscle component of vascular and non-vascular components (305). In humans, the striated muscle layer, the organised smooth muscle layers and the mucosa components are each estimated to contribute approximately equally to the final UCP (306). In contrast, the paramount importance of striated muscles to development of the UCP, both at rest and during physical activity, has also been proposed (307). Such contrasting reports are likely to be due to the difficulty of selectively inhibiting the individual components *in vivo* and therefore estimating their individual contribution.

Because a large proportion of male patients restore urinary continence after radical prostatectomy, smooth muscle, the dominant contractile component in the internal urethral sphincter (IUS)/bladder neck, is often considered to contribute little to urinary continence. Female patients who display an incompetent IUS are also capable of maintaining continence upon rises of abdominal/intravesical pressure, and thus the EUS is considered to play a predominant role in urethral closing (308). Nevertheless, at rest urine is normally stored at a level superior to the IUS in both men and women and preservation of the IUS results in an earlier recovery of urinary continence after radical prostatectomy (309). Therefore, both the 'smooth muscle predominant' internal sphincter and the 'striated muscle predominant' external sphincter contribute to the generation of the urethral closing pressure (310). Because of the differing contractile properties of smooth and striated muscles, the smooth muscles have a larger contribution to generation of a resting urethral pressure, whilst striated muscles play a predominant role in developing transient pressure rises.

Here, the morphological and contractile properties of urethral striated and smooth muscles, as well as the muscular components in the urethral mucosa will be described. Pathological changes, in particular with ageing, and their relevance as a therapeutic target will also be discussed.

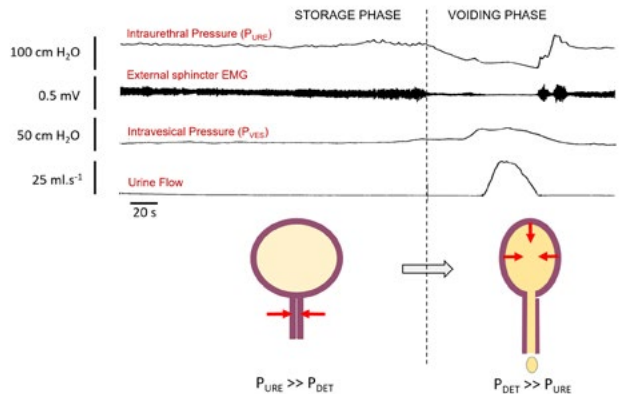

Figure 19. Functions of the urethra during storage and voiding phases. *Four traces from a urodynamic study on an awake subject from top to bottom are: urethral pressure (PURE), external sphincter EMG, intravesical pressure (PVES) and urine flow. The vertical dotted line indicates the timing of 'ask to void'. With thanks to Dr Sarah Knight and Prof Michael Craggs, the London Spinal Cord Injury Centre, Stanmore, UK.*

2. STRIATED MUSCLE

2.1. Morphological properties.

In the human, striated muscles exist along the length of both the male and the female urethra and constitute the EUS, or rhabdosphincter. With the male urethra, striated muscles inferior to the caudal prostate form an omega-shaped dense aggregation of circular fibres in the region of the membranous urethra. This structure runs longitudinally and becomes less apparent towards the bladder (310). With the female urethra, the relatively thick striated muscle fibres begin at the bladder neck and are in a horseshoe-shaped configuration with the opening on the dorsal side (311). Starting at the midpoint of the urethra, the EUS continues to the compressor urethrae and the urethrovaginal sphincter. With the use of immunohistochemical techniques, 3D reconstructions of the muscle structure in the foetal urethra demonstrated different compositions of muscular structures along the urethral length (311). Thus, the proximal third consists of predominately circular smooth muscle fibres, with the middle third of both smooth and striated muscle fibres arranged in circular orientation. The distal third consists of circular smooth muscle fibres surrounded by an omega-shaped layer of striated muscle fibres.

Several animals have provided important models for physiological studies of the urethra. With the male pig, the striated muscle component is less evident cranially, towards the bladder, but forms a thick sphincter caudal to the prostate body that almost completely surrounds the urethra (312). With the female pig, the striated muscle layer starts at the midpoint and becomes dominant in the distal one-third of the urethra (301). In female rats, striated muscle fibres start at the end of the proximal third of urethra and increase to a maximum density in the middle third of the urethra to make up the EUS (313). Thus, the arrangements of striated muscles in the urethrae of the animal models are basically similar to that of human urethra.

2.2. Contractile properties.
In the human urethra, slow-twitch, aerobic, oxidative (type-I) muscle fibres are predominant, whilst fast (type-II) fibres are distributed throughout. Fast (type-II) fibres are subdivided into type IIA (fast, fatigue-resistant) and type IIB (fast, fatigable) fibres distinguished by their differential staining with myofibrillar ATPase or myosin heavy chain isoforms (314). Type I and types IIA fibres are adapted to develop the resting UCP in coordination with smooth muscles, whilst types IIB fibres are recruited on sudden rises if the abdominal/intravesical pressure. In contrast to the human urethra, striated muscle fibres in rat and mice predominantly express fast myosin heavy chains, with a smaller proportion of slow myosin heavy chain fibres (315). This predominance of fast fibres (Figure 20) is consistent with the behaviour of the EUS during voiding which demonstrates oscillatory bursts of EMG activity consistent with a staccato voiding pattern. This differs considerably from that of humans by in whom EUS activity ceases during the voiding period (316).

Contractile activity of the EUS is exclusively regulated by somatic motor neuron inputs from S2-S4 nerve roots originating in Onuf's nucleus, via the pudendal nerve. EUS motor units are highly excitable and easily recruited allowing tonic, synchronous contractions of EUS fibres to efficiently close the urethral lumen (317). The EUS motor pool consists of both fast and slow motor units, and their mode of recruitment depends on the size principle, that becomes evident in spinally-transected animals (242).

In the isolated lower urinary tract of the greyhound dog, pudendal nerve stimulation triggers rapid, transient rises of urethral pressure, while pelvic or hypogastric nerve stimulation causes more slowly-developed and prolonged pressure increases (318). In isolated EUS muscle strips, electrical field stimulation (EFS) at a frequency of greater than 20 Hz develops smooth tetanic contractions that are sensitive to d-tubocurarine, indicating that the contractions are mediated by the activation of nicotinic receptors from neurally-released acetylcholine. In the membranous urethra where fast, fatigue-resistant (type IIA) fibres predominate, the contraction amplitude is well maintained during a prolonged stimulation (319), suggesting that type IIa fibres can contribute not only to phasic activity but also to maintenance of sustained urethral tone.

Striated muscle fibres of the greyhound membranous urethra have a resting membrane potential of -75 mV and are capable of generating action potentials with amplitudes of over 90 mV – i.e. a significant overshoot (318). In myoblast cultures established from the human or porcine EUS, voltage-gated Na^+ channels, that play a fundamental role in action potential generation, have been identified (320). Voltage-gated Ca^{2+} channels, that function as a voltage sensor rather than a Ca^{2+} influx pathway, have also been identified (320). The activation of sarcolemma voltage-gated Ca^{2+} channels would trigger the opening of ryanodine receptor Ca^{2+} release channels located in the sarcoplasmic reticulum, resulting in voltage-induced Ca^{2+} release to contract the muscle fibre. However, detailed descriptions of intracellular Ca^{2+} dynamics in excitation-contraction coupling of EUS muscle fibres, including Ca^{2+} release and sequestration by sarcoplasmic reticulum and/or mitochondria is very limited to date (Figure 21) and deserves greater investigation. Fluorescently-labelled reporter mice have confirmed that T-tubular plasma membrane also express Piezo1 mechano-sensitive Ca^{2+}-permeable cation channels in EUS muscle fibres (321). Thus, Piezo1 channels may well sense urethral wall tension and allow Ca^{2+} influx

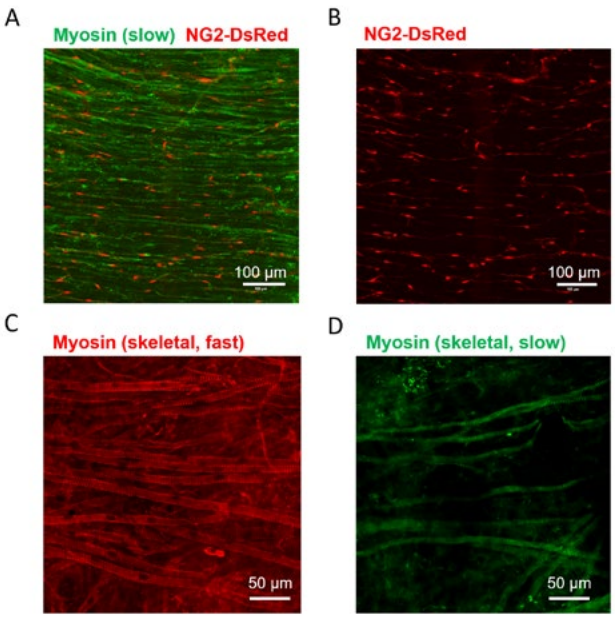

Figure 20. Striated muscle fibre types and capillary network in striated sphincter. *A: slow myosin heavy chain labelling of the striated urethral sphincter of an NG2-DsRed mouse. Small diameter muscle fibres expressing slow myosin heavy chain (green). B: dense network of capillary pericytes in the muscle layer identified by expression of the red fluorescent protein DsRed. C: mouse urethra; dense distribution of thick muscle fibres expressing fast myosin heavy chain. D: sparser distribution of thin slow muscle fibres. Striations seen in both fast and slow muscle fibres. Dr Retsu Mitsui, Nagoya City University, Nagoya, Japan; unpublished data.*

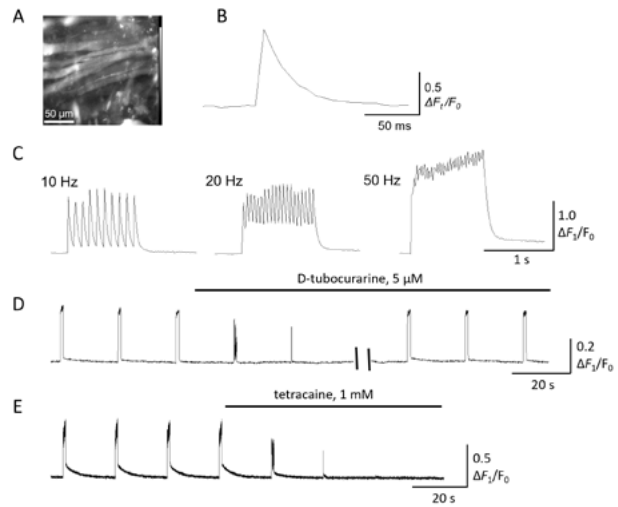

Figure 21. Ca2+ transients in striated sphincter muscle fibres. *A: mouse external urethral sphincter; basal fluorescence image of Cal-520 loaded striated muscle fibres. B: Ca2+ transient induced by single 20 µs electrical field stimulation (EFS). C: tetanic Ca2+ transients triggered by 20 µs EFS pulses at 10, 20 or 50 Hz for 1-s. D: D-tubocurarine (5 µM) abolished EFS (50 Hz for 1s)-induced Ca2+ transients but increasing pulse duration from 100 µs restored Ca2+ transients. E: abolition of Ca2+ transients by tetracaine (1 mM) – EFS stimulation (50Hz, 1s, pulse duration = 100 µs) in the presence of D-tubocurarine. Increasing ∆F/F0 represents a rise of the [Ca2+]i. Prof Hikaru Hashitani, Nagoya City University, Nagoya, Japan; unpublished data.*

into EUS muscle fibres, independently of α-motor neuron-mediated excitation-contraction coupling.

2.3. Nitric oxide (NO).
In EUS muscle fibres of the male membranous urethra, nitric oxide synthase (NOS) immunoreactivity and NADPH diaphorase activity have been detected in the sarcolemma of about 50% of muscle fibres, particularly fast-twitch fibres (322). Although neuronal NOS (nNOS) is also localised in nerve trunks and fibres of pudendal motor neurons innervating EUS, skeletal muscle itself, in general, contains high concentrations of potent NO scavengers that could limit any neurohumoral action of NO. Therefore, NOS located in the sarcolemma or sarcoplasm of EUS muscle fibres could produce NO that acted particularly on closely-neighbouring target proteins.

In healthy males, sublingual administration of an NO donor, reduces not only the resting UCP but also the maximal urethral pressure induced by magnetic stimulation of the sacral roots (323). Nevertheless, since NO functions as a major inhibitory neurotransmitter causing the relaxation of urethral smooth muscles, the site of actions of systemically administrated NO should be carefully considered. In the EUS of the guinea-pig urethra where β-NADPH-diaphorase activity is preferentially expressed at the neuromuscular junction, NO donors reduce peak UCP evoked by pudendal nerve stimulation (324), although NOS inhibition or cGMP blockade fails to enhance resting urethral pressure. In sheep EUS, where distinct nNOS-positive and cGMP immunoreactive striated muscle fibres are distributed, basal cGMP immunoreactivity is strongly enhanced by a PDE5 inhibitor and reversed upon inhibition of guanylate cyclase activity (325). This suggests that nNOS-positive fibres could be the source of endogenous NO, that stimulates cGMP production in neighbouring cGMP immunoreactive fibres. However, pharmacological manipulation of cGMP again failed to modulate nerve-evoked contractions. Overall, cGMP appears not to play a significant role in NO-mediated regulation of the EUS contractile function. In skeletal muscle in general, nNOSμ, the splice variant of nNOS located in the sarcolemma or the inner membrane of the nuclear envelope, plays a fundamental role in NOS signalling via S-nitrosylation of target proteins (326).

2.4. Age-related changes.
In the urethra, the relative volume of striated muscles and blood vessels decline with age and is associated with an increase in connective tissue. However smooth muscle relative volume does not undergo any significant change (327). In both males and females, the density of striated muscle in EUS declines with age, from 87% to 30% over 0 to 90 years, and due to apoptosis and subsequent replacement by connective tissues (328). This indicates that striated muscle in the urethra displays the age-related deterioration known as sarcopenia. However, unlike sarcopenia seen in musculo-skeletal striated muscles (329), mean fibre diameter is not significantly changed, and may reflect the slow twitch fibre dominance in the EUS. Indeed, in the EUS from nulliparous rabbits, in which the proportion of fast and slow myosin fibres is about 4:1, there was a selective decrease in the volume of type-II (fast) muscle fibres and/or conversion of type-II to type-I (slow) muscle fibres, as occurred in the EUS of old multiparous animals (330). In the human female EUS, the density of nerves also declines with age and displays a close correlation with the reduction of muscle fibre numbers (331). Considering the fact that EUS plays a predominant role in preventing genuine stress incontinence (SUI), an age-related decline, particularly in motor neurons and fast muscle fibres may be an important causal factor

The volume and/or strength loss of EUS function in association with SUI has also been demonstrated by clinical measurements. Intraurethral ultrasound examination in combination with urodynamic studies in patients with SUI have demonstrated that reduction of the thickness and contractile function of the EUS correlates well with the severity of SUI (332). Studies using magnetic resonance imaging have reported that patients with SUI have thinner urethral striated muscle than continent subjects, while the thickness of the smooth muscle layers and mucosa are not different between continence and incontinence groups (333). This further suggests a dominant role in the decline of striated muscle volume and function in the pathogenesis of SUI. EUS needle biopsies have confirmed that muscle fibres are largely replaced by connective tissue in the EUS of patients with SUI (334,335). Abnormal EMG recordings of patients are characterised by a reduced number of motor unit potentials and decreased maximum voluntary electrical activity. This indicates that muscle atrophy results from a denervation of α-motor neurons. Older women who have suffered UI symptoms also developed a generalised sarcopenia indicated by a significant decline in their physical performance, specifically standing and balance (336).

In females, the decline in oestrogen levels during peri-menopause and post-menopause periods is a possible aetiological factor in development of SUI. In rats, ovariectomy was associated with a decline in both baseline and active urethral pressure induced by sneezing associated with SUI. Oestrogen replacement partially restores baseline pressure values, but not active pressure or improvement of continence (337), suggesting that oestrogen enhances smooth muscle tone rather than EUS mediated urethral contractile function. However, in humans, oestrogen receptors are predominantly expressed in the squamous but not transitional cell epithelium in the female urethra, while no significant amount of receptor expression is found in the muscle layers (338). Systemic hormone replacement therapy generally worsens SUI, while local vaginal oestrogen treatment may improve SUI (339).

2.5. Plasticity and therapeutic strategies.
Myostatin, a negative regulator of skeletal muscle mass and satellite cell proliferation inhibits proliferation of myotubes developed from EUS satellite cells (340). Inhibition of myostatin, caused an increase of EUS muscle fibre and elastin fibre number, associated with a rise in leak point pressure in rats that had undergone pudendal nerve crush and vaginal distention (341). This suggests that inhibition of myostatin could be a therapeutic strategy for treatment of SIU.

In aged mice, injection of recombinant insulin-like growth factor-1 (IGF-1) into the urethral wall activated satellite cells that became incorporated into existing striated muscle bundles (342). The IGF-1/Akt/PKB pathway controls skeletal muscle growth via mechanistic (or mammalian) target of rapamycin (mTOR), a conserved serine/threonine kinase that forms a multiprotein complex (mTORC1) (343). Since mTOR/mTORC1 plays a critical role in resistance exercise-induced muscle hypertrophy independently of the IGF-1/Akt/PKB pathway, an exploration of the role of this pathway in maintenance and improvement of EUS function would be of great interest.

For women with SUI, pelvic floor muscle (PFM) training increased EUS cross-sections in ultrasound imaging (344) or EUS thickness, cross-sectional area and volume imaged with MRI (345). Thus, PFM training appears to effectively induce hypertrophy of EUS. PFM training may also trigger the release of myokines from trained individuals, as some myokines positively increase skeletal muscle mass (346). If this is the case, a combination of PFM training with

systemic resistance training would be beneficial for the conservative treatment of SIU.

Downstream targets of the protein sonic hedgehog (SHH) that plays a critical role in the development and maintenance of smooth muscle have also been identified in human EUS tissue (347). Nanofibre-based delivery of SHH protein increases the growth of EUS muscle cells, while SHH inhibition results in a reduction in the cell growth, and thus such an approach also offers a strategy to improve regeneration of muscle mass. Several other regenerative strategies for the treatment of SUI have been introduced. Injection of autologous myoblasts and fibroblasts into EUS increases its thickness and contractility resulting in a better improvement of SUI in women compared with collagen injection (348). Periurethral injection of autologous adipose-derived regenerative cells reduces the urine leakage in patients with post-prostatectomy SUI (349).

3. SMOOTH MUSCLE

3.1. Tone development.

There is no doubt that contractions of circular smooth muscle generate a concentric force to narrow the urethral lumen. In contrast, the roles of longitudinal smooth muscle contraction in maintaining the UCP is less readily recognisable. In rabbit urethra, longitudinal smooth muscle cells (SMC) have a higher sensitivity to ACh and demonstrate less pronounced nitrergic relaxations compared with circular SMCs (350). In addition, longitudinal SMCs, compared to circular SMCs, have a three-times greater shortening which suggests a phasic nature of longitudinal SMC contraction (351). Based on such characteristics of longitudinal SMCs, it has been suggested that their contractions result in urethral shorting, which in turn would promote opening of the proximal urethra upon the micturition and reduces overall urethral hydraulic resistance. Nevertheless, because sympathetic nerves project to both circular and longitudinal muscle layers, neurally-released noradrenaline should contract longitudinal SMCs during the bladder filling phase.

In the gastrointestinal (GI) tract, longitudinal muscle is considered to concentrate circular muscle fibres within a fixed longitudinal segment. Such an effect increases the total force available to maintain closure for the same individual fibre force by increasing the number of circular fibres within the segment (352). Conversely, for a given total closure force required to maintain closure of a fixed longitudinal segment, the force per circular muscle fibre is reduced allowing more energy efficient muscle work. Therefore, longitudinal urethral SMCs could also indirectly contribute to the UCP during the storage phase.

Smooth muscles of the urethra, particularly those in the proximal urethra, develop spontaneous sustained tone contributing to the resting UCP (353). With pig urethral smooth muscle, phasic contractile activity is not consistently evident during sustained tone, but phasic contractions become evident during the relaxing phases. Since urethral muscle strips taken from several species develop phasic rather than sustained contractile activity, it was envisaged that the UCP results from the summation of several phasic contractions (Figure 22).

The urethral tone is largely diminished upon the blockade of L-type voltage-dependent Ca^{2+} channels (LVDCCs; Cav1.2) (354,355), indicating that influx of Ca^{2+} via LVDCCs has a fundamental role to generate smooth muscle tone. Consistently, LVDCC, as well as T-type voltage-dependent Ca^{2+} channel (TVDCC)-currents have been demonstrated in SMCs of human and rabbit urethra (356,357).

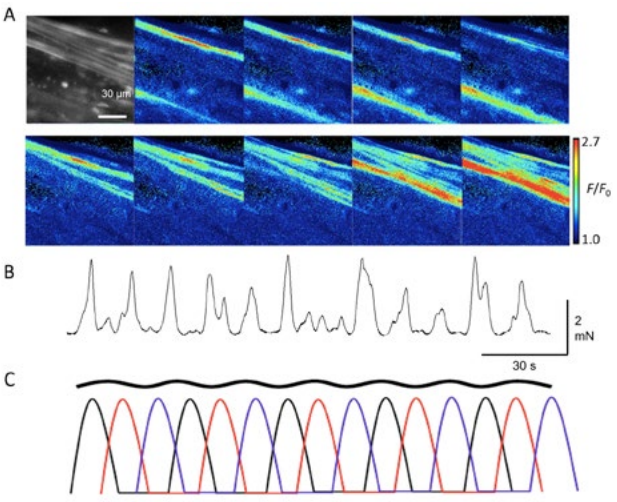

Figure 22. Basis of urethral smooth muscle tone. *A: rabbit urethra smooth muscle bundles; spontaneous Ca2+ transients generated as either 'non-propagating' Ca2+ transients (upper) or intercellular Ca2+ waves (lower): frame interval 100 ms. Modified from [404]. B: spontaneous phasic contractions of muscle fibres exhibit varied amplitudes. C: schematic of spontaneous phasic contractions generated independently in different muscle bundles (black, red, blue). Urethral smooth muscle tone (upper thick black wavy line) is maintained by spatio-temporal summation of the contraction of multiple muscle bundles.*

Ca^{2+}-activated Cl^- channels (CaCCs), anoctamin-1 (Ano1), and also known as transmembrane member 16A (TMEM16A), are expressed in urethral SMCs of sheep, rat and mouse, and their pharmacological blockade diminishes EFS- or noradrenaline-induced contractions (358). This suggests that depolarisation due to the opening of CaCCs depolarises the resting membrane potential to the threshold of LVDCC opening. However, spontaneous Ca^{2+} waves in isolated mouse urethral SMCs appear to arise from release of Ca^{2+} from sarcoplasmic reticulum Ca-stores. This release occurs via type 1 inositol trisphosphate ($InsP_3$) and ryanodine (RyR)-receptor Ca^{2+} release channels, maintained by Ca^{2+} influx through store-operated Ca^{2+} entry but not VDCCs (359).

Sex differences in development of spontaneous tone may be contributed by differential activity of some of the above components. Spontaneous contractile activity was more readily developed by in vitro preparations from female patients and rats than male counterparts (360). The expression level of Ano-1(CaCC) and Ano-1 inward current, as well as dependent increase of $[Ca^{2+}]_i$ were higher in tissue from females compared to males. By contrast, in pig SMCs, where spontaneous tone is predominantly generated by Ca^{2+} influx via LVDCCs, Ano-1 blockers have no effect on the urethral tone, while store-operated Ca^{2+} entry contribute to the tone generation (355).

In pig urethra, the blockade of Rho kinase (ROK) or the inactivation of Rho GTPase diminishes spontaneous tone without reducing $[Ca^{2+}]_i$, suggesting the additional role of ROK-dependent Ca^{2+} mechanisms in developing spontaneous tone (354). RhoA-ROK dependent Ca^{2+} sensitisation in SMCs may arise from inhibition of myosin phosphatase (MLCP) resulting in greater phosphorylation of myosin light chain (MLC). Alternatively, the ROK/LIM kinase/cofilin pathway could cause actin polymerisation to develop smooth muscle contractions. However, in rabbit urethral SMCs, ROK ap-

pears to play a role in developing muscle contractions neither via the inhibition of MLCP or actin polymerisation (361).

3.2. Electrical properties.

Urethral SMCs have a resting membrane potential ranging between -70 mV and -35 mV that varies amongst species and/or circular/longitudinal muscle layers (357,362-364). Urethral SMCs develop individual or bursting spike-like action potentials (357,362). Urethral SMCs also generate spontaneous transient depolarisations (STDs) and electrical slow waves (363,364). In isolated sheep urethral SMCs in which fast-activating LVDCC current and slowly-developing CaCC currents were recorded, the blockade of LVDCCs prevented action potential generation leaving STDs that were abolished after the blockade of CaCCs (365). Thus, CaCCs function as pacemaker currents and the resultant depolarisation triggers the opening of LVDCCs to contract urethral SMCs. Unlike sheep urethral SMCs, in isolated SMCs of rabbit urethra that display LVDCC currents, CaCC currents are seldom recorded, whilst urethral interstitial cells exhibit CaCC currents or STDs (366), see also section IV.5). Similarly, only fast-activating LVDCC currents but not slowly-developing CaCC currents are observed in isolated human urethral SMCs, while interstitial cells display slowly-activating inward currents upon depolarisation and prominent tail currents upon repolarisation, characteristic of CaCC currents (367). In rabbit urethra, slow waves are developed in circular SMCs, while longitudinal SMCs generate action potentials (368). Such differences in the form of electrical activity between the two layers may partly explain the fact that shortening velocity of contraction of the longitudinal SMC layer is greater than the circular SMC layer (351). By contrast, slow waves but not action potentials are generated in the longitudinal smooth muscles of the guinea-pig urethra (364). Thus, there are considerable differences between species differences in urethral electrical activity (Figure 23). Of importance is to demonstrate which animal models provide the greatest translational potential to human urethral activity.

The blockade of LVDCCs diminishes or abolishes action potential discharge (357,368), indicating a predominant contribution of LVDCCs to action potential configuration. LVDCC blockade also inhibits the plateau phase of slow waves to shorten their duration without affecting the initial depolarising phase (363,364). Thus, both action potentials and slow waves permit Ca^{2+} influx via LVDCCs resulting in smooth muscle phasic contractions. In contrast, the blockade of TVDCCs reduces the frequency of action potentials without diminishing their amplitude (357). Thus, TVDCCs may be activated at resting membrane potentials of around -50 mV (351) and any resultant depolarisation would increase the probability of LVDCC-dependent action potential generation (356,357).

In isolated sheep urethral SMCs, blockade of large-conductance Ca^{2+}-activated K^+ (BK) current abolishes the depolarisation-evoked early transient outward currents and also diminishes sustained outward currents, however small-conductance Ca^{2+}-activated K^+ (SK) current has only a marginal contribution (369). BK channel blockade abolishes transient repolarisation of action potentials and increases their amplitude and plateau duration, indicating a fundamental role of BK channels in stabilising urethral SMC excitability. In rabbit urethral SMCs, BK currents are suppressed by the blockade of LVDCCs or RYRs but not $InsP_3$-induced Ca^{2+} release. This suggests that Ca^{2+} influx through LVDCCs triggers Ca^{2+}-induced Ca^{2+} release (CICR) via RYRs to activate BK channels (370). In urethral SMCs taken from mice in which transient receptor potential mucolipin-1 (TRPML1) channels are genetically deleted, spontaneous Ca^{2+} sparks and resultant BK-STOCs are impaired (371). TRPM1 channels localised to the membranes of late endosomes and lysosomes may allow Ca^{2+} release that triggers CICR via RYRs in close vicinity. After suppression of the BK channel currents in USMCs, the blockade of voltage-sensitive K^+ (Kv) channels, predominantly Kv2.1 subtype, increases the amplitude and duration of action potentials of urethral SMCs (356,372). This suggests that Kv2.1 channels function as a backup mechanism to ensure action potential repolarisation. The blockade of ATP-sensitive K^+ (KATP) channels causes a membrane depolarisation (373), and thus a small propor-

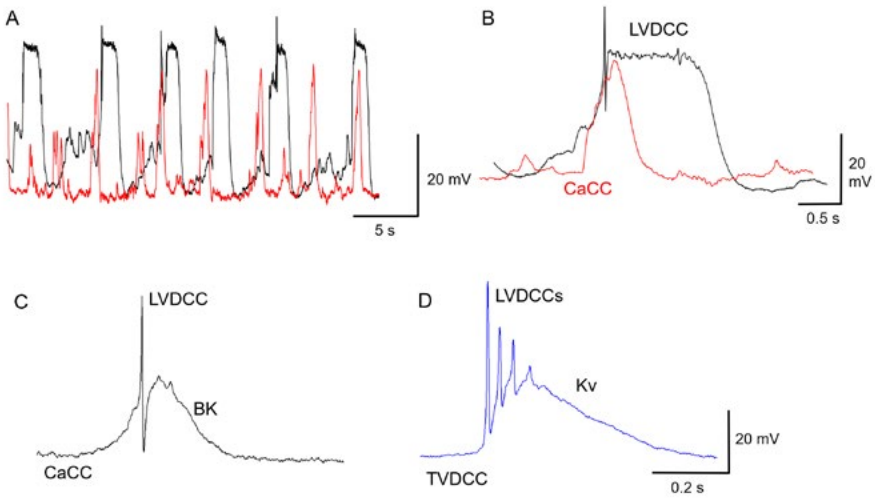

Figure 23. Spontaneous electrical activity in urethral smooth muscle cells (SMCs). *A: guinea-pig longitudinal layer SMCs; slow waves (black) and spontaneous transient depolarisations (STDs, red) on a slow (left) and fast (right) time-base. B: rabbit longitudinal layer SMCs in the absence (left, black) and presence of cyclopiazonic acid (CPA, 10 μM) to block the sarcoplasmic-endoplasmic reticulum Ca pump (right, blue). CPA prevents the transient repolarisation and prolongs action potential repolarisation. Ion channels contributing to different components of slow waves or action potentials are shown: CaCC, Ca2+-activated Cl- channel; LVDCC/TVDCC, L/T-type voltage-dependent Ca2+ channel; BK, large-conductance Ca2+-activated K+ channel; Kv, voltage-sensitive K+ channel. Modified from: A; [364], B [368].*

tion of KATP channels appear to stay open at rest and contribute to the maintenance of the resting membrane potential.

4. SMOOTH MUSCLE NEURAL MODULATION

4.1. Excitatory innervation.

In human urethral smooth muscle, in which the density of cholinergic nerves is much greater than adrenergic nerves noradrenaline causes contractions by activating α-adrenoceptors, whilst in comparison ACh activating muscarinic receptors has no or relatively little contractile effect compared with noradrenaline (374,375). In dog urethra, contractions induced by hypogastric nerves are largely diminished upon the blockade of α-adrenoceptors but not muscarinic receptors, indicating the predominant role of neurally-released noradrenaline to generate urethral contractions (376). In rabbit urethra, EFS-induced contractions in the circular smooth muscle layer are predominantly mediated by α-adrenoceptors activation from neurally-released noradrenaline. The blockade of muscarinic receptors largely diminishes nerve-evoked contractions in the longitudinal smooth muscle (350). Thus, the relative contribution of noradrenergic and cholinergic contractions varies between the circular and longitudinal muscle layers. In addition, there is a regional variation in the neural control of urethral smooth muscle contractility along the length of urethra. In pig urethra, in which the density of sympathetic nerves is higher in the distal than the proximal urethra, sympathetic nerve-mediated contractions are more pronounced in the distal urethra (377). Distribution of cholinergic nerves is uniform along the length of urethra, but larger muscarinic contractions are developed in the proximal than distal urethra (377) (Figure 24).

With circular smooth muscles of the rabbit proximal urethra, EFS evokes an initial excitatory junction potential (EJP) followed by a late depolarisation (378). The initial EJPs are mediated by the activation of α-adrenoceptors, whilst late depolarisations are mediated by neural-released acetylcholine that activate muscarinic receptors. Consistently, noradrenaline depolarises the membrane and increases the frequency of spontaneous slow waves, indicating that neurally-released noradrenaline contracts urethral smooth muscle at least partly by enhancement of depolarising electrical activity resulting in Ca^{2+} influx via LVDCCs (363). In longitudinal smooth muscle of the guinea-pig urethra, EFS evoked EJPs that could sum to trigger the generation of slow waves (364). Both EJPs and evoked slow waves are non-adrenergic, non-cholinergic (NANC) in nature and mediated by neurally-released ATP. In the rabbit urethra, where EFS-induced NANC contractions are mediated by P2X purinoceptor activation, bath-applied ATP induces inward currents in isolated SMCs arising from activation of these receptors (379). Of interest, bath-applied ATP can also generate smooth muscle contractions via activation of P2Y purinoceptors. These appear to be attributable to increases of spontaneous Ca^{2+} transients and inward currents in urethral interstitial cells but not urethral SMCs (380). In the urethra of hamster, ATP induces relaxation of precontracted smooth muscles via the activation of P2Y receptors, predominantly $P2Y_1$, but not P2X receptors (381). Thus, the effects of ATP on the contractility of urethral smooth muscle are complex and may depend on basal muscle tone, as well as vary between species.

With circular smooth muscle of the rabbit urethra, EFS-induced increases of spontaneous Ca^{2+} transients are prevented by α-adrenoceptor blockade, while α-adrenoceptor agonist increases the frequency of spontaneous Ca^{2+} transients (363). Thus, neurally-released noradrenaline contracts urethral smooth muscle at least partly by increasing intracellular $[Ca^{2+}]$. In rabbit urethral smooth muscle, EFS- or α-adrenoceptor stimulation-induced contractions

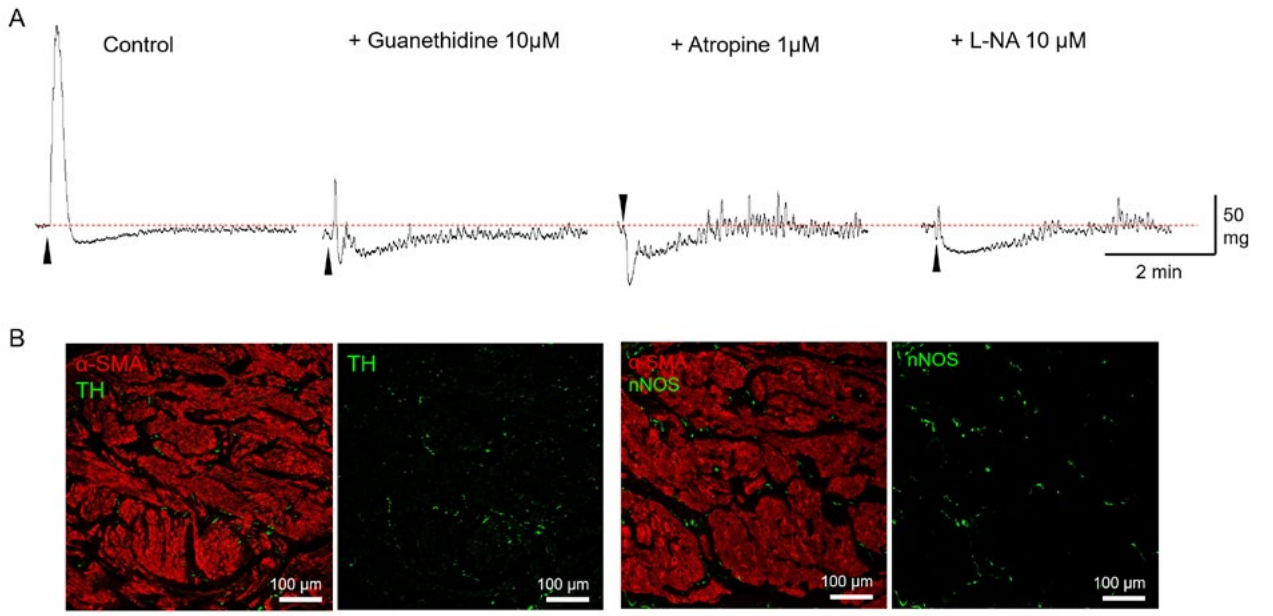

Figure 24. Excitatory and inhibitory innervations of urethral smooth muscle. *A: guinea-pig longitudinal smooth muscle; contractile responses to EFS (20 Hz, 50 μs pulses, 1-s train) in control and in the presence of guanethidine (10 μM), atropine (1 μM) and nitro-L-arginine (L-NA,10 μM). Note: guanethidine almost abolishes the contraction and unmasks a transient relaxation; atropine abolishes the small residual contraction and enhances the transient relaxation; L-NA blocks only the transient relaxation. B: tyrosine hydroxylase (TH)-positive sympathetic nerve fibres (left) and nNOS-positive nitrergic nerves (right) are distributed in the circular smooth muscle layer. Modified from [415].*

are suppressed by ROK inhibitors but not an inhibitor of PKC that can cause Ca^{2+} sensitisation via CPI-17 (361). This suggests the involvement of ROK-mediated Ca^{2+} sensitisation in α-adrenoceptor mediated contractions. However, α-adrenoceptor stimulation fails to induce phosphorylation of myosin light chain (LC20), MYPT1 or cofilin, and thus the mechanism underlying α-adrenoceptor induced contractions remain to be elucidated.

4.2. Inhibitory innervation.

Nitric oxide (NO), released from nitrergic nerves that are identified by their NOS-immunoreactivity or NADPH diaphorase activity (382,383), functions as a predominant inhibitory neurotransmitter causing relaxations of urethral smooth muscle. In precontracted urethral smooth muscles, relaxations induced by EFS, particularly at low frequency, are blocked by inhibitors of NOS (382,384). The relaxant action of NO is further supported by the findings that NO or NO donors induce a potent smooth muscle relaxation. During nerve-evoked relaxation of urethral smooth muscle, guanosine 3':5'-cyclic monophosphate (cGMP) is increased (384), consistent with cGMP functioning as a second messenger of nitrergic signalling. A fundamental role of cGMP in the relaxation of urethral smooth muscle is corroborated by the finding that the NO-dependent relaxations are abolished in mice lacking a soluble guanylate cyclase – PKG pathway (385). *In vivo* recording of urethral pressures in rats has demonstrated that reflex urethral relaxations during the voiding phase are abolished or diminished by an NOS inhibitor, indicating physiological relevance of NO as an endogenous relaxant of urethral smooth muscle (386). In the proximal urethra where a greater spontaneous tone is generated, EFS induces greater relaxation than other urethral regions, suggesting the role of inhibitory nitrergic innervation is to open the bladder outlet on micturition (377).

In circular smooth muscle of rabbit urethra, in which EFS evokes NANC inhibitory junction potentials (IJPs) (378), an NO donor or cGMP analogue reduced the frequency of spontaneous slow waves without hyperpolarising the membrane (363). Thus, neurally-released NO may cause relaxation of urethral smooth muscle by mechanisms other than membrane hyperpolarisation. Nevertheless, neurally-released NO or NO donor inhibits spontaneous Ca^{2+} transients associated with a reduction in basal Ca^{2+} level, indicating that NO-mediated relaxation of urethral smooth muscle is at least partly attributable to a reduction of intracellular Ca^{2+} concentration (368). In mouse urethral SMCs, spontaneous Ca^{2+} transients are also reduced by an NO donor (359). ROK inhibitors greatly suppress spontaneous or α-adrenoceptors-mediated contractions, involvement of Ca^{2+} desensitisation in NO-mediated relaxations remains to be determined (354,361).

Relaxations of urethral smooth muscle induced by high frequency electrical field stimulation consists of an initial, fast relaxation followed by a slowly-developing, prolonged component (384). The initial component, but not the slowly-developed component, is abolished by blockade of NOS, suggesting that slowly-developing relaxations are mediated by a neurotransmitter other than NO. Nerve-evoked relaxations are not inhibited upon the blockade of β-adrenoceptors, VIP receptors or the depletion of sensory neurotransmitters with capsaicin (387). In addition, blockers of several K^+ channels, including BK, SK, intermediate conductance Ca^{2+}-activated K^+ (IK) channels or KATP channels, failed to inhibit non-NO, nerve-evoked relaxations. In rat urethra, in which calcitonin gene-related peptide (CGRP)-containing nerve fibres originating from L6-S1 ganglia are distributed (388), capsaicin or CGRP induces relaxations of precontracted urethral preparations in a manner partially inhibited by CGRP antagonist. Thus, CGRP released from afferent nerves can function as an inhibitory neurotransmitter (389).

With pig urethral smooth muscle, in which neuronal and non-neuronal carbon monoxide (CO)-forming enzymes, namely haem oxygenase isoenzymes, are expressed CO causes a relaxation associated with an increase in cGMP, but not cAMP production (390). This suggests that CO may act as an inhibitory neurotransmitter in the urethra. In human urethra, haem oxygenase-2 immunoreactivity is colocalised with neuronal NOS immunoreactivity in ganglionic cell bodies, while some haem oxygenase-2 positive nerve trunks also appear to express nNOS (391). Nevertheless, urethral smooth muscle relaxation induced by neuronally-released CO has not been proven.

5. URETHRAL INTERSTITIAL CELLS (UICS)

UICs are variable in their morphology, typically being shaped, characterised by a varying numbers of branches or processes (366). UICs are easily distinguished from urethral SMCs by their abundant vimentin intermediate filaments and little α-smooth muscle myosin. In rabbit urethra, UICs expressing Kit immunoreactivity are distributed in both circular and longitudinal layers where they are individually scattered preferentially in parallel with the SM bundles without forming an extensive network (392). In rat or sheep urethra, where UICs are identified as cGMP immunoreactive cells, they also express vimentin and Kit (393).

The question of UICs acting as pacemaking cells to smooth muscle myocytes has remained contentious. Pacemaking functions of Kit-positive UICs, with respect to mouse cells, has not been directly shown, by their lack of associated Kit immunoreactivity, in spite of their ability to generate spontaneous Ca^{2+} transients and spontaneous transient depolarisations (STDs) (394). Sustained tone generated by urethral smooth muscles arises from the temporal summation of spontaneous phasic contractions that are tonically accelerated and augmented by neurally-released noradrenaline through the activation of α1-adrenoceptors (see section V.3.1). Spontaneous phasic contractions are driven either by action potentials or slow waves that trigger Ca^{2+} influx into SMCs via LVDCCs. Such spontaneous electrical activity has been considered to be generated within the SMCs themselves as shown in sheep myocytes expressing 'pacemaker currents', namely CaCCs, to develop spontaneous electrical activity (365). Thus, this has been termed as 'myogenic' activity.

It is now recognised that myogenic activity could also originate from a population of UICs, at least in those from rabbit urethra. Isolated rabbit UICs develop spontaneous transient inward currents (STICs) and corresponding STDs arising from the opening of CaCCs, whilst isolated urethral SMCs lacking CaCCs are electrically quiescent (366). Thus, UICs function as pacemaker cells to electrically drive SMCs that are capable of generating LVDCC-dependent action potentials with the depolarising input from UICs. Expression of TMEM16A (or Ano1)/CaCCs has been demonstrated by single-cell RT-PCR, and TMEM16A inhibitors suppress CaCC currents, STICs and STDs (395). By contrast, in mice, rat and sheep urethra TMEM16A/Ano1 is expressed in urethral SMCs but not UICs (396).

Generation of STICs/STDs in UICs are triggered by spontaneous Ca^{2+} oscillations that primarily depend on Ca^{2+} release from SR/ER intracellular Ca^{2+} stores via $InsP_3$ and ryanodine receptors (397,398). Ryanodine receptors (RyR2 and RyR3 subtypes) function as primary Ca^{2+} release channels, while $InsP_3$ receptors ($InsP_3R1$ and $InsP_3R2$ subtypes) are required to convert localised Ca^{2+}

release to propagating intercellular Ca^{2+} waves (399). Maintenance of spontaneous Ca^{2+} oscillations also depends on extracellular Ca^{2+} influx via or reverse mode the sodium-calcium exchanger (NCX), rather than capacitative Ca^{2+} entry (399-401). Similar to the role of $InsP_3$-mediated Ca^{2+} release, Ca^{2+} influx via NCX converts localised Ca^{2+} release to propagating waves Ca^{2+}, presumably by increasing cytosolic and/or luminal SR/ER Ca^{2+} levels, resulting in the facilitation of Ca^{2+} release.

Blockade of LVDCCs reduces the amplitude and duration of spontaneous Ca^{2+} oscillations and corresponding slow waves in UICs, with little effect on their frequency (398,402). It was originally thought that summed STDs generated in UICs are transmitted to urethral SMCs presumably via gap junctions to activate LVDCCs and generate the plateau phase of slow waves. However, slow waves appear to be generated in UICs themselves that then propagate to the urethral SMCs. However, UICs are scattered amongst the urethral SMCs without forming an extensive network (392), so that the close similarity in the shape of slow waves in UICs and urethral SMCs is probably due to the high input resistance of the SMCs. Indeed, spontaneous Ca^{2+} transients in urethral SMCs are often generated in individual cells independently of each other rather than forming intracellular Ca^{2+} waves (403), indeed suggestive of poor intercellular coupling between individual urethral SMCs. Thus, scattered UICs may be capable of driving only adjacent urethral SMCs, resulting in asynchronous Ca^{2+} transients and associated SMC contractions. (Figure 25).

Mitochondria, in addition to the SR/ER, also have a role in the generation of spontaneous Ca^{2+} oscillations by buffering cytoplasmic Ca^{2+}, rather than merely producing ATP to drive the SERCA Ca^{2+} pump that plays a fundamental role in ER/SR store refilling (404,405). Spontaneous Ca^{2+} waves preferentially originate from the perinuclear region where clusters of mitochondria and ER/SR surround the nucleus. Perinuclear Ca^{2+} dynamics are characterised by a gradual rise of basal Ca^{2+} that precedes each regenerative Ca^{2+} wave. In addition, small Ca^{2+} fluctuations are generated in the cell periphery where short filamentous mitochondria are scattered (405). Inhibition of mitochondrial Ca^{2+} uptake reduces the frequency and amplitude of spontaneous Ca^{2+} waves, while increasing small, non-propagating Ca^{2+} fluctuations. Thus, mitochondria Ca^{2+} buffering may prevent 'premature' CICR from the ER allowing sufficient ER Ca^{2+} sequestration that is to initiate regenerative Ca^{2+} waves (405). Inhibition of mitochondrial Ca^{2+} efflux slows spontaneous Ca^{2+} waves by suppressing the initial gradual rise in perinuclear Ca^{2+} and eventually prevents Ca^{2+} waves. This suggests that Ca^{2+} efflux through the mitochondrial NCX may be transferred to the ER/SR stores.

In isolated UICs, two types of spontaneous transient outward currents (STOCs) are also developed by the opening of BK channels (397). Generation of large STOCs with a long duration (slow STOCs) that are usually coincident with STICs appear to require spontaneous Ca^{2+} release involving $InsP_3$ receptors, whilst smaller STOCs with a fast time-course (fast STOCs) depend on RyR-mediated Ca^{2+} release. At a membrane potential more negative than -40 mV, namely within the range of resting membrane potentials in UICs, STICs predominate over the slow STOCs, and thus UICs preferentially fire STDs. Since UICs are capable of generating fast STOCs at a membrane potential of -50 mV, STOCs could contribute to the maintenance of the cell resting membrane potential.

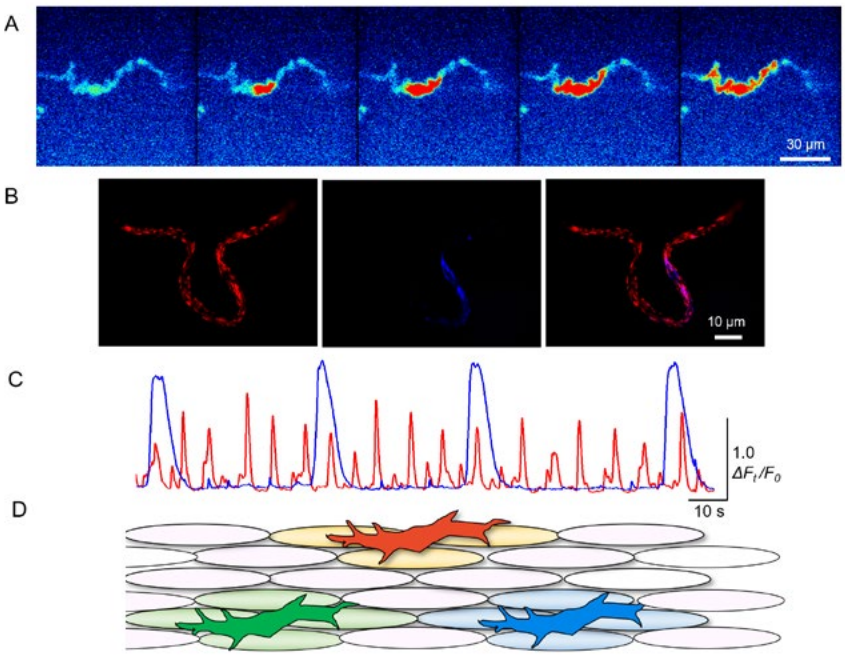

Figure 25. Spontaneous activity in urethral interstitial cells (UICs). *A: rabbit urethra: Isolated UICs develop spontaneous Ca2+ transients that preferentially originate from the perinuclear region. B: mitochondria (red, MitoTracker-Red) are clustered around the nucleus, while short filamentous mitochondria are scattered in the non-nuclear area. Endoplasmic reticulum (ER, blue, ER-Tracker) are also clustered around the nucleus. Merged image on the right. C: spontaneous Ca2+ transients in UICs (blue) do not exhibit a close temporal correlation with those in neighbouring urethral SMCs (red). D: because of poor intercellular coupling between urethral SMCs, spontaneous activity in SMCs triggered by UICs (green, orange, blue) is often restricted to adjacent urethral SMCs. Traces in A-C modified from [403,405]*

Bath-applied noradrenaline increases the frequencies of STDs or STICs recorded in isolated urethral UICs of the rabbit, via the activation of α1-adrenoceptors. This results from an increase of $InsP_3$ production to trigger Ca^{2+} release from SR/ER Ca^{2+} stores with subsequent opening of CaCCs (366,406). Stimulation of α1-adrenoceptors also accelerates spontaneous Ca^{2+} transients in UICs *in situ* (403). In isolated rabbit UICs, ATP also induces CaCC inward currents to increase STIC frequency or spontaneous Ca^{2+} oscillations by activation of P2Y purinoceptors (380). Thus, UICs may act as intermediaries of noradrenergic and/or purinergic excitatory neuromuscular transmission in urethral smooth muscles.

NO donors or cyclic GMP (cGMP) diminishes the spatial spread of spontaneous Ca^{2+} transients in isolated rabbit urethral UICs by inhibiting $InsP_3$-induced Ca^{2+} release (407). NO donors also diminish spontaneous Ca^{2+} transients in UICs *in situ*, suggesting that UICs may also play a role in inhibitory, nitrergic neuromuscular transmission in the urethra. This hypothesis is morphologically supported by the frequent points of contact between Kit-positive UICs and nerves, particularly nitrergic nerves (392). While cGMP acts as an inhibitory second messenger, activation of cAMP/PKA does not affect spontaneous Ca^{2+} transients in UICs, although PKA inhibitors diminish the generation of spontaneous Ca^{2+} transients (408). Of interest, in rabbit UICs that express cyclic nucleotide-gated (CNG) channels, a CNG channel inhibitor attenuates spontaneous Ca^{2+} transients or STOCs. Thus, non-selective cationic CNG channels allowing Na^+ or Ca^{2+} influx may contribute to maintenance of spontaneous activity by inducing depolarisation or increasing Ca^{2+} (409). Such roles of CNG channels will act in contrast to the inhibitory actions of the NO/cGMP pathway, unless CNG channels are preferentially activated by constitutively activated PKA but not NO-induced production of cGMP.

In rat or sheep urethra, where UICs express connexin43, a gap junction protein, neither the contractile effects of noradrenergic nerve stimulation, nor the relaxations induced during nitrergic neurotransmission are modified by gap junction blockers, questioning the role of UICs as an intermediary of neuromuscular transmission (410).

6. MUCOSA

6.1. Mucosal blood vessels.

Coaptation of the urethral mucosa forms a watertight seal contributing to urethral closure during the bladder storage phase and help to maintain urinary continence. Different components of the urethral mucosa, including the epithelium, blood vessels, SMCs in the *lamina propria* and connective tissue, are involved in the development of mucosal sealing. Because filling of urethral vascular bed contributes to about one-third of closing pressure (305,306), it is reasonable to assume that the mucosal vasculature contributes substantially to mucosal sealing.

In the *lamina propria* of dog urethra, the vascular plexus with inflow from small arteries is composed of interconnected longitudinal tubular vessels in the proximal urethra, while a network of sinusoidal vessels are located in the distal urethra (411). With the rat urethra, a pronounced venous plexus, lying immediately below the *lamina propria*, is distributed in the distal urethra where both smooth and striated muscles are only sparsely located, suggesting a predomi-

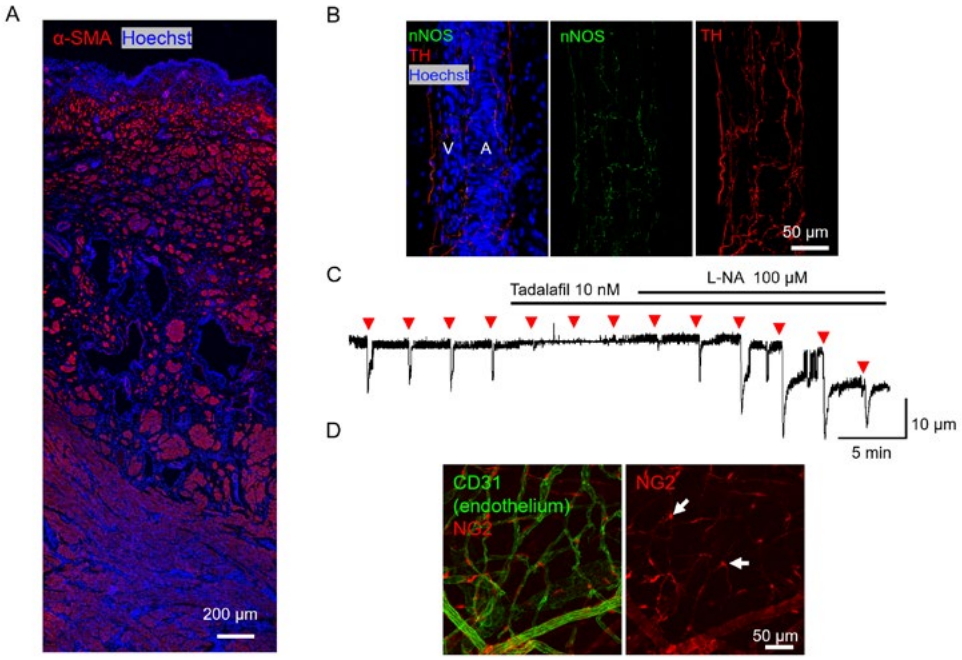

Figure 26. Microvasculature of the urethral mucosa. *A: the pig lamina propria is highly vascular with large venules, a-SMA (red, a-smooth muscle actin; Hoechst, blue, nuclear label). B: Both arterioles (A) and venules (V) receive dense innervation of TH-positive sympathetic and nNOS-positive nitrergic nerves. C: reduction of mucosa arteriole diameter with EFS (20 Hz, 100 μs pulses for 2-s, at arrowheads), tadalafil (10 nM) and L-NA (100 μM) added where shown – tadalafil abolished responses, reversed by L-NA. Modified from[415]. D: NG2-DsRed mouse urethral mucosa; the vascular network is visualised by endothelium labelling with CD31 (left). A network of capillary pericytes (arrows) expressing DsRed, a red florescent protein (right). Dr Retsu Mitsui, Nagoya City University, Nagoya, Japan; unpublished data.*

nant role of vascular plexus in the closure of urethral lumen (412). Clinical evaluation of urethral mucosa vascularity using colour Doppler has demonstrated that the mucosal vascular dimension correlates with the increases of maximal UCP and its decreases with age (413). It has also been demonstrated that continent multiparous women demonstrated a significant reduction in urethral vascularity parameters compared with continent nulliparous women (414). Nevertheless, the function of mucosal blood vessels in the urethra is less well understood compared to those in the bladder (Figure 26).

In mucosa of the pig urethra, double immunostaining for tyrosine hydroxylase (a label for dopaminergic neurons) and nNOS revealed that perivascular sympathetic fibres around mucosal arterioles and venules are intermingled with, but distinct from, nitrergic nerves (415). CGRP-containing primary afferent nerves are also distributed around both arterioles and venules, in close apposition with but distinct from perivascular nitrergic nerves, and thus there are at least three different innervations to mucosal blood vessels. This finding is consistent with a previous study demonstrating that chemical denervation of sympathetic nerves with 6-hydroxydopamine or primary afferent denervation with capsaicin did not diminish nitrergic relaxations in the rat urethra (416). This indicates that nNOS-containing nerves originate from neither sympathetic nor afferent nerves. In the rat major pelvic ganglion, NOS immunoreactive cell bodies also display choline acetyltransferase immunoreactivity (417). Moreover, nitrergic relaxation of the rat urethral smooth muscles are abolished by bilateral cryo-ganglionectomy of the major pelvic ganglia (417), suggesting that nitrergic nerves projecting to the urethra are predominantly parasympathetic in origin. In the mucosa of rat urethra, blood vessels receive vesicular acetylcholine transporter-positive cholinergic, nNOS-positive nitrergic nerves and CGRP-immunoreactive afferent nerves (412).

In the pig urethra, a reduction of urethral pressure during voiding is accompanied by greater mucosal blood flow (303). Because in parasympathetic neural activity to the lower urinary tract is dominant during voiding, the increased blood flow could result from arteriolar dilatation, mediated by NO released from parasympathetic nerves. Considering that emptying the mucosal vascular plexus would reduce mucosal sealing, while its expansion with blood would help luminal occlusion, the increased mucosal blood flow during voiding seems contradictory. This paradoxical phenomenon may result from the increased blood flow velocity due the simultaneous rise in arteriolar inflow and venular drainage.

In mucosal arterioles of the pig urethra, EFS-induced vasoconstriction is abolished by tetrodotoxin and largely suppressed by guanethidine (10 μM), and thus is predominantly mediated by sympathetic nerves (415). EFS-induced vasoconstriction is suppressed by tadalafil, a PDE5 inhibitor, in a manner sensitive to L-NA (L-nitro arginine, a NOS inhibitor). This indicates that NO released from nitrergic nerves act as an inhibitory neurotransmitter. Since L-NA also reduces the basal vessel diameter, NO may also be continuously released from the endothelium. The vasorelaxant effects of NO is possibly due to its inhibitory actions on arteriolar SMCs, mediated by cyclic GMP. In addition, the proximity of nitrergic and sympathetic nerve fibres in the mucosal vasculatures may allow NO-induced presynaptic inhibition of sympathetic transmitter release. Neurohumoral regulation of the contractility in different vascular segments in the urethral mucosa needs to be explored further.

6.2. Smooth muscle cells in the lamina propria (SMC-LP).
In the urethral mucosa, sparsely distributed, longitudinally-arranged SMCs in the *lamina propria* (SMC-LP) have been described (418). Rabbit urethral *lamina propria* contracts upon activation of α-adrenoceptors with EFS or bath-applied noradrenaline (418),

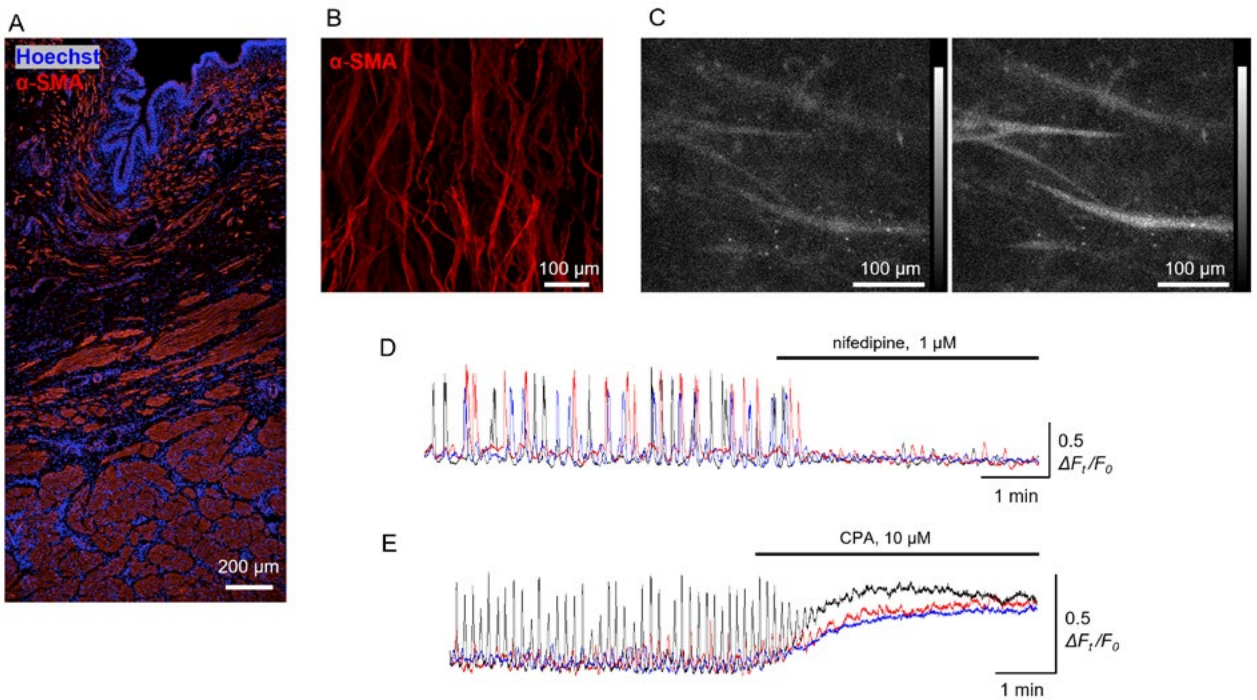

Figure 27. Ca2+ dynamics of pig lamina propria SMC (SMC-LP). *A: SMC-LP visualised by α-smooth actin (α-SMA) immunoreactivity. B: mucosa whole-mount, α-SMA positive SMC-LPs are loosely arranged predominantly along the longitudinal urethral axis. C: SMC-LPs develop asynchronous spontaneous Ca2+ transients independently of each other and largely suppressed by 1 μM nifedipine. D: residual Ca2+ transients abolished by the blockade of the SR with 10 μM CPA. Modified from [415].*

although it was not determined whether this was ascribed to the SMC-LP or vascular smooth muscle. In pre-contracted rabbit urethral *lamina propria*, neurally-released NO or bath-applied ACh, that triggers NO release, induces relaxation (419), suggesting that the contractile properties of SMC-LP are similar to those of urethral SMCs (Figure 27).

In the *lamina propria* of pig urethra, α-SMA-immunoreactive SMC-LP are sparsely scattered throughout but predominantly arranged in the longitudinal direction (415,420). However, they do not form muscle bundles comparable to the *muscularis mucosae* in the bladder. SMC-LP develop spontaneous Ca^{2+} transients associated with weak contractions in individual cells. These transients are often generated in individual SMC-LP independently of each other, although a few adjacent SMC-LP can display near synchronous behaviour, suggesting that the summed contractility of multiple SMC-LP is not very vigorous. Spontaneous Ca^{2+} transients in SMC-LP are largely diminished or abolished after the blockade of LVDCCs, suggesting that they generate LVDCC-dependent action potentials or slow waves. Transients are prevented upon the blockade of SR Ca^{2+} ATPase, and thus spontaneous activity in SMC-LP appears primarily to depend on SR Ca^{2+} handling.

Unlike SMC-LP in the rabbit urethra, SMC-LP in the pig urethra do not respond to EFS, indicating that they lack a functional innervation. This is consistent with the absence of sympathetic, nitrergic or CGRP-containing afferent innervation to SMC-LP. Nevertheless, noradrenaline suppresses spontaneous Ca^{2+} transients or abolishes their generation with a reduction in the basal Ca^{2+} level in a manner sensitive to propranolol, a β-adrenoceptor antagonist. ACh first accelerates spontaneous Ca^{2+} transients, and then causes a sustained raise in the basal Ca^{2+} level, that is sensitive to atropine, a muscarinic receptor antagonist. Thus, SMC-LP in the pig urethra have a contractile phenotype similar to bladder *muscularis mucosae*, although SIN-1, an NO donor, fails to affect their spontaneous Ca^{2+} transients. Because of anatomical proximity of SMC-LP to the epithelium, they may be readily affected by epithelium-derived factors that inhibit urethral smooth muscle contractions induced by muscarinic or adrenergic stimulation (421).

V. THE UROTHELIUM

The urothelium can be thought of as a first responder to various types of stress that can include physiological, psychological and disease-related factors. The urothelium is an interface between the urinary space and underlying tissues (Figure 28A) and as such, forms a high resistance barrier. Beside this necessary function, the urothelium can modulate the volume and composition of urine (422) and actively participates as an integral part of what has been termed a 'sensory web' where it receives, integrates, amplifies and transmits information about the external environment to underlying nervous and muscular systems. Alterations of bladder urothelium at the molecular and structural levels have been reported in both patients and animals modelled for various bladder disorders. It is likely that many therapies currently used in the treatment of bladder disease may target urothelial receptors and/or their release mechanisms.

1. INTRODUCTION TO THE ANATOMY AND BARRIER FUNCTION OF THE UROTHELIUM.

The urothelium is the epithelial lining of the lower urinary tract between the renal pelvis and the urinary bladder. Adult urothelium is composed of at least three layers with distinct cell types (the exact number of layers is species dependent) and can be distinguished by expression of keratin-5, p63 and uroplakin (Figure 28B,C). These consist of a basal cell layer attached to a basement membrane in close proximity to capillary endothelial cells, an intermediate layer, and a superficial or apical layer that is in contact with urine and microorganisms and composed of a single layer of large 'umbrella cells' (423-426). These umbrella cells exhibit a distinctive plasma membrane that contains both 'hinge' and 'plaque' regions (Figure 29A,B). The umbrella cells (which are also termed facet or superficial cells) are the only cells that are interconnected by tight junctions (composed of multiple proteins such as the claudins). Another characteristic of the apical or umbrella cells is the expression of discoidal fusion vesicles or DFVs (Figure 29C). In response to bladder

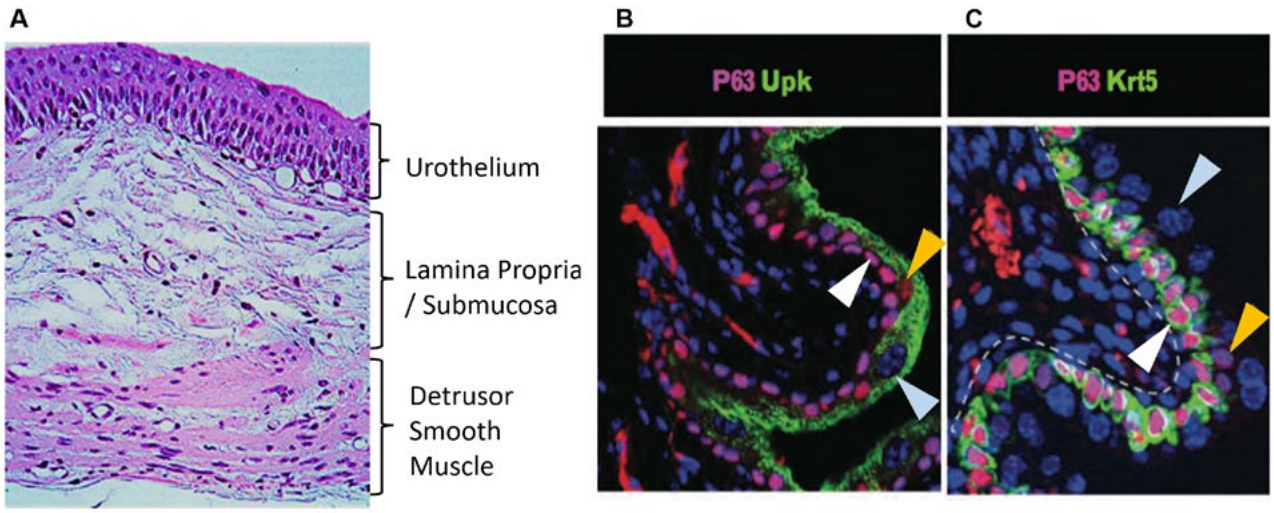

Figure 28. Structure of the bladder wall and urothelium. *A: Structure of the bladder wall. B,C. Three cell types of the urothelium distinguished by expression of p63 (purple), uroplakin (Upk, green, part B) and keratin-5 (Krt5, green part C)). Basal cells (white arrows) express keratin-5 and p63, but not uroplakin. Intermediate cells (orange arrows) express p63 and uroplakin, but not keratin-5. Superficial cells (light blue arrows) express uroplakin, but not p63 or keratin-5. Parts B,C [458], modified with permission.*

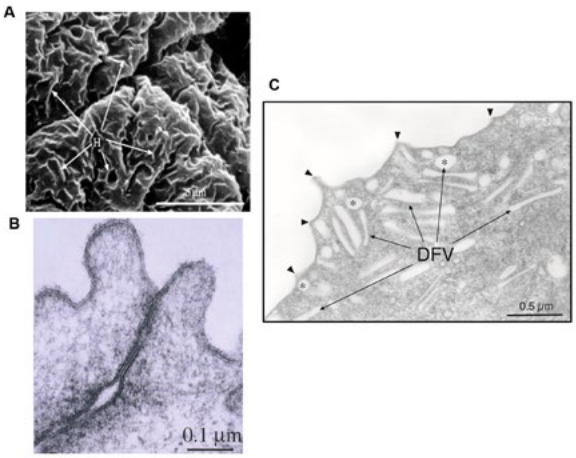

Figure 29. Ultrastructural features of the umbrella cell. *A: Scanning electron micrograph of apical surface of rabbit umbrella cell layer (hinges "H" marked with arrows, calibration bar 5 µm). B: high power view of a tight junctions. ([423,425], with permission). C: Transmission electron micrograph of the apical pole of a rat umbrella cell. Examples of discoidal/fusiform-shaped vesicles (DFV) are marked with arrows and hinges with arrowheads. Plaques in the intervening membrane between hinges. Apical cytoplasm contains disc-shaped (*) and fusiform-shaped vesicles. Multivesicular bodies (MVB; i.e., late endosomes) are indicated by arrows. ([426], with permission)*

filling, these DFVs fuse with the apical membrane releasing crystalline proteins termed uroplakins to the cell surface that assembles into hexagonal plaques (426-429). The attachment of *Escherichia coli* type I fimbriae to uroplakins also initiates the host-pathogen response, described more fully in later sections. It has been suggested that 'non-plaque' proteins that include receptors and ion channels, may be located to the hinge areas of these cells.

Uroplakins and other urothelial cellular differentiation markers, such as cytokeratin 20, are not expressed in the stratified epithelium of the urethra. There have been suggestions in early studies in some species, that umbrella cells and perhaps also the intermediate cells may have projections to the basement membrane (425). The ability of the bladder to maintain a highly effective barrier, despite large alterations in urine volume and increases in pressure during bladder filling and emptying, is dependent on several features of the umbrella cell layer. These features include specialised lipid molecules and tight-junction proteins (such as zona occludens-1, occludins, claudins) that reduce the movement of ions and solutes between cells (425,430) These proteins can adapt to mechanical stretching of the urothelium during filling and emptying. For example, the claudins are a family of integral membrane proteins (at least 24 members identified in mice and humans) and can be classified as either pore-forming (makes the epithelium leakier) or barrier-forming. The importance of claudin-based tight junctions *in vivo* has been studied in a number of tissues under various conditions. For

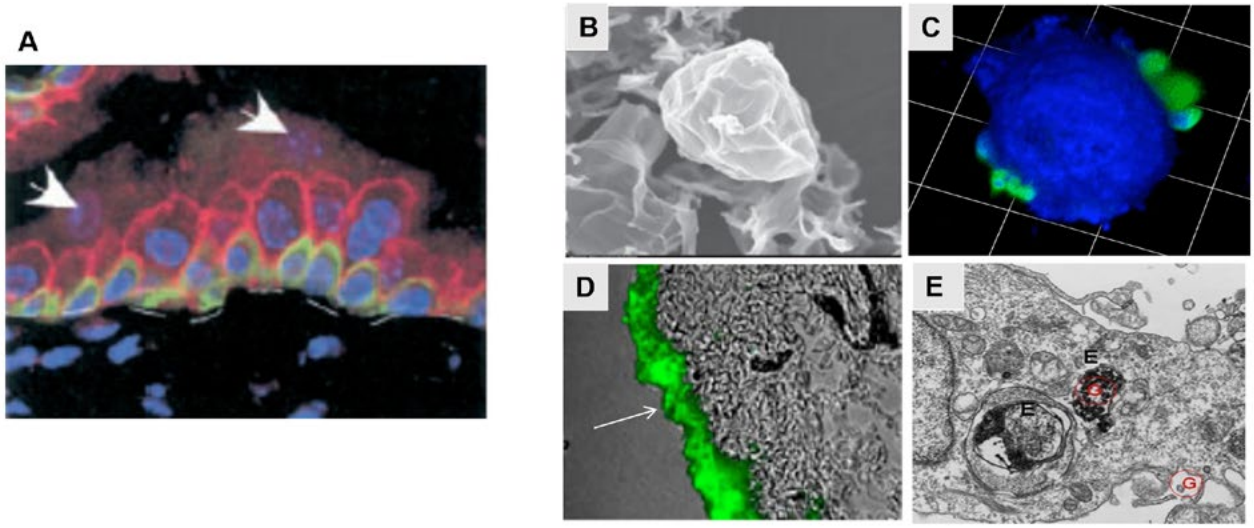

Figure 30: UPEC infection and liposomes. *A: UPEC infection leads to increased expression of the tight junction protein claudin-4 in intermediate cells. Levels of claudin-4 (red) are increased in intermediate cells 3.5 hr after UPEC infection. Cytokeratins 5/6 label basal cells (green). Nuclei are stained blue with bis-benzimide. Note: claudin-4 is absent in superficial cells, white arrows ([431], with permission). B: EM picture of liposome. C: liposomes (green) attached to primary cultured urothelial cell membrane. D: liposomes instilled in a rat bladder forming a coating (green) on urothelial surface. E: vesicle-like structures in urothelial cell endosomal compartment (E) containing liposome encapsulated gold (G) marker. ([435,436], with permission).*

example, claudins (in particular claudin 4) may play a role in regulation of urothelial proliferation. There is evidence that attachment of uropathogenic *Escherichia coli* (UPEC) to urothelial superficial cells triggers the rapid induction of claudin-4 within the intermediate cells of the urothelium (Figure 30A) (431).

This increase in claudin-4 may explain how the urothelium is able to maintain the integrity of the urothelial barrier following infection and exfoliation of the apical urothelium. In another study, overexpression of the pore-forming claudin-2 in rat urothelium resulted in increased urothelial permeability that seemed to trigger inflammation and altered bladder function (432). It has not been established whether disruption of the urothelial barrier alone is sufficient to trigger inflammation and altered bladder reflexes or whether association with other factors (such as urine) may be needed to facilitate this response (433).

In addition, there is evidence in many types of epithelium (including uro-epithelium) that adhesion molecules such as members of the cadherin family play important roles in establishing and maintaining epithelial-cell contacts (434). Altered urothelial-cadherin expression has been reported in IC/BPS patient bladder urothelium.

The lipid composition of the apical membrane is unusual in composition and is rich in cholesterol, phosphatidylcholine, phosphatidylethanolamine and cerebroside (425). Recent studies suggest that liposomes, consisting of an aqueous core enclosed in one or more phospholipid bilayers, may help to restore urothelial-barrier function. Liposomes have typically been used to transport drug molecules in a variety of cells. Urothelial cells appear to take up liposomes via an endocytotic process, providing evidence for a possible mechanism by which liposomes act as a drug delivery system (435-437). In addition, empty liposomes have shown promise to repair and enhance the barrier function of a dysfunctional urothelium (Figure 30B-E)(438-440).

The apical surface of the urothelium is also covered with a sulphated polysaccharide glycosaminoglycan (GAG) or mucin layer that is thought to act as a nonspecific anti-adherence factor and as a defence mechanism against infection (441-443). In addition, during bladder filling the umbrella cells become flat and squamous and this shape change is accompanied by vesicular traffic (i.e. exocytosis/endocytosis), adding membrane to the apical surface thereby increasing overall urinary bladder surface area (426,444,445). This process of ongoing replacement of apical membrane by newly fused discoid vesicles also serves to maintain the urothelial barrier (446). There is evidence that this stretch-induced exocytosis is dependent on activation of epidermal growth factor receptor (EGFR) (447,448). These processes allow the bladder to accommodate increasing volumes of urine during filling without compromising the barrier function. There is some evidence that superficial urothelial cells exhibit a lower level of endocytotic activity, which may be a protective mechanism against internalisation of toxic substances excreted in the urine (449). Exocytosis/endocytosis (vesicular recycling) may also play an important role in modulating the release of a number of neurotransmitters/mediators as well as regulation of the function of many receptors and ion channels in urothelial cells (450,451).

2. REPAIR AND REGENERATION OF THE UROTHELIUM

Epithelial integrity is maintained through a complex process of migration and proliferation (to restore cell numbers) and differentiation (to restore function) (452). Basal cells normally exhibit a low (3-6 month) turnover rate, in fact the slowest turnover of any mammalian epithelial cell (444,453).

It has been suggested that neither urine-derived factors nor cyclic mechanical changes contribute to urothelial proliferation and differentiation. However differentiation of urothelial cells in culture can be stimulated by prostaglandin, which is abundant in the urine, (422,454) and accelerated proliferation and regeneration of the urothelium can occur in various bladder pathologies. For example, with acute injuries using agents (protamine sulphate; cyclophosphamide, chitosan) that damage the umbrella cell layer, it has been shown that the urothelium rapidly undergoes both functional and structural changes in order to restore the barrier in response to injury (449,455). Following disruption of the barrier, in the early stages of regeneration the superficial cells may appear smaller in size and

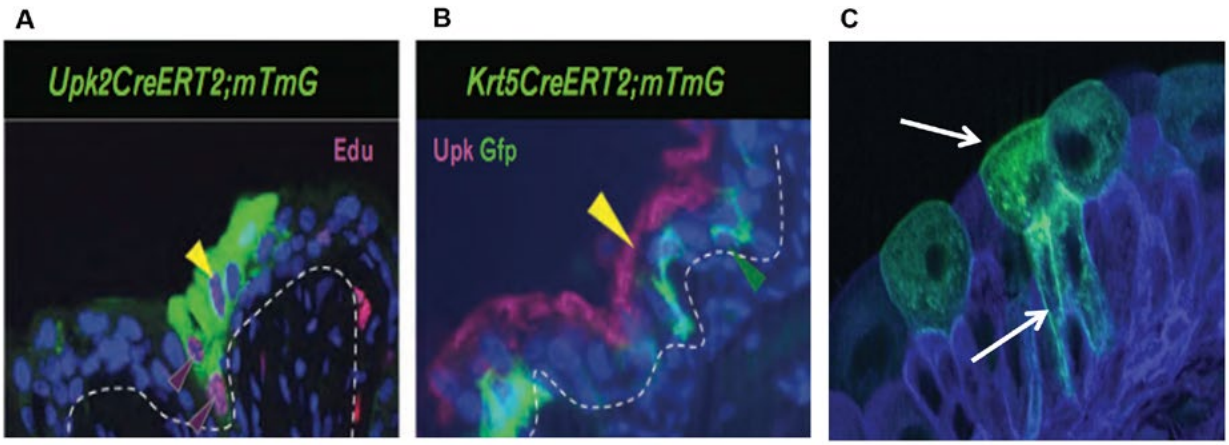

Figure 31. Intermediate cells as progenitors of superficial cells in adult urothelium. *A: Uroplakin-expressing cells labelled using a Upk2CreERT2;mtmg cell line. B: basal cells labelled using a Krt5CreERT2;mtmg cell line. Urothelial regeneration occurs after cyclophosphamide administration. Panel A shows intermediate cells are progenitors for superficial cells. Panel B shows basal cells proliferate but do not differentiate into intermediate or superficial cells. C: long, thin intermediate cells regenerate the outer protective layer - intermediate cells and progeny (white arrows) appear green ([458], with permission).*

often covered with microvilli (456). In some pathologies, deficiencies or defects in maturation or terminal differentiation of superficial umbrella cells have been reported, though the factors which may be involved are not yet known (457). Recent evidence has shown that following cyclophosphamide treatment of rodent bladders, there is a rapid desquamation, proliferation and regeneration of the urothelium. In this study, the intermediate cells (and not the basal cells) seem to be the adult progenitor cells for superficial cells, and are self-renewing (Figure 31)(458).

The processes underlying urothelial repair are complex; involving several structural elements, signalling pathways, trophic factors and the cellular environment. There is still incomplete understanding as to how the loss of umbrella cells is communicated to the underlying basal cell network and whether signalling pathways driving urothelial regeneration are similar for every type of injury. Furthermore, the interaction between these biochemical signals and mechanical forces in the bladder during the course of urothelial repair is not well understood. For example, the initiation of urothelial proliferation or differentiation of intermediate cells is thought to involve up-regulation of growth factors such as fibroblast growth factor and nerve growth factor (NGF) (459,460). In addition, members of the PPARγ and EGFR signalling pathways may contribute to urothelial 're-epithelialisation' in wound repair (454). PPARγ has been found to play an important role in a number of cellular functions including differentiation, maintenance and even regeneration of the urothelium (461). There is also evidence that Hedgehog/Wnt signalling acting across the basal urothelial cell-stromal cell boundary, contributes to increases in urothelial proliferation in response to injury (462). Retinoic acid (synthesised from underlying stroma) has been shown to be important for urothelial differentiation (463).

Though the urothelium maintains a tight barrier to ion and solute flux, a number of factors or stressors such as tissue pH, mechanical or chemical trauma, hormonal changes or bacterial infection and even changes in blood flow can modulate the barrier function of the urothelium(450,464). It has been shown that ischemia can augment release of inflammatory mediators such as reactive oxygen species or eicosanoids from urothelial and suburothelial tissues, altering bladder tone and contractility (465). Stress-mediated activation of the hypothalamic-pituitary-adrenal axis can result in increased production of corticotrophin releasing factor, which can regulate neuroendocrine and autonomic responses to stress. The net effect can include disruption of the epithelial barrier and increased prevalence of infection. In addition, altered levels of circulating oestrogens have been associated with changes to urothelial structure including epithelial shedding or mucosal atrophy (466,467). Other conditions such as bladder pain syndrome/interstitial cystitis (BPS/IC), senescence, diabetes or spinal cord injury are also associated with changes in the urothelial barrier(455,468). Studies utilising aged animals have demonstrated significant alterations to the bladder mucosa including areas of denudation(469,470).

3. OXIDATIVE STRESS, MITOCHONDRIAL DYSFUNCTION AND PURINE DYSREGULATION

Several bladder disorders, including those due to chronic psychological stress and the effects of age, can increase susceptibility to injury and apoptosis through pathways including oxidative stress (471). Oxidative stress, characterised in part by an increase in the level of proinflammatory mediators and reactive oxygen species or ROS, leads to disruption of various cellular components (472,473). Oxidative stress can be produced by bladder pathologies including ischemia or repeated ischemia/reperfusion during a micturition cycle (474,475). Indeed, the bladder mucosa exhibits a higher metabolic rate as compared to other regions in the bladder wall and the urothelium is highly vulnerable to any changes in blood flow. Both acute and chronic reduction in blood flow induce significant defects in the mucosal barrier, with disruption of urothelial tight junctions. Within the urethra and urinary bladder, age-related changes include a thinning of the epithelium and deceased vascularity. Findings from aged animals reveal that urothelial cells show a decreased antioxidant capacity with increased levels of markers for oxidative stress. This is associated with alterations in mitochondria and increased accumulation of an ageing pigment termed lipofuscin (Figure 32A) (476). In addition, ageing dramatically increases the volume of endolysosomes (organelles that degrade cellular debris), which may lead to accumulation of free radicals and decreased cel-

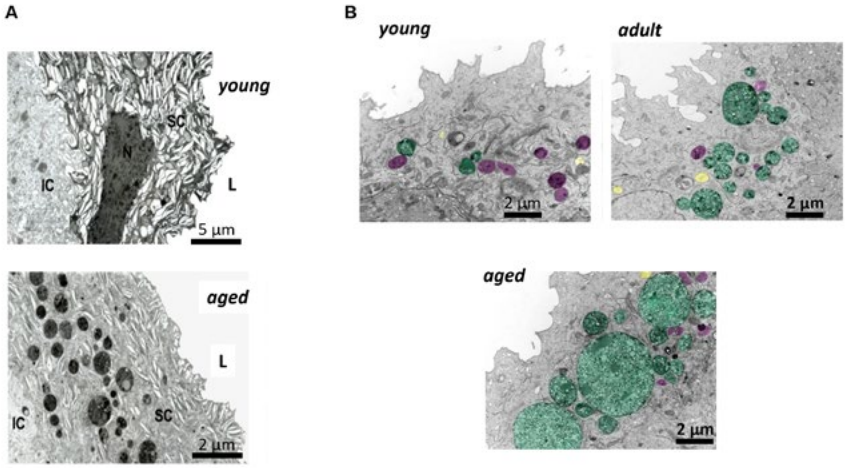

Figure 32. Structure of young and ageing mouse urothelium. *A: Ultrathin sections of a young mouse superficial cell (upper), with large amounts of fusiform vesicles in the cytoplasm but no lipofuscin granules, and of an aged mouse (lower) filled with vesicles and numerous osmiophilic lipofuscin granules. SC, superficial cell; IC, intermediate cell; L, bladder lumen; N, nucleus. ([476], with permission). B: The volume of endolysosomes increases in superficial cells with age from young, adult to aged mouse urothelium. Coloured structures show multivesicular bodies (MVBs, yellow), endolysosomes (green) and lysosomes (purple) ([477], with permission).*

lular functions (Figure 32B) (477). The decline in these various epithelial elements may lead to a decrease of both regenerative ability and also immunological defence mechanisms that are critical for maintaining epithelial integrity.

Mitochondria play a key role in cellular homeostasis, including generation of reactive oxygen species (ROS), apoptosis, and production of ATP via oxidative phosphorylation (478). Indeed, the study of bioenergetics and the influence of mitochondrial functions on cell signalling and disease is an emerging and exciting area of research. Mitochondrial dysfunction has been implicated in several disorders. These structures are highly sensitive to changes in their cellular environment and can be easily affected by a number of conditions. For example, chronic stress-associated activation of the sympathetic nervous system (using the water avoidance stress, or WAS model, in female rats) alters urothelial mitochondrial function, which may contribute to bladder dysfunction (Figure 33) (479). Studies have shown that mitochondrial abnormalities (such as increased ROS production) lead to changes in mucosal barrier function in several tissues, including the urinary bladder. Also, recent studies have shown some evidence demonstrating mitochondrial dysfunction and oxidative stress (elevated ROS) may play a role in urothelial barrier (and sensory) abnormalities observed in the urinary bladder with advanced age as well as in a number of conditions (480,481).

The purinergic nucleotide inosine is formed from the metabolism of adenosine and provides beneficial anti-inflammatory and protective effects to various target organ systems, including the LUT. Inosine and hypoxanthine can directly alter bladder function. Administration of exogenous inosine can exert protective effects on the urinary bladder following experimentally induced obstruction or spinal cord injury (482,483). The mechanism of action may involve actions on adenosine receptors and prevention of oxidative damage via scavenging of free radicals and peroxynitrite. This type of purine-sensitive mechanism is likely to improve motor and sensory functions, which is diminished in ageing.

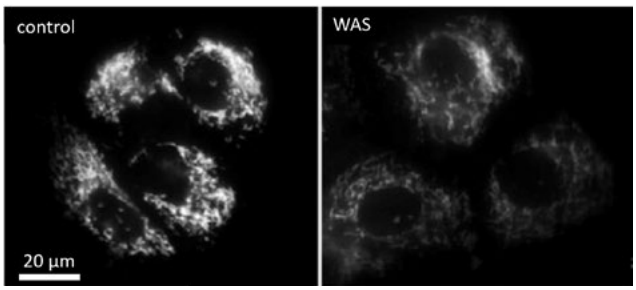

Figure 33. Urothelial cells isolated from rats exposed to water avoidance stress. *Examples of TMRM (tetramethylrhodamine) staining as a label for healthy (polarised) mitochondria from a control (left) and a WAS (right) rat. ([479], with permission).*

Increased oxidative damage by ROS is deleterious to cells and plays a key role in progression of a number of diseases. While there are several sources of free radicals (e.g. ROS), it is well established that the enzyme xanthine oxidase (XO) is able to generate a source of ROS due to metabolism of hypoxanthine to xanthine and then uric acid. Hypoxanthine (as well as XO) is able to cross easily the cell membrane (484) implying increased free radical production, which over time, may cause cellular and organ damage. Thus, though ROS can have physiological roles, sustained ROS levels (for example in age-related disorders) are likely to result in tissue injury due to oxidative damage and mitochondrial dysfunction - ultimately resulting in cellular loss/damage and excessive deposition of collagen fibres/loss of elasticity. Not surprisingly, treatments that inhibit oxidation of hypoxanthine suppress inflammatory cytokines and oxidative stress in a number of disorders. There is emerging evidence that changes in the levels of the enzyme purine nucleoside phosphorylase (PNPase) may reflect the extent of oxidative injury and cellular damage. Recent evidence has revealed that 8-aminoguanine (8-AG), an endogenous PNPase inhibitor, shows efficacy in reversing aging-associated functional, structural, me-

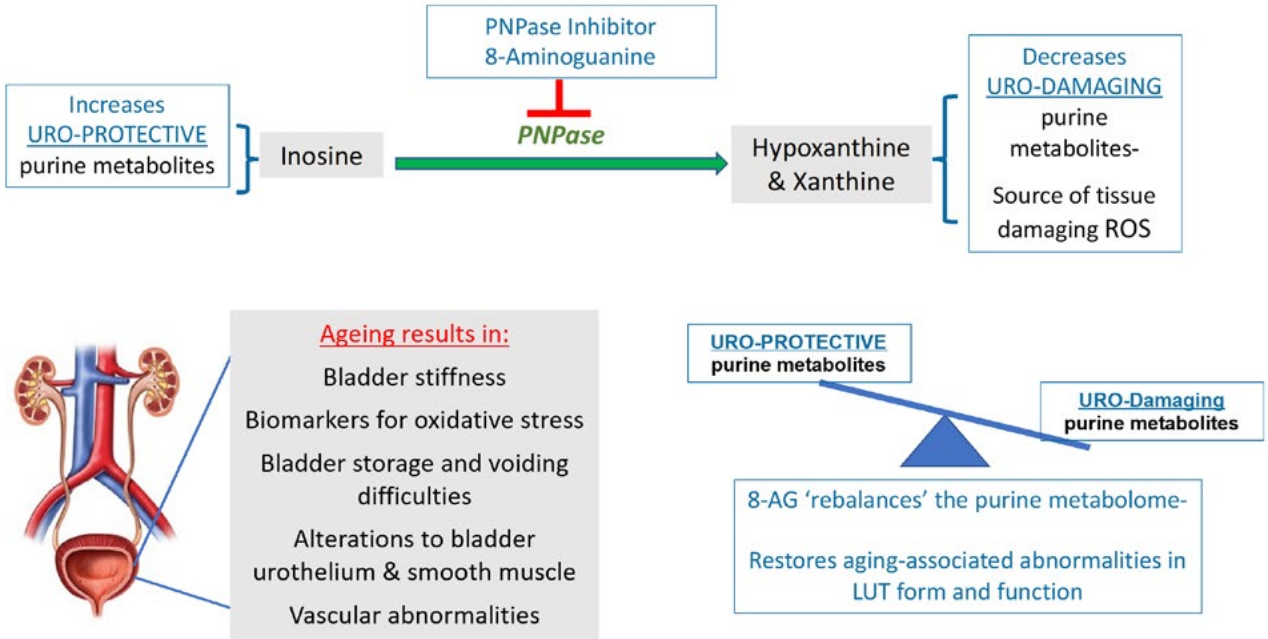

Figure 34. The purine nucleoside phosphorylase inhibitor, 8-aminoguanine (8-AG). *8-AG 'rebalances' the purine metabolome in the aged lower urinary tract; reversing ageing-related functional, structural, mechanical and biochemical urothelial/bladder abnormalities to that of a younger state ([485], with permission).*

chanical and biochemical urothelial/bladder abnormalities (485). The uro-protective effects of PNPase inhibitors in general, and 8-aminoguanine (8-AG) in particular, are likely due to simultaneous increases in tissue protective purines (inosine and guanosine) and decreases in tissue damaging levels of both hypoxanthine and xanthine (Figure 34).

4. ROLE OF THE UROTHELIUM IN IMMUNE AND INFLAMMATORY RESPONSES

There is new evidence that the human urinary tract contains a diverse microbiota that is likely to play an important role in bladder health and disease (486). Evidence in the GI tract supports a role for gut microbiota on intestinal barrier function that can be altered by psychological and physical stressors (487). With the urinary tract, the urothelium is the first line of defence against pathogens and irritative substances, with a number of mechanisms that limit inflammatory responses (488). Examples include uromodulin (or Tamm-Horsfall urinary glycoprotein), which prevents bacteria from interacting with the epithelial cell surface (489). Other factors such as β-defensin-1 are secreted from epithelial cells into the urine and restrict bacterial growth (490).

Both physiological and psychological stress can result in a failure of urothelial and suburothelial 'defensive' systems and thereby promote changes in both urothelial barrier and signalling function. For example, alterations in proteins including proteoglycans and bacterial defence molecules may lead to distinctive changes in urothelial structure and play a role in bacterial adherence (491). In this regard, urinary tract infections produced by uropathogenic *Escherichia coli* (UPEC) are initiated by bacterial adherence to uroplakin proteins on the apical surface of umbrella cells (464,492) UPEC express filamentous adhesive organelles (type-1 pili) that mediate bacterial attachment, invasion and apoptosis of the urothelial cells and urothelial differentiation (e.g. increased uroplakin III expression) may have a pivotal role in sensitising urothelial cells to UPEC-induced infections and possible cell death (493). Even acute contact (within hours) of the mucosal surface with bacteria may result in altered urothelial barrier function (494). UPEC can also internalise within umbrella cells forming intracellular colonies (biofilm-like pods) that has been implicated in generating chronic urinary tract infections. UPEC commandeer the endocytic/exocytic machinery of urothelial cells, residing inside fusiform vesicles (495). This permits bacteria to escape elimination during voiding and re-emerge into the urine during distension. When expelled into the urine during the storage phase, the urine may provide a nutrient-rich environment optimising bacterial survival. Infected urothelial cells also use their export machinery to reduce bacterial loads. For example, UPEC found in epithelial 'lysosomes' are sensed by transient receptor potential (TRP) mucolipin 3 (TRPML3) receptors. This is a cation channel expressed on lysosomes which leads to spontaneous exocytosis of the lysosome expelling the bacteria (Figure 35A) (496).

UPEC can trigger an inflammatory response within the urothelium with release of multiple mediators such as interleukins and cytokines (497). The result of this immune response is often structural damage to the urothelial barrier. Recent evidence has shown a role for hypoxia-inducible factor 1-alpha (HIF-1α) in modulating the innate immune cell function (498,499). Human urothelial cells treated with a HIF-1α stabilising agent exhibited less cell death when exposed to UPEC, further supporting a role for HIF-1α in defence against UPEC infections (500). State-of-the art imaging approaches in combination with mass spectrometry have revealed the presence of a chemokine-dependent crosstalk between the urothelium and macrophages during UPEC infection. Initiation of such crosstalk facilitates macrophage migration into the urothelium which in turn maintain the barrier function by reducing bacterial burden (501).

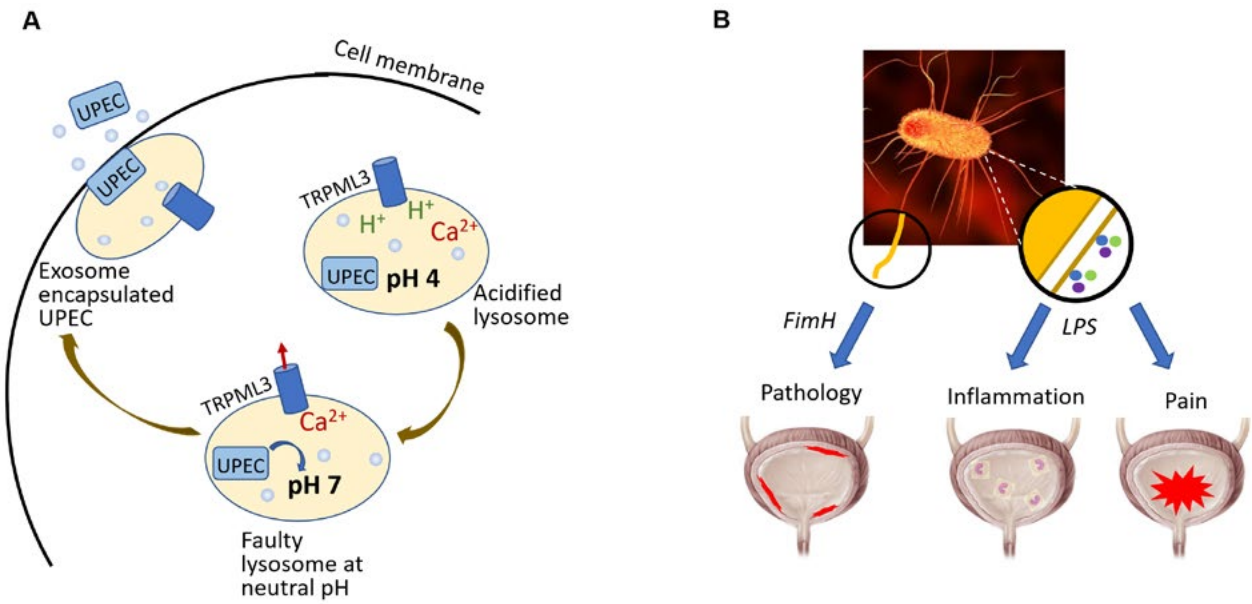

Figure 35. Lysosomal expulsion of UPEC and UPEC-induced pain. *A: After UPEC infection of urothelial cells, activation of the mucolipin TRP channel 3 (TRPML3) spontaneously initiates lysosomal exocytosis leading to an expulsion of exosome-encased bacteria. (modified from [496]). B: UPEC induces pain separable from other facets of UTI pathogenesis. FimH acts as a tethered toxin that mediates urothelial apoptosis and consequent bladder barrier dysfunction. LPS plays dual roles through its interactions with TLR4. In addition to triggering inflammation, LPS mediates pelvic-pain responses. (modified from [504]).*

There is also evidence for a role of endotoxin (lipopolysaccharide, LPS) on the bacterial cell wall in mediating pain associated with UPEC infections (502). This seems to function independent of urothelial damage, as erosion of the urothelial surface with protamine sulphate in mice failed to elicit bladder pain when instilled with UPEC. In addition, bacteria possess a wide range of pain phenotypes, largely dependent upon Toll-like receptors (Figure 35B) (503,504). Taken together, these findings support the view that UPEC-induced urothelial dysfunction is the transducer of the UTI pain signal.

Disruption of urothelial function can also be induced by more remote pathological conditions that influence neural or hormonal mechanisms. For example, spinal cord transection in rats leads to a rapid alteration in the urothelial barrier including ultrastructural changes and increased permeability (505). The changes are blocked by pre-treatment with a ganglionic blocking agent, suggesting an involvement of efferent autonomic pathways in the acute effects of spinal cord injury on bladder urothelium. Other types of urothelial-neural interactions are also likely, based on the recent reports that various stimuli induce urothelial cells to release chemical mediators that can in turn modulate the activity of afferent nerves (425,450). This has raised the possibility that the urothelium may have a role in sensory mechanisms in the urinary tract.

In summary, modification of the urothelium and/or loss of epithelial integrity in several pathological conditions can result in passage of toxic/irritating urinary constituents through the urothelium or release of neuroactive substances from the urothelium. This may lead to changes in the properties of sensory nerves and in turn sensory symptoms such as urinary frequency and urgency. Thus, chemical communication between the nervous system and the urothelial cells may play an important role in the generation of urinary bladder dysfunction.

5. EPITHELIAL HETEROGENEITY IN THE LOWER URINARY TRACT

Studies comparing a number of species have shown that the major part of the urinary tract is lined with a fully differentiated urothelium (422). Findings in cultured cells reveal a distinct difference in morphology of ureteral and bladder urothelial cells, supporting a difference in cell lineage. The present evidence suggests at least three lineages: 1) ureter/renal pelvis, 2) detrusor/trigone and 3) bladder neck/proximal urethra (506).

There seems to be no apparent difference between the urothelium of the trigone compared to the detrusor, in contrast to cells from the proximal urethra (422,507). In this region, there is a transition from urothelium to a stratified or columnar epithelium accompanied by a lack of urothelial-specific differentiation markers. In males, the proximal or prostatic urethra is lined by urothelium and distal to this is the membranous urethra where the urothelium is replaced by stratified columnal epithelium. In females, the transitional urothelium changes to stratified columnar epithelium. In addition, specialised chemosensory neuroendocrine cells are distributed within the urethral epithelia. These cells are often exposed to the lumen and may share similarities to GI enterochromaffin cells or chemosensory cells of the trachea or respiratory tract (often termed 'brush cells') (508), including expression of microvilli (Figures 36). These specialised urethral chemosensory cells are able to respond to potential noxious stimuli (using the classic taste transduction pathway) by releasing mediators such as acetylcholine (508,509). Similar to urothelial cells in the bladder wall, these urethral chemosensory cells are also in close proximity to sensory nerve fibres whereby intraurethral stimulation can lead to activation of underlying cells including bladder smooth muscle. In addition, there are also reports that have identified functional properties of sacral afferents that respond to changes in fluid flow through the urethra (510). While the

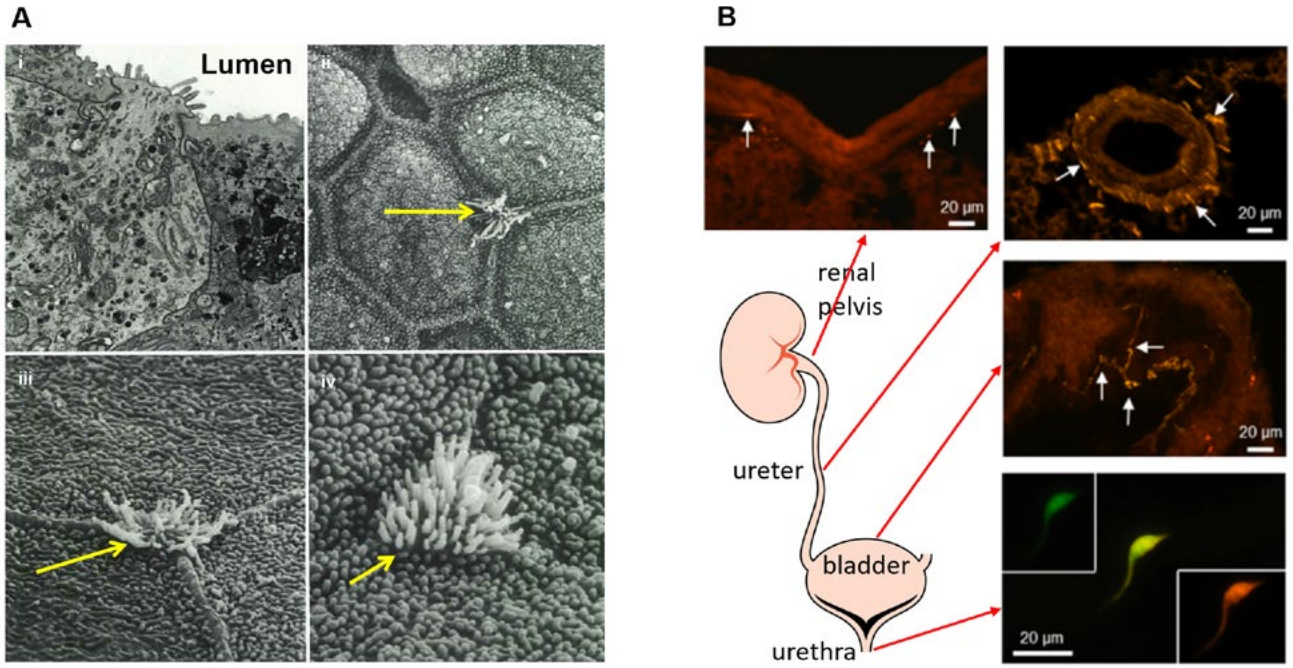

Figure 36. Urethral paraneurons and epithelial cells. *A: 'Open type' paraneurons in the dog urethra. i) paraneuron reaching the lumen (x14,000); ii-iv) microvillous cells among the epithelial cells (yellow arrows; ii), x4600, iii), x12,000, iv) x16,000. ([509], with permission). B: Cholinergic eGFP-expressing epithelial cells are restricted to the urethra in the urinary tract. In other parts of the urinary system, cholinergic nerve fibres (arrows) were visualised, but not ChAT-eGFP-expressing epithelial cells. ([508], with permission).*

functional significance of these findings are not yet be fully appreciated, it is clear that such 'sentinel' type cells are able to recognise potentially harmful stimuli (including bacteria) in the urethral lumen and in turn alter bladder function.

6. ROLES FOR UROTHELIAL CELLS IN VISCERAL SENSATION

While urothelial cells are often viewed as bystanders in the process of visceral sensation, recent evidence has supported the view that these cells function as primary transducers of some physical and chemical stimuli and are able to communicate with underlying cells including bladder nerves, smooth muscle and inflammatory cells. (Figure 37)

6.1. Influence of the extracellular matrix.

The urothelium can respond to a wide variety of mechanical stresses during bladder filling and emptying by activating a number of possible transducer proteins. Possibilities of mechanical signals include bladder pressure, tension in the urothelium or bladder wall, torsion, geometrical tension, movement of visceral organs and even urine tonicity and pH (511). Alterations in the composition of urine are a type of stress, and the contents can vary in both their rate of delivery as well as the particular constituents. Additionally, dynamic reciprocal interactions of the urothelium with underlying extracellular matrix (ECM) not only aid in maintaining normal bladder structure but also play an important role in generating signalling responses. The urothelium is highly sensitive to the mechanics of the underlying ECM, thus understanding the complexity and relationship between mechanics and biological activities of cells throughout the bladder wall is important. In this regard, studies using multiphoton imaging have revealed differences in collagen fibre structure and recruitment throughout the bladder wall (Figure 38) (512,513). For example, collagen type III fibres display specific orientations depending on bladder volume. During bladder expansion, these collagen fibres straighten in the direction of the applied force and lie parallel to the urothelium and smooth muscle. This arrangement could permit maximal bladder storage without imposing stress on the bladder wall, thus assuring adequate bladder compliance (513). Moreover, ECM pathology impacts on the ability of the urothelium to sense changes in mechanical deformation occurring during a micturition cycle and release mediators, such as ATP, that influence sensation. ATP released by the urothelium and purinergic receptors on subepithelial sensory nerve terminals constitute a key part of a primary mechanical sensing system in the bladder. This type of epithelial-neural communication is a key component of Burnstock's 'tubes and sacs' hypothesis (514,515). It is likely that pathology-induced changes of fibre architecture could alter neural-epithelial interactions, including the response to mechanical strain, that can influence bladder compliance and sensation.

Additional lines of evidence suggest that urothelial cells participate in the detection of both physical and chemical stimuli. Bladder nerves (afferent and efferent) are localised in close proximity, and some within, the urothelium (516-519). In addition, urothelial cells express numerous receptors and ion channels similar to those found in both nociceptors and mechano-receptors. Finally, these cells secrete a number of transmitters or mediators capable of modulating, activating or inhibiting sensory neurons.

6.2. Urothelial-neuronal-smooth muscle signalling.

Recent studies have shown that both afferent and autonomic efferent nerves are located in close proximity to the urothelium. Peptidergic, P2X- and $TRPV_1$- immunoreactive nerve fibres presumed to arise from afferent neurons in the lumbosacral dorsal root ganglia are distributed throughout the urinary bladder musculature as well as in a plexus beneath and extending into the urothelium (450,518). In humans with neurogenic detrusor overactivity intravesical admin-

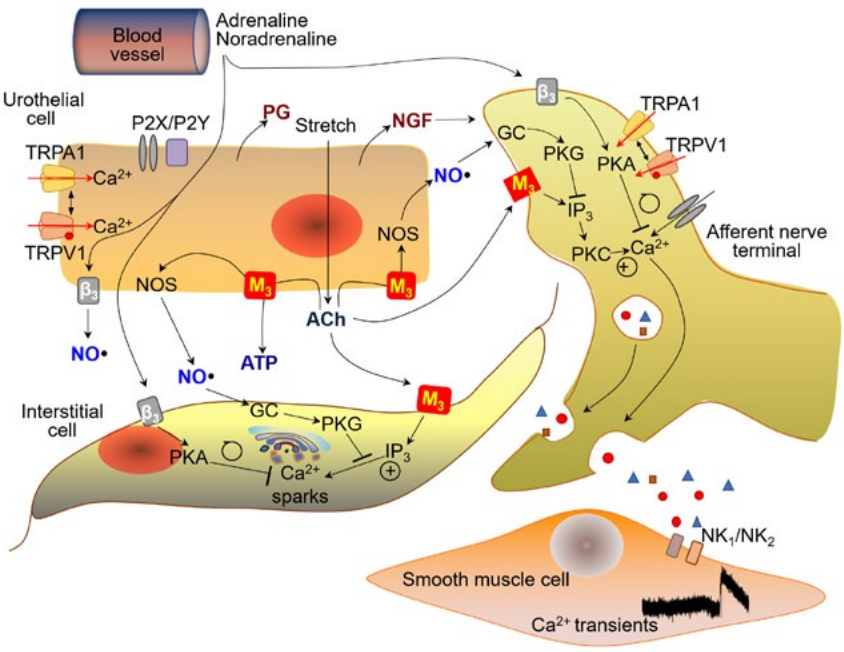

Figure 37. The sensory web. *Hypothetical model depicting possible interactions between bladder nerves, urothelial cells, smooth muscle, interstitial cells and blood vessels. Urothelial cells can also be targets for transmitters released from nerves or other cell types. Urothelial cells can be activated by either autocrine (i.e. auto-regulation) or paracrine (release from nearby nerves or other cells) mechanisms.*

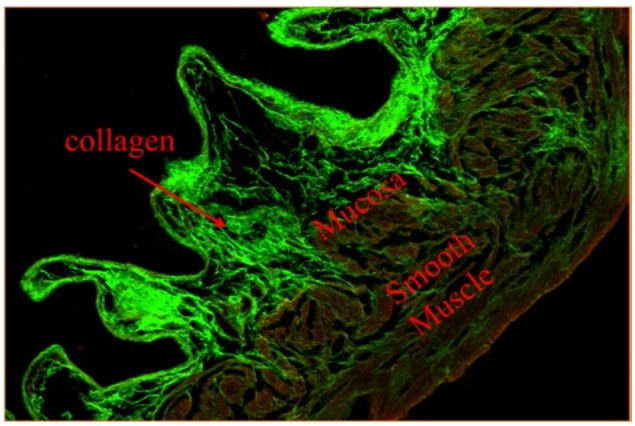

Figure 38. Collagen fibre orientation throughout the bladder wall. *([512], with permission).*

istration of resiniferatoxin, a C-fibre afferent neurotoxin, reduces the density of $TRPV_1$ and $P2X_3$ immunoreactive suburothelial nerves, indicating that these have sensory a sensory function (520,521). In addition, immunohistochemical studies have also revealed both adrenergic (tyrosine hydroxylase) positive as well as cholinergic (choline acetyltransferase, ChAT) positive nerves in close proximity to the urothelium (517).

A network of cells with morphologic characteristics similar to those of myofibroblasts or interstitial cells is also detected in the suburothelial space of the bladder in both humans and animals (522-525). These cells, extensively linked by gap junctions and have close contacts with nerves, can respond to neurotransmitters, such as ATP released from nerves or urothelial cells, suggesting that they could act as intermediaries in urothelial-nerve interactions (522,524,526). Thus, the anatomical substrate for bidirectional urothelial-neural communication exists within the urinary bladder.

As the urothelium functions as part of a 'sensory web', whereby these epithelial cells are likely to exert a local and direct influence on smooth muscle contractility. This type of modulation was initially reported as an inhibitory effect on bladder contractility in mucosal-denuded bladder strips (527). Studies by Hawthorn *et al.* suggested this effect was due to release of an unidentified 'urothelial-derived inhibitory factor' or UDIF (528). Subsequently, a series of urothelial-derived factors (such as ATP, acetylcholine, nitric oxide, prostaglandins) have been postulated to directly or indirectly modulate smooth muscle tone and contractility (529,530).

6.3. Involvement of the urothelium to 'sense' chemical and mechanical stimuli.

The involvement of urothelial function in sensory signalling is suggested by the finding that urothelial cells express various receptors that are linked to mechano- or nociceptive sensations. Examples of neuronal "sensor molecules" (receptors/ion channels) that have been identified in urothelium include receptors for purines ($P2X_{1-7}$ and $P2Y_{1,2,4}$), adenosine (A_1, A_{2a}, A_{2b} and A_3), noradrenaline (α and β), acetylcholine (muscarinic and nicotinic), protease-activated receptors (PARs), amiloride- and mechano-sensitive epithelial Na+ channels (ENaC), bradykinin (B1 and B2), neurotrophins (p75, trkA, EGF family ERbB1-3), corticotrophin releasing factor (CRF1 and CRF2), oestrogens ($ER\alpha$ and $ER\beta$), endothelins, PIEZO and various TRP channels ($TRPV_1$, $TRPV_2$, $TRPV_4$, $TRPM_8$ and $TRPA_1$) (84,531-542). The expression of these various receptors enable the urothelium to respond to a number of "sensory inputs" from a variety of sources. These inputs include increased stretch during bladder filling, soluble factors (many found in the urine) such as epidermal growth factor (EGF), or chemical mediators/peptides/transmitters such as substance P, calcitonin gene-related peptide (CGRP), corticotrophin releasing factor (CRF), acetylcholine, adenosine or noradrenaline released from nerves, inflammatory cells and even blood vessels (450,451,543,544).

Various stimuli can lead to secretion of numerous chemical substances such as neurotrophins, peptides, ATP, acetylcholine, prostaglandins, prostacyclin, nitric oxide (NO) and cytokines that are capable of modulating the activity of underlying smooth muscle (526,545) as well as nearby sensory neurons (450,451). For example, urothelial-specific overexpression of NGF results in increased bladder nerve 'sprouting' and increased voiding frequency (546,547). It has been shown that urothelial-derived NO can be released in response to mechanical as well as chemical stimulation and may either facilitate or inhibit the activity of bladder afferent nerves conveying bladder sensation (548). In this regard, activation of urothelial-receptors and release of inhibitory mediators may explain in part, the mechanism of action for therapies (e.g. β3-adrenergic receptor agonists) in treatment of bladder disorders such as OAB (549-551).

The mechanism underlying release of chemical mediators from the urothelium, including whether all sensory "inputs" stimulate membrane turnover (i.e., vesicular exocytosis) is not well understood. What little is known about the roles and dynamics of membrane-bound cytoplasmic vesicles in urothelial cell physiology is derived from measurements of membrane capacitance and microscopy of fixed tissues and cells (552). Alterations in membrane turnover can not only increase apical surface area (as described above) but also regulate the number and function of receptors and channels at the cell surface.

Epithelial cells in different organ systems may express similar receptor subtypes (553-555) Accordingly, epithelial cells could use multiple signalling pathways, whose intracellular mechanisms differ according to location and environmental stimuli. This would permit a greater flexibility for the cell to regulate function and respond to complex changes in their surrounding micro-environment. Whether urothelial-sensor molecules all feed into a diverse array of signalling pathways or share similarities with systems such as olfaction, whereby hundreds of receptors share identical transduction cascades (556), is yet to be uncovered.

Purinergic receptors. Since the first report of distension-evoked ATP release from the urothelium there is now abundant evidence supporting a role for urothelial-derived release of ATP in autocrine and paracrine signalling within the lower urinary tract (557). ATP is abundant in the cell cytoplasm and can be released extracellularly by several mechanisms including vesicular exocytosis, transporters such as a member of the ATP-binding cassette (ABC) transporter superfamily, or anion-selective channels such as the maxi-anion channel (84). ATP is released from both the apical and basolateral urothelial surfaces in response to bladder stretch and can act on $P2X_2$ and $P2X_3$ urothelial receptors to stimulate stretch-induced exocytosis (552). Furthermore, pannexin channels, which are expressed throughout the urothelium (Figure 39), may be involved in modulating voiding reflexes via urothelial release of ATP (538,558).

The expression of both P2X and P2Y receptors in nerve fibres and myofibroblasts in close proximity to the bladder lumen, and the sensitivity of these cells to ATP suggest that basolateral ATP release from the urothelium may also influence the function of myofibroblasts and bladder nerves (523,559). In addition, prolonged expo-

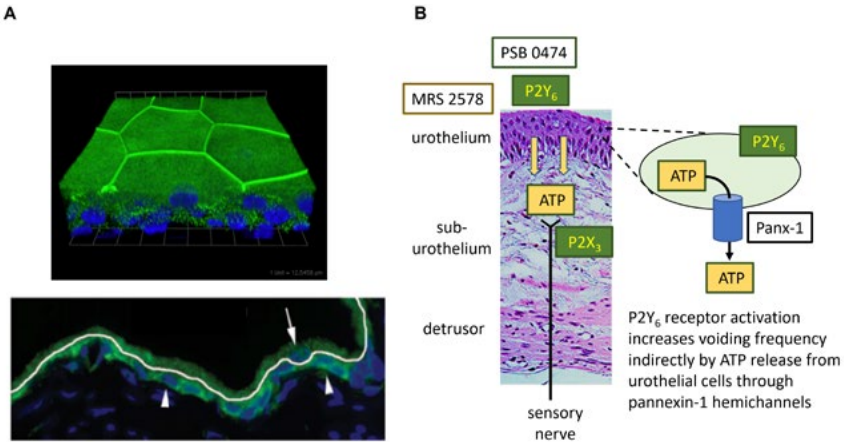

Figure 39. Purinergic receptors in the bladder wall. *A: upper panel; 3-dimensional confocal reconstruction showing urothelial localisation of P2X3 (green; nuclei blue) ([552], with permission). Lower panel; pannexin-1 channel expression in superficial, umbrella cells (arrow) as well as in underlying intermediate and basal cell layers (arrowheads). White line denotes boundary of umbrella cell layer, determined by cytokeratin staining, ([538], with permission). B: Activation of urothelial P2Y6 receptors (PSB 0474, P2Y6 receptor agonist; MRS 2578, P2Y6 receptor antagonist) can modulate urodynamic responses in the anesthetized rat. An increase of voiding frequency is postulated to be by increased ATP release from the urothelium through pannexin-1 hemichannels (modified from [558]).*

sure to a desensitising concentration of ABMA reduced the activity of mechano-sensitive pelvic nerve afferents in an *in vitro* model of rat urinary bladder (560). $P2X_2$ and $P2X_3$ receptors are expressed on unmyelinated afferent fibres innervating the bladder, and thus the hypothesis has been put forward that mechano-sensitivity, at least in those afferents in proximity to the urothelium, involve ATP release by stretch and activation of $P2X_2$ and $P2X_{2/3}$ receptors on afferents fibres (534,561). Mice lacking the $P2X_3$ receptor showed reduced inflammatory pain and marked urinary bladder hyporeflexia with reduced voiding frequency and increased voiding volume (562). This suggested that $P2X_3$ receptors are involved in mechano-sensory transduction underlying both inflammatory pain and hyperreflexia indicating a role in physiological voiding reflexes (562). Also, as $P2X_3$ null mice have a lower frequency of voiding contractions during bladder filling this suggests that P2X antagonists could play a role in treatment of OAB. The amiloride-sensitive apical Na^+ channel, ENaC, may be involved in mechano-transduction by controlling basolateral release of ATP (563,564). In addition, intercellular communication mediated by gap junctions in myofibroblasts could provide a mechanism for long-distance spread of signals from the urothelium to the detrusor muscle (526). Of interest, this type of nucleotide-mediated wave of cell-cell communication may also play a role in the response to injury (564). In the normal bladder, it may be hypothesised that a balance between the excitatory effects of ATP and inhibitory effects of nitric oxide (NO) release may determine micturition thresholds and frequency and that this balance may be disturbed in bladder disorders. For example, stimulation of muscarinic receptors localised near the luminal surface of the bladder affect voiding functions via mechanisms involving ATP and NO release from the urothelium that in turn altered the firing properties of afferent nerves (565). This supports the view that urothelial-afferent nerve interactions can influence reflex voiding functions. While evidence supports a role for ATP and purinergic receptors in modulating symptoms in several urological diseases, the mechanisms underlying activation of the micturition pathway at lower bladder volumes (during urgency) and mediators (amount; type) involved are not understood. In addition, the directionality of transmitter release, the mixture of receptor subtypes in the apical and basolateral domains and interactions between multiple transmitters is likely to affect the nature of the output in both health and disease.

TRPV1 channels.

The ability of capsaicin to evoke nitric oxide (NO) release from rat urothelium, first reported in 1998, provided, albeit indirect, demonstration that $TRPV_1$ channels are expressed in urothelial cells and that urothelial cells and afferent nerves, which also express these channels, share a number of common properties (566). This ion-channel protein is activated by capsaicin, as well as by moderate heat, H^+, nitro-fatty acids and lipid metabolites such as anandamide (an endogenous ligand of both cannabinoid and vanilloids receptors) (567,568). $TRPV_1$-positive nerves are in close contact with urothelial cells (569,570). Activation of urothelial cells with capsaicin or resiniferatoxin can increase intracellular Ca^{2+}, evoke transmitter (NO or ATP) release and elicit transient currents (518,571). Similar to that in sensory neurons, urothelial-response to vanilloids are enhanced by low pH, blocked by $TRPV_1$ antagonists and eliminated in $TRPV_1$ null mice (518). In afferent neurons, $TRPV_1$ is thought to integrate/amplify the response to various stimuli and to play an essential role in the development of inflammation-induced hyperalgesia. It seems likely that urothelial-$TRPV_1$ might participate in a similar manner, in the detection of irritant stimuli following bladder inflammation or infection.

Additional TRP channels.

Much less is known about the involvement of other TRPs in bladder function or disease. For example, the mouse urothelium expresses mRNA for an additional 19 TRP family members (572). $TRPV_4$, which is a nonselective cation channel activated by a number of stimuli including heat, shear stress, changes in osmolarity and lipid ligands, is expressed mainly within the epithelium of the urinary bladder (573). While a definitive role for $TRPV_4$ in bladder function has not been established, $TRPV_4$-null mice exhibit impaired voiding responses and, intravesical instillation of a $TRPV_4$ agonist in the rat triggers a novel voiding reflex that could regulate the late phase of micturition (519,574). Additional studies suggest activation of urothelial-$TRPV_4$ facilitates bladder reflexes via activation of mechano-sensitive, capsaicin-insensitive, C fibres (575). In addition, in the awake ewe, $TRPV_4$ may also be involved in a urethra-to-bladder reflex, proposed to facilitate bladder emptying (576). Another member of the TRP family, $TRPA_1$ (characterised as a thermoreceptor activated by noxious cold), is expressed in C-fibre afferents as well as urothelium and agonists to this channel induce bladder hyper-

reflexia (577). Of interest is the finding that hydrogen sulphide, which may be formed during infection/inflammation, is an activator of $TRPA_1$.

Acetylcholine and the urothelium.
The urothelium expresses the full complement of muscarinic receptors as well as enzymes necessary for the synthesis and release of acetylcholine (543,578). Furthermore, the urothelium releases acetylcholine following both chemical and mechanical stimulation (543). The mechanism underlying acetylcholine release from urothelium may be through organic cationic transporters (OCTs) rather than vesicular exocytosis, differing from that of bladder nerves (579). Once released, urothelial-derived acetylcholine is likely to exert effects via a number of sites including smooth muscle and nerves, as well as by urothelial associated-muscarinic or nicotinic receptors, the latter could contribute to feedback mechanisms modifying urothelial function (580). In addition, stimulation of urothelial-cholinergic receptors elicits release of mediators such as nitric oxide, prostaglandin as well as ATP, which could alter bladder sensation by stimulating nearby sensory afferent nerves (581-583).

Thus, targeting muscarinic receptors and/or urothelial synthesis or release mechanisms may play an important role in the treatment of several bladder disorders. By inhibiting SNARE-dependent exocytotic processes, botulinum toxin A (BTX-A) can prevent the release of transmitters from bladder nerves as well as translocation of various receptors and channels to the plasma membrane (584) Urothelial-derived acetylcholine may not be sensitive to BTX-A, however studies have shown that other transmitters (such as ATP) released by the urothelium can be blocked by this treatment in addition to normalising the expression of urothelial-receptors ($TRPV_1$; muscarinic) and trophic factors (585,586). These and other studies suggest that the urothelium may be a target for this treatment and that urothelial-released mediators may contribute to sensory urgency.

Cannabinoids.
The multi-centre CAMS (Cannabinoids in Multiple Sclerosis) study reported that the use of cannabis-based extracts significantly improved symptoms of urge incontinence and detrusor overactivity in patients with multiple sclerosis. This observation has provoked interest in the study of expression and function of cannabinoid receptors in the bladder. Endogenous cannabinoids can potentially interact with $TRPV_1$ but in addition can act on G-protein coupled cannabinoid receptors 1 and 2 (CB1, CB2). In the human bladder, both receptors could be identified in the urothelium and detrusor where CB1 receptors were more abundant than CB2 (587). In patients with bladder pain syndrome and idiopathic detrusor overactivity (IDO), a significant increase of nerve fibres expressing CB1 in the urothelium was observed, strongly suggesting a role for CB1 in overactive bladder (588). In contrast, Gratzke *et al.* (589) found CB2 receptors predominated in the urothelium, suburothelium and on sensory nerve fibres, In addition, that CB2 agonists inhibited nerve induced contractions of the bladder providing evidence that CB2 receptors are important in micturition.

Expression of CB1 receptors were also identified in the urothelium and on nerve fibres in the detrusor of mouse bladder (590). These receptors co-localised with $P2X_3$ receptors, suggesting an interaction between cannabinoid and purinergic systems. In addition, a synthetic cannabinoid active at both CB1 and CB2 receptor was shown to inhibit the evoked release of CGRP from afferent nerve terminals (591). Functional experiments also found a reduction in distension-evoked afferent firing in response to application of a CB1 agonist. In particular, high threshold afferents typically associated with noxious stimuli were directly affected. A recent study in the rat bladder by Aizawa *et al*. (592), used a peripherally restricted inhibitor (URB937) of the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH). Consequent upregulation of the peripheral endocannabinoid system reduced bladder overactivity and C-fibre hyperexcitability provoked by PGE2 and suggested an important role of the peripheral endocannabinoid system in bladder overactive conditions induced by afferent hypersensitivity. There is also evidence that the fatty acid amid anandamide, which activates both CB1 as well as $TRPV_1$ receptors on primary afferents, is upregulated in a model for inflammatory pain and induces bladder hyperreflexia (593). Taken together these studies suggest that CB receptors in the bladder may have a modulatory role in sensory afferent signalling; a greater understanding of which could lead to new therapeutic strategies for treatment of bladder disorders. Understanding the differential roles of CB1 and CB2 receptors may add a new dimension to our ability to target these pathways.

PIEZO channels.
Recent findings have revealed that a mechano-sensitive ion channel, PIEZO2, is involved in 'sensing' bladder filling (531). This channel is expressed in bladder urothelial (umbrella) cells in addition to nerves that innervate the urinary bladder. Further, PIEZO2-null mice exhibit a reduction in activation of bladder nerves to bladder stretch which in turn lengthens the interval between bladder contractions. PIEZO2-null mice also exhibit larger bladders, and this type of bladder wall re-modelling may suggest alterations of the extracellular matrix. During bladder filling, the matrix impacts on the ability of the urothelium to sense changes in mechanical deformation occurring during a micturition cycle and thus releases mediators that affect sensation. Findings in PIEZO2-null mice also has translational relevance, as humans lacking PIEZO2 exhibit a small number of voids per day though often suffer urinary urgency. The involvement of PIEZO2 in bladder mechano-sensation is important and also suggests a basis for the observation that urgency and frequency may be differentially regulated.

7. CLINICAL SIGNIFICANCE OF THE SENSORY WEB

Defects in urothelial sensor molecules and urothelial cell signalling are likely to contribute to the pathophysiology of bladder diseases. For example, a number of bladder conditions (BPS/IC, spinal cord injury (SCI), chemically-induced cystitis) are associated with augmented release of urothelial-derived ATP, which is likely to result in altered sensations or changes in bladder reflexes induced by excitation of purinergic receptors on nearby sensory fibres (536,594). ATP can also act in an autocrine manner that would act to facilitate its own release from urothelial cells. Augmented expression/release of urothelial-derived chemical mediators is likely to reduce the threshold for activation of nearby bladder afferents. Thus, the urothelium has the potential for amplifying signals, both within the urothelium and the bladder wall and contributing to a gain of function in sensory processing. Stressors that can impact on this 'gain of function' include alterations in levels of trophic factors as well as stress and steroid hormones. For example, altered levels of circulating oestrogens may play a role in urinary bladder dysfunction, including urgency and frequency (466,59) The resulting structural and functional abnormalities may lead to enhanced signalling between the urothelium and underlying cells.

Changes in epithelial signalling/barrier function are not unique to the urinary bladder. Activation of keratinocytes alone in mice expressing a light-activated channel can result in nociceptive re-

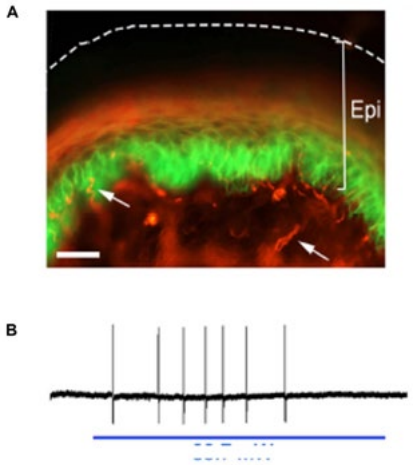

Figure 40. Blue light stimulates multiple types of afferents in KRT-ChR2 transgenic mice. *A: ChR2-YFP expression in glabrous skin of KRT-ChR2 mouse. PGP9.5 positive nerve fibres (red) are in dermis and epidermis (arrows); B: example of a cutaneous fibre activation in response to blue laser applied to KRT-ChR2 skin in an ex vivo preparation. ([596], with permission).*

sponses, demonstrating signalling between epithelial and neural tissues (Figure 40) (596). In addition, airways epithelia in asthmatic patients, as well as keratinocytes in certain types of skin diseases, also exhibit a number of similar abnormalities and compromised repair processes (553,597,598). This is particularly relevant given the high incidence of associated diseases that can include both visceral and somatic conditions, many of which exhibit a shared loss of epithelial barrier function. This altered urothelial permeability seen in many bladder disorders may actually be an advantage for drug delivery, as uptake of intravesical drugs is likely to be enhanced. Further, many of these systems do share a number of commonalities that include increased afferent activation of supraspinal centres in order to effectively coordinate efferent outflow as well as dependence on similar types of neurotransmitters (such as ATP) to mediate sensory responses. A recent example is the use of $P2X_3$ antagonists in the treatment of both respiratory and urological disorders (599). However, though major advances have increased our understanding of urothelial biology and potential impact on bladder physiology, there are still a number of unanswered questions that persist. These include mechanisms by which mediators are released, which mediators are most important for normal bladder function and the influence of pathology and co-morbidities on the urothelial 'sensory web'. Ideally, further knowledge of the unique properties of the urothelium could lead to the development of smart delivery systems (e.g., transporting drugs to intended sites and releasing drugs in response to specific signals) in addition to tissue engineering.

VI. THE CELL PHYSIOLOGY OF BLADDER WALL TISSUES

1. INTRODUCTION

For the majority of the 24-hour day/night cycle, the bladder is in a relaxed state, enabling the filling phase, accommodating increasing volumes of urine at low intravesical pressures until a convenient time is chosen to void. Voiding is achieved by forceful, coordinated contractions of detrusor smooth muscle with concomitant relaxation of the urethral sphincter and is completed in typically less than thirty seconds.

The relaxed state of the bladder during filling is anything but passive; multiple cellular players are active, sensing bladder volume, adjusting their length and surface area and relaying information locally to sensory afferents and neighbouring smooth muscle layers. Given the remarkable complexity of the bladder wall and the 'agility' of cells to respond to a constantly changing environment, it is not surprising that the cellular components have a rich array of physiological mechanisms and associated regulatory machinery.

This section will review our knowledge of the physiology of the smooth muscle tissues of the bladder wall, namely the *muscularis mucosae* contained within the *lamina propria*, and the detrusor. A helpful description of the term 'tissue' in this context has been given by Gabella who stated that '*the muscle is not just an assembly of cells but is a tissue, where interaction of all of its cells is of crucial significance'* (600). Focus will be given to the functional expression of ion channels and G-protein coupled receptors (GPCRs) and how these contribute to smooth muscle tissue physiology; consideration will also be given to putative modulatory non-muscle cells.

2. STRUCTURE OF THE BLADDER WALL

The multi-layered bladder wall is commonly considered to comprise the urothelium, *lamina propria* (potentially with a sub-urothelial layer), *muscularis mucosae* (in some species), detrusor, and serosa/adventitia (601) (Figure 41).

2.1. Urothelium.

The urothelial layer contains umbrella cells that luminally are in direct contact with the urine and basally, contact the underlying intermediate and basal cells. The base of the urothelium is adjacent to a basement membrane which delineates the *lamina propria* layer; moreover, the upper *lamina propria* is sometimes referred to as the sub-urothelium (602) and the deep *lamina propria* referred to as the submucosa. The urothelium is reviewed in Section V and briefly referred to here for context.

2.2. Lamina propria.

The *lamina propria* is a rich milieu of connective tissue, abundant collagen and is home to a variety of cells including mast cells, macrophages, afferent and efferent nerves and the bladder's microvasculature (603-605). Its main cellular residents - fibroblasts, interstitial cells (IC) and myofibroblasts have been the focus of morphological and physiological investigation in recent years; while there is not yet consensus on nomenclature, the evidence supports heterogeneity in terms of molecular phenotype and physiology.

The *lamina propria* provides the skeletal structure to the bladder, maintaining its overall ovoid shape across a dynamic range of volumes (605) that includes rapidly changing from full to empty following contraction of the surrounding detrusor smooth muscle during micturition. A demonstration of this important role and surprising strength of bladder *lamina propria* tissue is seen in *ex vivo* pressure-volume recordings of murine bladder where filling pressure curves were similar in intact and detrusor-free preparations (606-607).

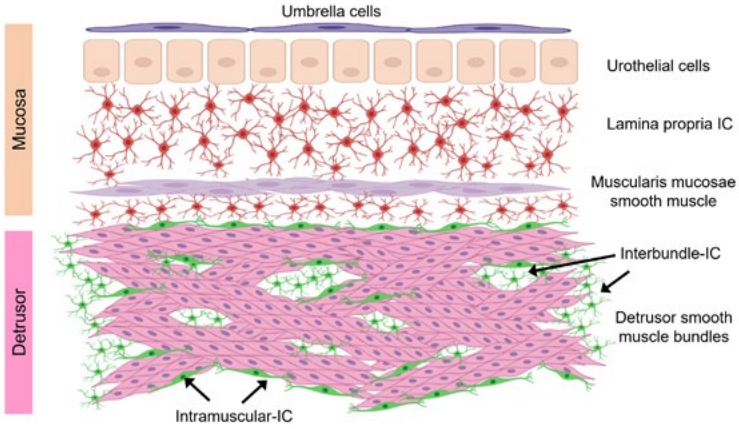

Figure 41. Schematic of major cell types in the bladder wall. *A simplified summary of the three major cell types in the bladder wall representing guinea-pig, pig or human bladder. The urothelium is shown comprising urothelial cells and the luminal-facing umbrella cells. Within the lamina propria is a network of interstitial cells (IC) and abundant collagen (not shown). Nerves and microvessels are abundant within the lamina propria and are not illustrated here. The relatively sparse smooth muscle component within the lamina propria, namely the muscularis mucosae is separated from the underlying bulk detrusor smooth muscle by IC and collagen (not shown). IC are associated with the detrusor smooth muscle bundles, either running in parallel with the bundles, intramuscular-IC, or a more stellate-shaped population, the interbundle-IC occupying the spaces between smooth muscle bundles. Graphic created in BioRender software.*

Histologically, the *lamina propria* shows specialisation from the base of the urothelium to the detrusor boundary. Transmission electron microscopy (TEM) studies of rat bladder demonstrate that the sub-urothelium or superficial/upper *lamina propria*, is rich in fibroblasts, afferent nerves, capillaries and associated pericytes and a loose arrangement of collagen. The deep *lamina propria*, abutting the detrusor layer has comparatively fewer fibroblasts and dense, woven, thick collagen fibrils (604). This structure explains the remarkable strength of the mucosa layer.

Within the *lamina propria* of several species, including human (608-614), pig (615) and guinea-pig (614,616,617) a further specialisation is found, specifically, a distinctive layer of smooth muscle, the *muscularis mucosae* (MM), that although less dense than detrusor tissue, has surprisingly robust contractile activity. Bladders of smaller laboratory mammals, namely rat and mouse, apparently do not contain MM tissue (614,618). In bladders containing an MM layer, a dense layer of connective tissue layer connects with the detrusor, regarded as the submucosa (604); this is notably absent in murine or rat bladder.

Cells in the *lamina propria* as described above, that are named fibroblasts, fibroblast-like cells, myofibroblasts, interstitial cells (IC), interstitial cells of Cajal (ICC), or ICC-like cells can be visualised in histological sections stained with traditional haematoxylin & eosin; moreover, immunolabelling studies with antibodies to e.g. smooth muscle α-actin, vimentin, PDGFRα (Figure 42) and other proteins, support the notion of diverse heterogeneous cells in this region (618-626). Species variability seems likely, given that some bladders have MM (see above) and others do not; similarly, intramural ganglia are absent from rat bladder but are present in guinea-pig (620,627) and pig bladder (628). Some TEM studies support the presence of cells with a fibroblast ultrastructure (605); others support cells with a myofibroblast-like ultrastructure (619,629-631), some have reservations about the presence of true myofibroblasts in healthy bladder (632,633) and some conclude that some combination of fibroblasts, myofibroblasts and IC that are ultrastructurally distinctive from each other are present (622,634). While a consensus has not yet been reached it is possible that the *lamina propria* contains cells which are ultrastructurally fibroblast-like and that there is heterogeneous expression of molecular markers and associated physiological phenotype.

The putative role(s) of such cells will be considered below in the context of their known physiological properties. Whether or not they make structural connections with each other, or with other players in the bladder wall is uncertain and understanding their role(s) will be enabled by knowing if they act individually or can communicate physiologically. A TEM study of rat bladder showed that while cells with a fibroblast ultrastructural profile were abundant and came into close proximity to each other (10-20 nm), there were no specialised junctions connecting adjacent cells (605). This contrasts with the findings of a TEM study of human, rat and mouse bladder which reported *adherens* junctions connecting *lamina propria* IC (624) and also contrasts with studies reporting gap junctions between *lamina propria* IC in human bladder (619).

2.3. Detrusor.

The detrusor is the main component of the bladder wall, comprising smooth muscle cells (SMC), nerves and IC. Detrusor smooth muscle has an idiosyncratic arrangement, with cells grouped in bundles that interlock and interweave with large spaces between the bundles in a full bladder that become smaller spaces when the bladder has emptied (601). This arrangement enables accommodation of varying volumes of urine, importantly at low intravesical pressures, a phenomenon described as compliance.

Communication between detrusor SMC within a bundle may be facilitated by the presence of gap junctions; evidence supporting their presence at the mRNA and protein level indicates low expression of connexins in normal bladder (635) compared with upregulation in obstructed rat bladder (636-638) and in cyclophosphamide-treated mice (639). TEM both supports (637,640,641) and fails to provide (600) ultrastructural evidence for gap junctions connecting SMC in the detrusor. *Adherens* junctions are reportedly common between detrusor SMC, with adjacent membranes around 30-50 nm apart (600). Interestingly, SMC are also structurally associated with each other via contacts from membrane digitations and also via fusion or adhesion of basal *laminae* forming a sealed region; areas of contact as close as 10 nm have been reported (600).

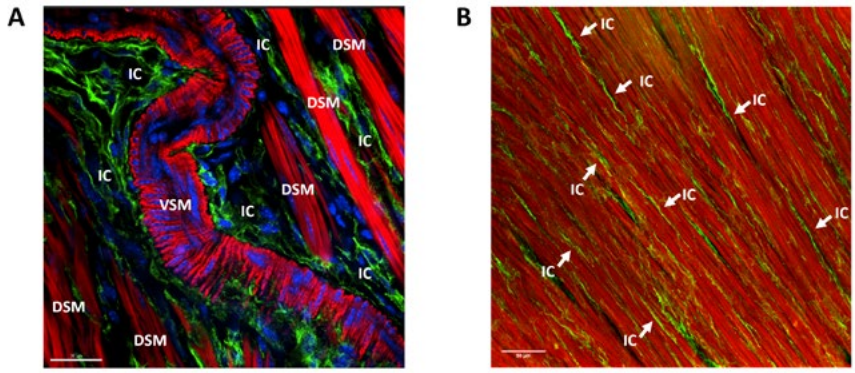

Figure 42. PDGFRα+-cells in murine bladder. *A: Fluorescence micrograph of C57Bl/6 murine bladder flat-mount stained with phalloidin (red) to show smooth muscle, anti-PDGFRα IC (red) and DAPI to counterstain nuclei (blue). Scalebar represents 30 μm. DSM – detrusor smooth muscle; VSM – vascular smooth muscle in arteriole; IC – interstitial cells. B: Lower magnification of C57Bl/6 murine bladder flat-mount stained with phalloidin (red) to show smooth muscle and anti-PDGFRα IC (red). Scalebar represents 50 μm. Images courtesy of Conor Breen and Karen McCloskey, Queen's University Belfast.*

Detrusor innervation is dense and efferent nerves are abundant although afferent axons are also present (642). In the detrusor, axons contact SMC commonly through the surface of a varicosity, with a glial-free 'window' that is concave to the SMC cell membrane, forming an intercellular gap of around 40nm (600). There is a rich literature on bladder innervation, spanning several decades where efferent nerves bring about detrusor contraction via parasympathetic signalling mediated by acetylcholine and ATP (643). A notable variance is human detrusor where contraction is considered to be almost exclusively mediated by acetylcholine, with emergence of purinergic components in pathophysiology (644,645)

As was the case for *lamina propria*, there is a body of evidence supporting the presence of interstitial cells (IC) in the detrusor, also described as ICC, ICC-like cells, Cajal-like cells and fibroblast-like cells (613,620,623,624,626,646-658). The functional relevance of these cells, and indeed their nomenclature and biomarkers have been the focus of debate in the field. Here, their physiological properties in relation to ion channel and GPCR expression will be reviewed and their potential relationship to detrusor smooth muscle physiology will be explored. In this article they will be referred to as 'IC' and no disrespect is intended to published works that have used a different nomenclature.

3. LAMINA PROPRIA PHYSIOLOGY

In addition to the important structural role of the *lamina propria* in acting as a *de facto* skeleton for the organ, it is increasingly recognised as having physiological relevance (603), particularly during bladder filling. Under-recognition of the contribution of the *lamina propria* to bladder physiology may in part be due to the traditional research focus on detrusor contraction and associated pharmacology. A substantial proportion of studies utilising *in vitro* myography/tension recordings tended to be carried out on bladder strips that were either 'intact' or had the 'urothelium' removed. This descriptor was often somewhat of a misnomer, as removal of the entire mucosa (urothelium and *lamina propria*) was carried out. Nevertheless, it is apparent that the presence of the mucosa could modify contraction measurements from bladder tissue strips, whether evoked by exogenously applied agonists, in response to electrical field (EFS) of intramural nerves, or indeed spontaneous activity stimulation (659).

Several hypotheses have been examined in relation to the contribution of the mucosa to bladder contraction, and in particular, modulation of detrusor contraction by elements of the mucosa. Firstly, release of transmitter substances from the urothelium, including excitatory (acetylcholine and ATP) and inhibitory substances impact detrusor contraction (for reviews see (660,661). An as yet unidentified urothelial-derived inhibitory factor (UDIF) is proposed to be the cause of mucosal/urothelial inhibition of detrusor contraction (662-666) ; a number of candidate substances have been eliminated from the identification of this elusive UDIF and we await further work in this area. A second possibility is that *lamina propria* IC or myofibroblasts themselves contract and therefore the contractility measured in intact strips of bladder is the sum of IC and detrusor SMC contraction. There is some evidence to support such a scenario in bladder (667); moreover, myofibroblasts are known to have a contractile phenotype and contribute to wound closure (668,669). A third explanation is the contribution of the *muscularis mucosae* (MM) smooth muscle which is discussed below.

3.1. Muscularis mucosae.

The *lamina propria* of bladders of larger laboratory animals including guinea-pig (614,616,617,670,671), as well as pig (614,615) and human (608-612,614,653,670) have a MM layer comprising a discontinuous layer of smooth muscle cells, separated from the underlying detrusor by a submucosa of connective tissue. The physiological relevance of this tissue is intriguing, and recognition of its properties may help to explain some of the aspects of mucosal contribution to bladder contraction.

Receptor-mediated contraction/relaxation.

Accumulating evidence indicates that MM smooth muscle is physiologically different from detrusor smooth muscle even though, like the detrusor, MM smooth muscle also exhibits spontaneous contractions, Ca^{2+}-waves and flashes, and contracts in response to EFS and exogenously applied agonists. A study of contractile activity in MM and detrusor strips of porcine bladder, found that MM exhibited contractions in response to agonists, EFS or that were spontaneous. In contrast to the detrusor, in MM strips, inhibitors of muscarinic, adrenergic and purinergic receptors did not affect tetrodotoxin-sensitive EFS-contractions, nor did a nitric oxide synthase inhibitor (672). Functional evidence supporting expression

of muscarinic and purinergic receptors in porcine MM is seen in its ability to contract to carbachol and αβ-methylene ATP (672,673), thereby suggesting that neural release of acetylcholine, ATP or noradrenaline to MM does not occur during EFS. Conversely, another study found EFS-contractions to be inhibited by the muscarinic inhibitor, atropine (614) but also agreed that adrenergic inhibition had no effect. The situation is reportedly different in guinea-pig bladder where EFS-contractions in both MM and detrusor strips were sensitive to cholinergic and purinergic inhibitors (616) and were largely indistinguishable from each other in terms of pharmacological sensitivity.

Relaxation of MM occurs via nitrergic and adrenergic signalling although the mechanisms are not yet fully elucidated. Porcine MM inhibitory nitrergic innervation is seen in EFS-relaxations in preparations pre-contracted by the thromboxane A2 agonist, U46619, that were abolished by the nitric oxide synthase inhibitor, L-NNA. Interestingly, while a β-adrenoceptor agonist relaxed the tissue (614), similar to effects on detrusor (674), EFS-relaxations were insensitive to guanethidine (sympathetic nerve depletion) indicating that β-adrenoceptors are functionally expressed but neurally-released noradrenaline does not mediate MM relaxation. The study also showed that sympathetic nerves were not structurally associated with MM but with the mucosal vasculature, paralleling observations in the detrusor layer (614).

Spontaneous activity.
Spontaneous activity in the MM from porcine and guinea-pig preparations, as per detrusor smooth muscle, is considered 'myogenic' as it is unaffected by tetrodotoxin, muscarinic, purinergic or adrenergic inhibitors. This non-neuronal origin is further understood as not being generated by release of acetylcholine, ATP or noradrenaline from nearby non-neuronal cells (616,672) although as described below, the activity can be modulated by transmitters.

Interestingly, the force generated by a MM spontaneous contraction was found to be similar to that of a spontaneous contraction from a detrusor strip; this seems remarkable given that histologically, the smooth muscle content of detrusor strips is markedly greater than the loose arrangement of SMC in the MM (616). An explanation may be found in the observations that (a) detrusor strip maximal contraction to depolarisation with 60mM K^+ is reportedly 40-fold greater than MM strips and (b) the maximal depolarisation-evoked contraction in MM strips was not significantly larger than its preceding spontaneous contractions, suggesting that MM spontaneous contractions are generated by the majority of SMC present, whereas in detrusor strips, only a fraction of available SMC were active.

MM spontaneous contractions are modulated by chemical and mechanical signalling native to the bladder wall. Human and guinea-pig MM typically exhibited spontaneous contractions and further contracted in response to carbachol although the P2Y agonist UTP did not modify or evoke contractions (670). The amplitude of porcine bladder MM spontaneous contractions amplitude were also enhanced by carbachol (658); moreover the contractions were markedly larger in juvenile vs adult bladders. The rate of spontaneous activity of porcine mucosa was found to be increased during mechanical stretch; this phenomenon was sensitive to atropine and M3-preferring anti-muscarinic drugs (673).

These observations are consistent with substances released from the adjacent urothelium and a recent study examined the effect of the urothelium on MM contractility. Comparison of spontaneous contractions in MM that were either urothelium-intact or had the urothelium-removed, showed similar amplitude and frequency (615) suggesting that the urothelium was not the *origin* of activity and that under basal experimental conditions, did not release modulators that impacted spontaneous activity. Receptor-operated contractions e.g., evoked by angiotensin II, carbachol or U46619 (thromboxane A2 agonist) were smaller in MM/urothelium strips than in MM-alone leading the authors to speculate that these agonists may also have evoked release of a UDIF that then acted on MM smooth muscle. In another study, adrenergic agonists (α1) increased the rate of spontaneous contractions in MM and enhanced basal tension, whereas β-agonists slowed events and relaxed the preparations (674), giving further sites of action for β-agonists (675). Given the possibility that adrenergic nerves do not directly innervate the MM, the source of adrenergic agonists may be from nearby cells.

Ion channels.
There is a modest body of information on functional expression of ion channels in MM SMC to date. In guinea-pig MM strips, spontaneous contractions were unaffected by pharmacological blockade of BK or SK channels, in contrast to detrusor SM where these modulators significantly increase contraction force integral; moreover, BK current density in enzymatically-dispersed SMC from MM was around 20% that of detrusor SMC (616).

Activation of $TRPV_4$ channels in guinea-pig bladder MM by GSK-1016790A increased basal tension and prevented spontaneous contractions, effects that were sensitive to a $TRPV_4$ antagonist (676). In spite of BK blockers having no effect on MM spontaneous contractions (616), they were able to restore spontaneous activity in GSK-contracted MM preparations (676), this was not true when the SK blocker, apamin, was tested. Further, pre-treatment of MM to block BK channels and subsequent $TRPV_4$ activation with GSK evoked a sustained contraction but did not abolish spontaneous contractions, although there were notably smaller. A putative mechanism encompasses BK channels being largely closed at resting levels but due to being functionally coupled to $TRPV_4$, can be activated by $TRPV_4$-mediated Ca^{2+}-influx during a sustained contraction, resulting in suppression of spontaneous contractions (676).

Intracellular microelectrode recordings and tension recordings from guinea-pig MM has further elucidated the contribution of ion channels to MM physiology. Influx of Ca^{2+} via L-type, voltage-dependent Ca^{2+} channels are responsible for the upstroke of the action potential, depolarisation and subsequent contraction (616,671). On a mean resting membrane potential of -42.5mV, MM typically exhibit spontaneous action potentials with the majority of preparations having a bursting pattern of activity (671). In contrast, detrusor preparations typically exhibit individual action potentials, although bursting patterns are possible. In MM, bursts of spontaneous action potential were converted to individual action potentials by an SK channel opener (NS 309) with prolonged after-hyperpolarisations; moreover, the SK blocker apamin increased the number of action potentials during bursts. These observations may suggest that SK channels have low open probability at rest in MM; furthermore, the bursts may explain the larger unit force in MM compared with detrusor (671).

In microelectrode recordings, blockade of BK channels enhanced action potential amplitude and duration as well as unmasking a slow after-hyperpolarisation in MM preparations. In addition, in contrast to a previous study which used MM-urothelium preparations (616), BK modulators had the expected effects on spontaneous contractions of urothelium-denuded MM (671). Absence of the urothelium may have removed confounding factors such as the effect of BK modulators on urothelial cells, evoking release of urothelium-de-

rived contracting factors that might mask the effect of BK modulators on MM contractility.

Kv7 channels, reported to be functionally active in detrusor smooth muscle from a number of species (677-680) are expressed in guinea-pig bladder MM and had a small effect on the resting membrane potential (671); however, their role is modest compared with BK or SK channels.

3.2. Interstitial cells in the lamina propria. Ion channels and GPCRs.

IC in the *lamina propria* are widely reported in the literature, across many species, in studies based on histology, immunolabelling and TEM (see earlier section). A number of scenarios in which they contribute to bladder physiology have been proposed including participation in bladder sensation or mechano-transduction (603) and initiation of spontaneous activity (681). There are indications that their expression changes in various pathophysiological manifestations (613,681,682).

Patch-clamp studies of IC from guinea-pig bladder *lamina propria* demonstrated spontaneous transient inward currents that were Ca^{2+}-activated Cl^- currents (683). Similar conductances and intracellular Ca^{2+}-transients could be activated by reduced extracellular pH (684), purinergic agonists including ATP, UTP or ADP but not αβ-methylene-ATP, suggesting P2Y receptor activation; this was supported by immunodetection of $P2Y_6$ receptors (523). Such data suggest that *lamina propria* IC could respond to ATP and purines released from the urothelium (606,631,685,686) potentially transducing sensation information to afferent nerves and other cellular players.

Ex vivo tissue sheets or whole-mount preparations of bladder mucosa support physiological signalling within a *lamina propria* IC network, notwithstanding the lack of clarity in the literature whether the cells are structurally connected or coupled. A study of IC located at the suburothelium/upper *lamina propria* of rat pups found spontaneous Ca^{2+} transients across a network with varying levels of coupling. Evidence for $TRPC_4$ activity was found when an agonist increased the number of IC firing and their integration; a similar effect was found with ATP, suggesting that *lamina propria* IC can behave in network fashion, modulated by $TRPV_4$ channel activity and purinergic receptor stimulation (616). A similar scenario has been reported in guinea-pig bladder whole-mount mucosal preparations where IC-LP (identified morphologically) exhibited Ca^{2+}-transients that sometimes appeared to be transmitted to neighbouring IC, and could also occur individually (687). EFS evoked simultaneous signals Ca^{2+}-transients in neighbouring cells that were sensitive to atropine or suramin, indicating that the *lamina propria* IC may receive a functional innervation (687).

IC in the *lamina propria* may also respond to acetylcholine, either released from nerves (687) or perhaps released from the urothelium. Although muscarinic activation with carbachol neither evoked currents nor Ca^{2+}-transients in dispersed IC in one study (683), M3 receptors have been visualised on IC in morphological studies (688,689). Understanding the functional relevance of muscarinic signalling in *lamina propria* IC may be important in the context of the mechanism of action of anti-muscarinic drugs to treat bladder dysfunction, commonly regarded to act on detrusor SMC.

Increased IC numbers in the upper *lamina propria* or sub-urothelium in spinal cord injured rat bladders were considered to be the origin of Ca^{2+}-waves in the bladder wall that then propagated to the urothelium and detrusor (681). P2Y agonists ADP, UTP and UDP and selective $P2Y_6$ agonists enhanced spontaneous contractions and the conduction velocity of Ca^{2+}-waves or depolarisation throughout the mucosa. An interesting observation in this spinal cord injured study was that excitation (Ca^{2+} or electrical signalling) originated in the suburothelial space, that is rich in IC, and subsequently propagated to the detrusor and the urothelium. Opinions on the origin of spontaneous activity in the bladder include the *lamina propria*, the smooth muscle itself in the myogenic hypotheses of MM and detrusor tissues and contribution/modulation from other elements including the urothelium (659).

3.3. Summary.

The research community is using a relatively new lens on the bladder, specifically on the components of the *lamina propria* and integrating new evidence to understand its contribution to bladder physiology. Focus has largely been directed at understanding the role of the MM and IC during bladder filling or the storage phase. If the primary function of the *lamina propria* is indeed structural, its other functions are likely to be just as important.

In species where there is a MM layer, this discontinuous smooth muscle tissue is surprisingly active in terms of generation of spontaneous contractions and force production per unit area. The purpose of MM spontaneous activity is not known but has been suggested to include rearrangement of the mucosa, including the urothelium during bladder filling, when the rugae folds are ‘smoothed out’ in high volumes. Another suggestion is that it acts to prevent excessive stretching of the bladder microvasculature during filling and storage phases. If the origin of MM spontaneous activity is myogenic, its sensitivity to transmitters released from the urothelium (including acetylcholine, nitric oxide, ATP, other purines) indicates local regulation. The functional expression of a number of Ca^{2+}, K^+ and TRP channels, and undoubtedly others, provide the electrophysiological machinery to responsively tune up and tune down spontaneous action potentials and associated spontaneous contractions within a dynamic range.

Mucosal preparations from rat or murine bladder which lack a MM layer fail to display spontaneous contractions, or generate very small amplitude events, supporting the hypothesis that the MM is responsible for the generation of mucosal contractions (614). It has been suggested that in rat mucosa, the small amplitude spontaneous contractions could in fact have been generated by mucosal venues as the frequency of events are similar (614,690). In support of this, is the unexpected finding that noradrenaline increased the basal tone of rat mucosa preparations, a reasonable explanation may lie in the change of tone actually being generated by vascular contraction within the preparation. Yet, one might expect alternative mechanisms to structurally rearrange the mucosa during filling in species where a MM is not present. This role may be delivered by contractile myofibroblasts in mouse or rat bladder *lamina propria* and further research is needed.

The identity of contractile cells other than MM SMC or detrusor SMC remains unresolved. A species comparison of human, pig, guinea-pig, rat and mouse bladder failed to find cells immunopositive for αSMA apart from MM or detrusor SMC (614). Others have found αSMA-positive IC in the suburothelial region of human *lamina propria* but not the submucosa/deep *lamina propria* (634).

The question of whether MM and indeed *lamina propria* contraction contributes to whole bladder contraction either in non-voiding/spontaneous/autonomous contractions, better described as changes in intravesical pressure or in large voiding contraction, is interesting. *Ex vivo* pressure-volume recordings of intact murine

bladder demonstrate non-voiding contractions that are notably absent or non-detectable in preparations where the detrusor has been removed (606). Given that murine bladder does not have a MM, perhaps this is to be expected and any contraction of *lamina propria* fibroblasts or IC would be below threshold detection. Similar experiments on the bladders of larger animals e.g. guinea-pig will enable this question to be addressed.

In elucidation of the contribution of MM to whole bladder contraction, comparison of intact, detrusor and mucosa strips from porcine bladder demonstrated that (1) carbachol-evoked contractions in detrusor and mucosal strips were similar and (2) these were significantly larger than contractions generated in intact strips (667). Removal of smooth muscle bundles from mucosal strips by micro-dissection, confirmed by absence of smooth muscle immunostaining, did not prevent contraction of the mucosa by neurokinin A, suggesting that non-muscle players, likely suburothelial myofibroblasts or mucosal vessels were generating the contractions in these preparations. Returning to the intact vs detrusor or MM contractions, the smaller agonist-evoked contractions observed in intact preparations may argue in support of UDIF limiting contraction amplitude or force integral and may represent how the physiological integration of the tissues bring about optimal contraction that can be increased for voiding or diminished during filling.

4. DETRUSOR PHYSIOLOGY

Our knowledge of detrusor smooth muscle physiology and related pharmacology is extensive and evidenced by a rich body of evidence in the literature. The aim of this section is not to provide a comprehensive review (the reader is referred to published reviews for overview of ion channels and receptors in the detrusor (643,644,691-694) but to highlight our current understanding of the roles of key ion channel and GPCR players in detrusor smooth muscle physiology. IC in detrusor tissue will also be considered and their potential interactions with detrusor smooth muscle will be discussed.

4.1. BK channels.

Perhaps the most widely studied ion channel in detrusor smooth muscle is the large-conductance, Ca^{2+}-activated K^+ channel (BK) that is highly expressed on the plasma membrane of detrusor SMC (695). BK channels are activated by depolarisation and Ca^{2+}, generating hyperpolarisation of the membrane potential and relaxation of detrusor SMC as demonstrated in earlier patch-clamp experiments (696-699), microelectrode recordings of detrusor tissue (700) and *in vitro* recordings of tissue strips (701,702). As the bladder fills and the wall stretches, BK channel activation appears to be enhanced, supporting the hypothesis of a 'brake', limiting spontaneous contractions (703). Their functional importance in bladder physiology seems to lie in limiting depolarisation of detrusor SMC during bladder filling, preventing aberrant coordination of low-amplitude, normally uncoordinated spontaneous contractions (695).

In normal physiology, BK channel activity is impacted by and responsive to the local environment. An example is seen in modulation by circulating hormones; 17β-oestradiol enhanced BK currents in human detrusor SMC, translating to hyperpolarisation of the resting membrane potential, decreased spontaneous and EFS-mediated contractions (680,704). Similarly, testosterone enhanced BK currents in guinea-pig detrusor SMC and hyperpolarised the resting membrane potential thereby reducing excitability (705). BK channels are functionally coupled to other channels indicating the presence of other modulatory mechanisms. In guinea-pig detrusor SMC, Ca^{2+}-influx via $TRPV_4$ is thought to activate BK/$TRPV_4$ coupled channels that then bring about suppression of spontaneous contractions (676).

Muscarinic M3 receptors may also be functionally coupled to BK channels as carbachol evoked large transient outward currents in human and guinea-pig detrusor SMC, followed by abolition of spontaneous transient outward BK currents and associated transient hyperpolarisations, leading to overall depolarisation (706,707). Such a mechanism would act to release the 'BK brake' during EFS or during voiding when acetylcholine, released from parasympathetic nerves, evokes large-amplitude contractions via M3 receptor signalling. It is not known whether ATP or other purines similarly inhibit BK to enable depolarisation and detrusor SMC contraction.

Activation of β3 adrenoceptors causes relaxation of the bladder (708,709) and there is a compelling literature on the potential of β3-agonists to relieve urgency in overactive bladder syndrome (675,710). A number of mechanisms of action have been reported (710) including contribution from β3-adrenoceptors expressed on detrusor SMC that include inhibition of cholinergic-evoked Ca^{2+} oscillations (711), reduction of purinergic postjunctional contractions via inhibition of $P2X_1$-currents and activation of BK channels (712-715).

There is limited indication of BK channel expression in murine detrusor IC with a study of PDGFRα-IC from GFP mice reporting low expression of the BK αslo gene transcript (657). A patch-clamp study of outward currents in guinea-pig detrusor IC, identified on the basis of morphology and inability to contract, reported paxilline-sensitive BK currents (716). To date, BK expression in detrusor SMC has significant functional relevance and increasingly, the role of these channels in urothelial cells is being elucidated (717,718)

BK channels have long been considered as a promising therapeutic target for overactive bladder (OAB) (719,720) as BK openers cause hyperpolarisation and suppression of action potentials in detrusor SMC (705,721) whereas BK blockers increase contraction amplitude and frequency (722). In spite of this, BK openers have little effect on contractility of neurogenic bladder (723), explained by reduced expression of the BKα-subunit, encoded by KCNMA1 in neurogenic bladder (724,725), in the pBOO rabbit bladder model (726) and also in high-fat diet induced obesity in rats (727). Conversely, in pBOO rat detrusor, the BKα-subunit was not significantly affected whereas the β1 subunit was increased (728). In diabetes, reduced functional expression of KCNMA1 and changes to methylation of the gene was not corrected by insulin treatment, known as hyperglycaemic memory (729). An alternative approach to the use of BK channel openers that may be effective in neurogenic bladder or diabetes, may lie in gene therapy to restore expression of KCNMA1 in detrusor SMC via a non-viral, naked plasmid (725,730). This approach has been shown to be promising in pre-clinical obstructed rat bladder models (731) and early human trials although statistical significance of primary endpoints was not reached (730).

4.2. SK channels.

The presence of SK channels in detrusor tissue, presumed to be in the SMC has been reported over the last two decades. Pharmacological modulators such as the SK channel inhibitor apamin, enhances spontaneous contractions in detrusor strips (702,722,732,733) and mRNA/WB/immuno-fluorescence data supports SK expression in detrusor tissue at gene or protein level (734,735). Apamin-sensitive SK currents have been reported in murine and guinea-pig detrusor SMC (733,736) although the former authors noted relatively low current density of SK compared with BK.

Building on the hypothesis that BK currents in detrusor SMC act as a 'brake' mechanism to limit excitability and contraction during bladder filling, the detrusor IC may also act to limit detrusor SMC activity. Detrusor IC reportedly express a number of K^+ channels based on evidence from studies using patch-clamp electrophysiology, immunofluorescence and recordings of intracellular Ca^{2+}-signalling. To date, SK3 (626,657,737), BK (716,738) and Kv7 (738) have been explored in detrusor IC. Functional expression of K^+ channels might enable IC to generate hyperpolarisation and a potential mechanism is one of a 'damper' where instead of originating depolarisation and therefore spontaneous activity in detrusor SMC, hyperpolarisations from IC could transmit to neighbouring detrusor SMC and limit their excitability. As discussed above for BK channels, such a scenario would be physiologically beneficial during bladder filling to enable sufficient spontaneous contractions to maintain optimal bladder tone and 3D shape but provide a limiting mechanism to prevent coordination of contractions that might to bring about urgency or even incontinence (659,739).

Evidence supporting the existence of such a system within detrusor IC came from studies using a PDGFRα-GPF mouse and are based on SK channel expression in IC. Patch-clamp recordings of enzymatically-dispersed PDGFRα-expressing IC and detrusor SMC showed significant SK3-currents in the IC and comparatively currents in the SMC (657). Prior to this, apamin-sensitive SK channels were considered to be functionally active in detrusor SMC (see above), a reasonable conclusion given that SK blockade with apamin enhanced the amplitude of spontaneous contractions in tissue strips; moreover, studies of a transgenic SK3-overexpressing mouse bladder showed reduced frequency of spontaneous contractions in tissue strips (722,733,734). In another study, SK openers had been found to increase duration of after-hyperpolarisations in guinea-pig detrusor SMC followed by abolition of action potentials (721) (Figure 43).

Clarification of high SK expression in PDGFRα-detrusor IC through cell sorting and subsequent characterisation of selected gene expression provided compelling evidence of an SK3-hyperpolarising mechanism in the IC (657). These cells responded to ATP and a $P2Y_1$ agonist with large outward currents and hyperpolarisation; the sustained component of EFS-contraction was shown to be partly mediated by a $P2Y_1$-mechanism to limit tissue contraction (740). The cells also express $P2Y_2$, $P2Y_4$ and $P2Y_{14}$ at gene level; activation of apamin-sensitive currents and hyperpolarisation by the $P2Y_2$/$P2Y_4$ antagonist, UTP, supports a functional role for these P2Y receptors in detrusor IC physiology (741). Further support for a novel hyperpolarising SK3 mechanism in the detrusor PDGFRα-detrusor IC, was seen in patch-clamp experiments where Ca^{2+}-influx via $TRPV_4$ activated SK channels in detrusor IC, and the suppression of non-voiding contractions in *ex vivo* bladders during filling by an SK activator (737).

While an attractive hypothesis with accumulating evidence, support for some of the constitutive steps has not yet emerged, specifically communication of the SK3-hyperpolarisation from detrusor IC to detrusor SMC. In fact, another study concluded that such IC-SMC signal transduction does not occur in murine bladder as purinergic agonists increased Ca^{2+}-transients in the IC without concomitant suppression of Ca^{2+}-signalling in neighbouring detrusor SMC nor of spontaneous contractions (626). The findings also did not support a functional innervation of PDGFRα-detrusor IC in contrast to detrusor SMC, as the former did not respond to electrical field stimulation. The lack of proof for specialised junctions between IC and detrusor SMC (600) may also be consistent with the absence of functional coupling evidence. Another area of contradiction is

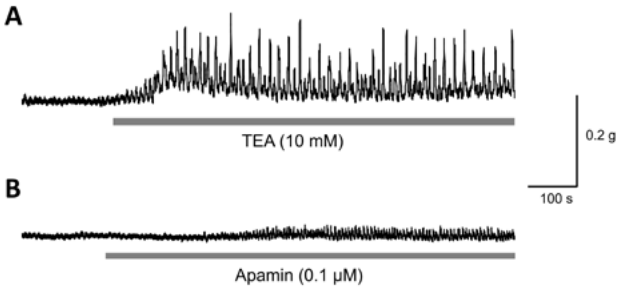

Figure 43. Effect of potassium channel inhibitors on mouse bladder spontaneous activity. *A: Sample trace of in vitro tension recording from mouse detrusor strip showing marked increase in spontaneous contraction amplitude with the non-selective-K+ channel blocker, tetraethylammonium chloride (TEA). B: Sample trace of in vitro tension recording from mouse full-thickness bladder strip showing the effect of the SK blocker, apamin which enhanced spontaneous contraction amplitude. Figures courtesy of McCloskey group, Queen's University Belfast.*

that P2Y1R stimulation was found to evoke transient contraction, but not subsequent inhibition of spontaneous contractions in murine detrusor. Furthermore, in PDGFRα-IC-GFP bladders, P2Y1 agonists, ADP or ATP all increased intracellular Ca^{2+}- in the IC but did not inhibit spontaneous Ca^{2+}-transients or spontaneous contractions in detrusor SMC leading the authors to conclude that the SK3-dependent hyperpolarisation in IC is unlikely to be transmitted to SMC to limit their activity. Undoubtedly, further research will build our knowledge of detrusor SMC-IC interactions and either establish or shift the existing paradigms.

Similar to the situation for BK channels, a number of studies have reported altered expression of SK channels in bladder in pathophysiology. In 2010 it was reported that the obstructed female rat detrusor (six weeks post-obstruction) had increased SK3 expression; moreover, apamin significantly enhanced spontaneous contractions, in excess of its effect on control bladders (728). Gene expression for SK1, SK2 and SK3 channels were reportedly downregulated in isolated SMC from obese rats along with reduced SK current density and a smaller hyperpolarisation in response to SK agonists compared with control rats (742); similar findings were reported in obstructed guinea-pig bladder (743). A recent paper reported reduced detrusor, PDGFRα-IC in spinal cord injured mouse bladder (744), consistent with a number of reports of reduced detrusor IC in spinal cord injured rat bladder (613,745). In the murine bladder study, decreased gene and protein expression of PDGFRα and SK3 was associated with enhanced non-voiding spontaneous contractions in *ex vivo* bladders (744). Taken together, the evidence supports altered SK3 expression across several rodent models of detrusor overactivity and strongly suggests that detrusor cells, likely IC are affected.

4.3. Voltage-dependent K^+ channels.

A number of voltage-dependent K^+ channels are functionally expressed in detrusor and their role remains an emerging area of research. A recent review (694) summarised findings supporting diversity of Kv channel expression including Kv1.2, Kv1.3, Kv1.5, Kv1.6, Kv2.1, Kv2.2, Kv3.2, Kv4.2, Kv4.3, Kv5.1, Kv6.1, Kv6.2, Kv6.3, Kv7.1-Kv7.5, Kv8.2, Kv9.1, Kv9.2, Kv9.3, Kv11.1. Kv channels have been characterised in patch-clamp experiments and contribute to action potential repolarisation and maintenance of the resting membrane potential. Perhaps the most promising of the Kv expressed in detrusor in terms of potential clinical relevance are

those of the Kv7 family. There are a number of drugs targeting these channels that have been used in clinical settings e.g. retigabine, a Kv7 channel opener that was trialled to treat epilepsy but had a number of adverse effects including urinary retention (746). Laboratory experiments support gene, protein and functional expression of Kv7 in detrusor across several species, reporting sensitivity of outward currents and membrane potential from dispersed detrusor SMC and IC to Kv7 pharmacological modulators (677,678,738,747). *In vitro* tension recordings and Ca^{2+}-imaging has shown contribution of Kv7 to spontaneous activity where Kv7 blockers or openers respectively enhanced or diminished spontaneous contractions and action potentials (678,721,748-751).

The evidence to date supports the need for further research in this area, particularly whether Kv7 expression is altered in pathophysiologies relating to detrusor overactivity. If their expression in these conditions is similar to normal bladder or even upregulated, then there may be opportunity for Kv7 openers to reduce excitability and diminish aberrant contractions. Should this be achieved without impacting neurogenic voiding contractions in view of a side effect of urinary retention with regitabine, this would be a promising area of enquiry. Lessons should be noted from the early potential of BK openers being useful to treat neurogenic bladder overactivity was not realised as BK channels were markedly under-expressed. There is therefore a present need to focus efforts on characterising Kv7 in overactive human bladder tissue.

4.4. CaV channels.

Early electrophysiological studies revealed the dependence of the upstroke of the detrusor SMC action potential on Ca^{2+} ions and demonstrated the presence of inward L-type Ca^{2+} currents (696,700,752). Contraction of detrusor smooth muscle is dihydropyridine-sensitive (722) and both L-type $Ca_V1.2$ and T-type $Ca_V3.1$ currents have been characterised in a number of animal models and human detrusor SMC (753-756). Our knowledge of the essential role of $Ca_V1.2$ channels in detrusor contraction contrasts with rather incomplete understanding of the importance of T-type $Ca_V3.1$-3.3 currents which may be upregulated in bladder dysfunction (756). This remains an area where research efforts should be focussed.

4.5. Other ion channels.

An emerging picture of the contribution of TRP channels shows that these are integrated with other ion channels and GPCRs in detrusor physiology. They are involved in mechano-sensory signalling and pain sensation and their roles in bladder afferent signalling and related filling disorders are discussed in section V. Several TRP channels are expressed on detrusor SMC and other cells in the bladder wall, including urothelium. In murine detrusor SMC, $TRPC_4$ channels mediate Ca^{2+} influx followed by Ca^{2+} release from IP_3-intracellular stores during muscarinic-evoked contractions; this is in addition to the well-known Ca^{2+} influx via L-type Ca_V channels during muscarinic receptor stimulation (757). In support of this role, carbachol-evoked contractions are smaller in detrusor of TRPC4 deficient mice and spontaneous contractions were also smaller (757).

Activation of $TRPA_1$ in rat bladder detrusor strips increased basal tone and EFS-contractions (758); this channel also activates afferent nerve signalling in rat bladder (759) consistent with immunofluorescence studies showing expression in urothelium, *lamina propria*, detrusor and around blood vessels suggesting multiple sites of action on bladder activity (760).

$TRPM_4$ in rat detrusor SMC are active in contraction regulation as channel inhibition reduced intracellular Ca^{2+} and diminished spontaneous and neurogenic contractions (761,762). In human detrusor, $TRPM_4$ expression is confirmed at gene and protein level; moreover, patch-clamp experiments revealed currents that were sensitive to a $TRPM_4$ inhibitor which also evoked hyperpolarisation (763). Importantly, $TRPM_4$ inhibitors reduce spontaneous activity, carbachol-generated contractions and EFS-induced contractions in human and murine detrusor (763,764). $TRPM_4$ is overexpressed in spinal cord injured murine detrusor SMC and this is associated with enhanced spontaneous activity in detrusor strips which was inhibited by a $TRPM_4$ blocker (765). The independently corroborated evidence of the functional expression of $TRPM_4$ across human and rodent bladders makes this a promising area of translational research; furthermore, $TRPM_4$ overexpression in detrusor overactivity suggests it could be a drug target. Further research will undoubtedly investigate whether $TRPM_4$ inhibition will dampen non-voiding contractions without impacting neurogenic, voiding contractions and potentially avoid urinary retention.

$TRPV_4$ channels regulate detrusor SMC and MM contraction via BK channel coupling, where Ca^{2+}-influx mediated by $TRPV_4$ causes a tonic contraction and also activates BK to inhibit spontaneous contractions in a so-called self-limiting mechanism (676). $TRPV_4$ is functionally expressed in mouse and rat detrusor, where an activator contacted the strips of normal and spinal cord injured rat bladder (766,767)

Ca^{2+}-activated Cl^- channels have prominent roles in some smooth muscles, generating spontaneous transient depolarisations and activated by Ca^{2+}-oscillations (365,768-770). Yet, despite the detrusor having spontaneous Ca^{2+}, electrical and mechanical activity, the limited available data highlighting the presence of Ca^{2+}-activated Cl^- channels is not yet fully supported by patch-clamp characterisation. A study of *ex vivo* whole rat bladder showed that the channel blocker niflumic acid, reduced frequency of spontaneous pressure changes (771). Gene expression of Ca^{2+}-activated Cl^- channels in normal rat bladder is enhanced in obstructed models and imaging methods indicated that channel modulators may change the membrane potential (772). In rat detrusor strips, niflumic acid inhibited spontaneous contractions and immunofluorescence showed expression of the channel protein (Ano1) in vimentin$^+$ IC rather than in detrusor SMC (773). Further information from patch clamp experiments from guinea-pig detrusor SMC revealed a Ca^{2+}-independent, voltage-dependent Cl^- channel that was sensitive to niflumic acid (774). Immunofluorescence studies in murine bladder showed expression Ano1 on IC (656) in contrast to a study of human, rat, guinea-pig and mouse bladder where the authors failed to find Ano1-positive IC (775).

4.6. HCN channels.

Hyperpolarisation-activated nucleotide-gated (HCN) channels are expressed in bladder and in recent years, have been studied in normal and dysfunctional bladder models. HCN1-HCN4 are expressed in rat and human bladder mucosa and detrusor (776-778). In human or mouse bladder detrusor strips, HCN inhibition enhanced baseline tone and increased the amplitude of superimposed, phasic contractions (779). In another study of human bladder, HCN inhibition increased resting tension and amplitude of phasic contractions; however, had no effect on EFS or carbachol contractions (780). In rat and human detrusor strips, activation of β3-adrenoceptors decreased baseline tension of rat bladder strips, an effect that was prevented by HCN inhibitors thus suggesting interaction of HCN channels and β3-adrenoceptors (778).

Evidence from patch-clamp recordings of detrusor IC showed typical HCN currents that were modulated by cAMP (781), in keeping

with the effect of β3-adrenoceptors above; interestingly HCN1-4 was reportedly lower in diabetic rat bladder and cAMP activation of the HCN current was reduced although the number of IC was not changed (781,782). In contrast, HCN1-4 expression was upregulated in obstructed rat bladder along with increased HCN current density in detrusor ICs, detrusor strips, furthermore, HCN inhibition reduced the spontaneous contractions suggesting upregulated HCN contributed to detrusor overactivity (783).

4.7. Receptor-mediated contractions.
Detrusor smooth muscle expresses muscarinic, purinergic, adrenergic and other GPCRs (643) that mediate contraction or relaxation. Muscarinic agonists e.g. acetylcholine or its stable analogue carbachol, elicit large-amplitude contractions (784); moreover, in non-human mammalian bladder, EFS-contractions are significantly inhibited, around 50%, by muscarinic receptor antagonists (785). In human bladder, EFS-contractions are almost exclusively mediated by acetylcholine and a purinergic-mediated component emerges in some pathophysiological conditions (644).

An important consideration at tissue physiology level is functional connectivity between receptors and ion channels to bring about or prevent contraction. Cooperation between M3 muscarinic receptors and BK channels in rat detrusor SMC was seen in large, transient BK currents that were evoked by carbachol followed by inhibition of spontaneous, transient BK currents and concomitant inhibition of spontaneous transient hyperpolarisations. Mechanistically, M3 activation evoked mobilisation of intracellular Ca^{2+} via PLC-PIP_2-IP_3 which initially activated BK, followed by depletion of intracellular Ca^{2+} and cessation of BK-mediated transient currents (706). Cooperation between M3 receptors and $TRPC_4$ channels was described above (757,786) is another example of the integration of M3 and ion channels in detrusor SMC physiology.

Similar interactions are reported for BK channels. Cholinergic and purinergic contractions in murine detrusor, are increased by BK pharmacological blockade, or in BK-knockout mice (deletion of mSlo1), indicating that BK channels normally act to reduce receptor-mediated detrusor contractions (787,788). BK channels also interact with β-adrenoceptors as shown in patch-clamp studies where isoproterenol or forskolin enhanced BK currents via cAMP/protein kinase A signalling (789). The bladder's inhibitor sympathetic innervation is of particular translational relevance as it causes relaxation. The success of β-adrenoceptor agonists, in particular the β3-adrenoceptor agonist, mirabegron, is positively impacting many patients with overactive bladder. The reader is directed to a number of recent reviews on this topic (675,790,791)

Detrusor IC also express purinergic and muscarinic receptors and will respond to extracellular acetylcholine or ATP. Detrusor IC from guinea-pig bladder respond to carbachol with Ca^{2+}-transients via release from intracellular stores and Ca^{2+}-influx (784); furthermore, in whole-mount tissue preparations, detrusor IC respond to EFS with Ca^{2+}-transients that are sensitive to tetrodotoxin (687). As noted above, $P2Y_1R$ activation by a selective agonist or ATP, evoked SK currents in murine detrusor PDGFRα-IC (740) showing multiple cellular targets and effects of purinergic agonists.

5. INTEGRATION OF PHYSIOLOGY IN TISSUES OF THE BLADDER WALL DURING FILLING AND EMPTYING

The integration of nerve and SMC activity in the bladder is paramount to its dual functions of filling and emptying. The spontaneous contractions, regarded as important for setting bladder tone, may also communicate fullness to afferent nerves and we need to be clear when describing activity from the intact bladder, MM, SMC or indeed muscle-free activity in the *lamina propria*. Experimental data from a seminal paper by Heppner et al, provided insights into how the cellular elements of the bladder might work together during filling. An experimental design incorporating simultaneous recordings of pressure, volume and afferent nerve activity in *ex vivo* mouse bladder illuminated the mechanism where spontaneous detrusor (absence of MM in this species) contraction (changes in pressure) evoked significant afferent nerve activity and the rising phase of a spontaneous contraction was correlated with action potential frequency (792). In this setup, BK or SK channel inhibition increased spontaneous contraction amplitude and subsequent afferent activity demonstrating the ability of BK and SK channels to 'tune up' afferent signalling during intravesical volume increases (792). The authors proposed an elegant model of activity during bladder filling based on these findings and proposed that the interstitial cells, known to highly express SK channels, may act as a 'gain regulator', transducing pressure to afferent nerves (Figure 44).

Further work is needed to understand how the tissues of the bladder and their cellular components work together during the main storage function of the bladder. Do BK channels in detrusor SM act as a primary brake mechanism, secondary to the IC SK-limiting pathway, and/or are both mechanisms regulated dynamically by modulators e.g. acetylcholine, ATP, purines etc? Another question is whether SK channels in detrusor IC can be activated therapeutically to dampen aberrant detrusor contraction without bringing about urinary retention? We are learning more about the MM in terms of physiological properties; however, it is not yet known whether it contributes to overactivity. If not, it would be better to develop detrusor-targeting therapies that spare the role of MM tissue e.g. in dynamically regulating the architecture of the mucosa and potentially preventing over-distension of blood vessels.

A final remaining question is the identity of the pressure/filling sensor, whether it sits within IC, SMC or both. A promising candidate lies with the mechano-sensitive ion channels, Piezo 1 and Piezo 2, channels which transduce mechanical stress into Ca^{2+} signals. There is emerging evidence of Piezo-1 and -2 expression in the bladder, including within urothelial cells, sensory neurons and IC (321,531,793,794). Mouse models and humans lacking functional Piezo 2 have bladder dysfunction and patients reported deficient sensation of bladder filling (531). Enhanced understanding how Piezo channels operate in urothelial cells, afferent nerves and other cells of the bladder wall in relation to all of the signalling processes that bring about contraction and relaxation will undoubtedly shed further light on this area.

VII. NOVEL APPROACHES TO STUDY THE PATHOPHYSIOLOGY OF LUT DYSFUNCTION

This chapter section will discuss the use of animal models and experimental approaches to investigate the pathophysiological mechanisms and therapeutic potentials for detrusor overactivity (DO).

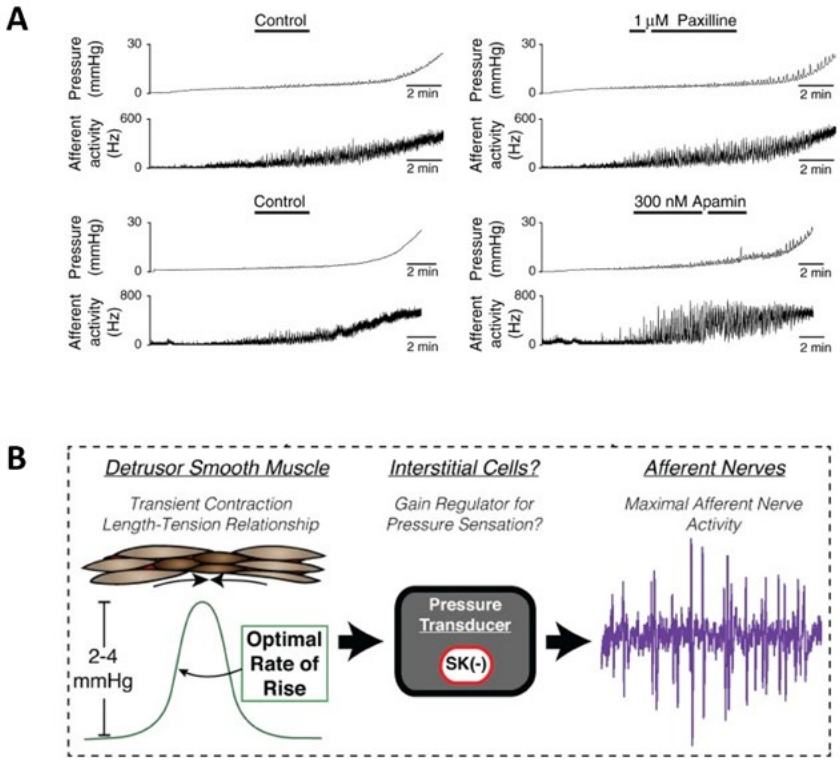

Figure 44. Integration of spontaneous (transient) contractions and afferent nerve activity during bladder filling. *A: Recordings of intravesical pressure and afferent nerve activity in ex vivo murine bladder, adapted from Heppner et al (792). During bladder filling, a low pressure is maintained and is followed by development of small non-voiding pressure changes (contractions) and a more rapid pressure rise at the end of the recording. The initial quiescent tracing of afferent nerve activity changes to substantial firing as the bladder fills. Inhibition of BK channels with paxilline enhanced the amplitude of pressure waves. Blockade of SK channels with apamin markedly enhanced afferent nerve firing with concomitant increase in spontaneous pressure changes. B: Proposed model by Heppner et al (792) showing a transient change in pressure/contraction with an optimal rate of rise which is a function of detrusor smooth muscle's length-tension relationship. The model proposes that transient contractions stimulate bursts of afferent nerve activity; SK+-interstitial cells may act as a gain regulator as their inhibition enhanced afferent firing and subsequent transient contractions. Figures modified from (792), with permission of Professor Mark Nelson.*

This may arise from neuropathic or idiopathic (NDO or IDO) causes and is associated with afferent sensitisation and increased bladder micromotions. The utility of these models and approaches will be demonstrated by using an example of the nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signalling in LUT pathophysiology and modulation of the pathway for treatment of various bladder conditions. For example, the clinically relevant effects of phosphodiesterase type-5 (PDE5) inhibitors, *e.g.,* sildenafil, on LUT dysfunction may be investigated using mouse models of T_8-T_9 spinal cord transection (SCT) and acrolein- or irradiation-induced cystitis (Figure 45). Selective irradiation of the colon causes bladder NDO and thus may be used to investigate organ cross-innervation. Also discussed will be different approaches to study bladder outlet obstruction (BOO).

1. ANIMAL MODELS: NEUROGENIC DETRUSOR OVERACTIVITY.

1.1. Bladder/colon irradiated, acrolein-induced cystitis and SCT mouse models: pathological changes to bladder function.

Radiation cystitis is a chronic condition that in humans develops months to years following radiotherapy for pelvic malignancies. Acutely, radiation cystitis is associated with extensive inflammation and NDO symptoms that can resolve over time. However, a small proportion of patients will experience chronic inflammation resulting in fibrosis, poorly compliant bladders and potentially fatal haemorrhagic cystitis. The consequences of chronic radiation cystitis can be demonstrated in a mouse model by selective irradiation of the urinary bladder that has been temporally removed from the abdominal cavity without disruption to its vascular or nervous supplies (Figure 46A). In his way, the bladder can be selectively exposed to an otherwise lethal dose of irradiation (10 Gy, 1 Gy = 100 Rads) without compromising surrounding pelvic organs or affecting survival (*e.g.,* disruption of haematopoiesis) (795). This minimises injury to pelvic organs near to the bladder, mediated by cross-innervation

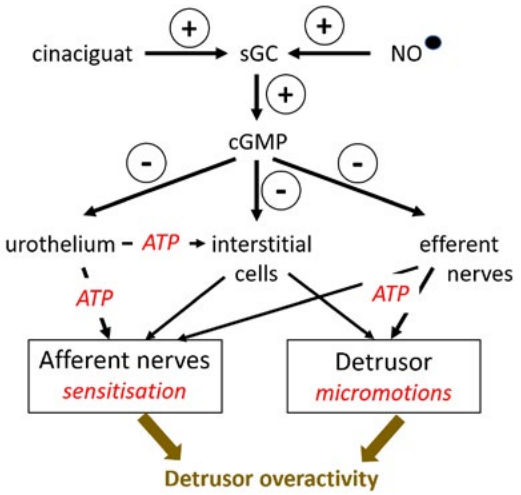

Figure 45. Flow diagram of soluble guanylate cyclase (sGC) activity to ameliorate the pathophysiology of detrusor overactivity. *Naturally-occurring pathways (mediated here by nitric oxide (NO)) and drugs (here cinaciguat) increase cGC activity and hence cGMP levels. This is turn modulates the release of agents, such as ATP, from several cell types that reduce aberrant activity of detrusor smooth muscle and afferent nerves that underly symptoms of detrusor overactivity (DO). IC: interstitial cells.*

of sensory projections. Such cross-sensitivity has been demonstrated with instillation of chemical irritants to the descending colon, with associated bladder overactivity (796). A similar effect can be achieved by selective irradiation of the externalised descending colon (Figure 46B).

Such irradiation models show indications of bladder overactivity with shortened voiding intervals and the presence of non-voiding contractions (Figure 46C). However, tension recordings of isolated bladders from the same animals are generally quiescent (Figure 46D) indicating that *in vivo* observations are neurogenic in origin. Chemically induced cystitis also mimics the effect of the radiation injury. The best described model is that induced by cyclophosphamide, a chemotherapy agent that generates acrolein as a urinary by-product. Acrolein is an alkylating agent that covalently modifies and activates transient receptor potential ankyrin-1 ($TRPA_1$) channels (797), abundant on bladder sensory projections and urothelial cells (760). Bladder acrolein instillation and $TRPA_1$ channel activation is associated with severe inflammation and nociceptive responses (798) that contribute to chronic pain conditions (799). Accordingly, chemical cystitis such as that caused by acrolein mainly enhances neurogenic activity of the bladder and is not associated with large amplitude, autonomous bladder micromotions that are observed with neurogenic injury (639) (Figure 46C,D).

Urine storage and voiding depends on coordination of the contractile activity of bladder/urethral smooth and striated muscle. During storage, the bladder is quiescent and urethral muscles are active to maintain continence; upon micturition, the bladder contracts and the urethra relaxes. Following spinal cord injury rostral to the lumbosacral spinal segments, voluntary control of micturition is lost, and the bladder becomes areflexic. However, after recovery from the initial spinal shock, reflex bladder activity emerges due to the formation of a spinal micturition reflex. Ultimately, the bladder becomes hyperreflexic (Figure 46C) as detrusor-sphincter dyssynergia develops, decreasing voiding efficiency and resulting in urinary retention (800). Accompanying overdistension, there is urothelial hyperplasia but decreased numbers of terminally differentiated umbrella cells (801), increasing the risk of urinary tract infections. Furthermore, chronic overdistention causes bladder wall hypertrophy, hyperplasia and greater gap junction connectivity of *lamina propria* ICs (526) that enhance detrusor micromotions, stimulate sensitised afferents (802) and promote DO (Figure 46D). Accordingly, this SCT model may be used to induce and study neurogenic and myogenic overactivity and radiation- and acrolein-induced cystitis models of neurogenic dysfunction. Thus, it is possible to address

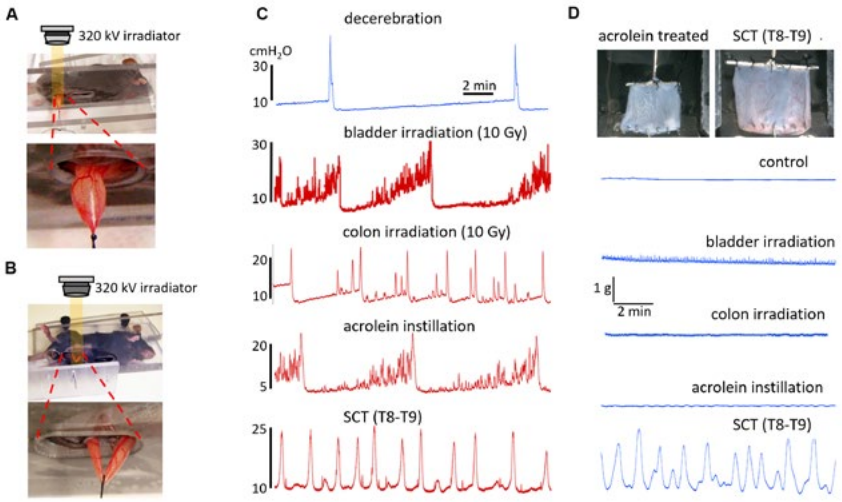

Figure 46. Mouse models of bladder overactivity and associated pathological features. *A: Externalisation procedure for selective bladder irradiation. B: Similar procedure for the descending colon to induce pelvic organ cross-sensitisation. C: Representative filling cystometrogram (CMG) traces from decerebrated normal adult, colon and bladder irradiated, acrolein-instilled and SCT mice. D: Corresponding isometric tension traces from isolated whole bladders of mice in C. Inset images show bladder sheets from acrolein-treated and SCT mice, where the latter is approximately double in size due to outlet obstruction-induced overdistention and hypertrophy. Figures courtesy of Drs AJ Kanai, Y Ikeda and IV Zabbarova.*

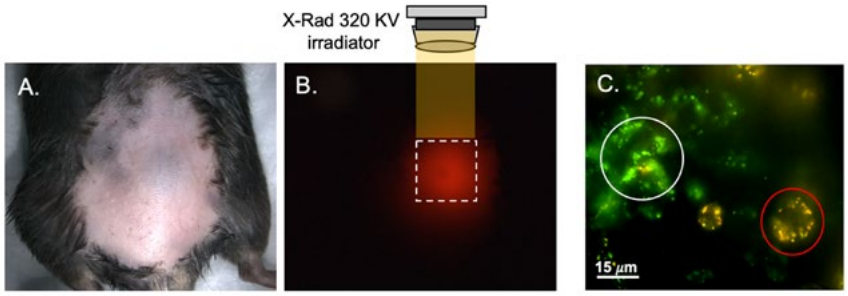

Figure 47. Fluorescence guided bladder irradiation; visualisation of urothelial mitochondria. *A: White light image of depilated mouse abdomen after bladder instillation with infrared dye. B: Fluorescence (excitation 675±25 nm) from the bladder, visualised under infrared light with a long wave pass (LWP, 695 nm) filter, for targeted irradiation. C: Image of urothelial cells from mt-keima mouse one day after irradiation. The mt-keima protein is conjugated to mitochondria, with green fluorescence at neutral pH (pH 7.0-7.5, white circle) and red fluorescence in acidic environments (red circle, e.g. within lysosomes). Figures courtesy of Drs AJ Kanai, Y Ikeda and IV Zabbarova.*

the mechanisms that induce the respective pathologies and study the therapeutic benefits of different agents.

1.2. Novel methods for selective bladder irradiation.
The externalised organ irradiation model, described above, is useful to isolate radiation effects to the LUT. However, the method does not fully mimic radiation therapy utilised clinically which does not involve surgery and is performed by targeted application with the potential to affect surrounding tissues. A novel method to selectively irradiate mouse urinary bladders *in situ* is by installation of an infrared dye, 680RD, reproducing the key features of radiation cystitis (Figure 47A,B).

1.3. The mt-keima mouse to evaluate mitochondrial function.
Oxidative stress is a key feature of radiation injury and there are a broad range of cellular pathways affected, with damage to mitochondria featuring predominately. Previous studies have relied heavily on cell-based assays with relatively few intact-tissue or *in vivo* studies. A model to monitor mitochondrial damage *in vivo* is the mt-keima transgenic mouse. These mice ubiquitously express a pH sensitive, dual excitation ratiometric fluorescent protein that localises selectively in mitochondria (803). When mitochondria are damaged, they are processed for lysosomal degradation (mitophagy) and in neutral cytosolic environments the mt-keima protein fluoresces more readily at shorter excitation wavelengths. In contrast, in the acidic environment of lysosomes, the emission predominates at longer excitation wavelengths. Thus, the model allows dynamic monitoring of mitochondrial degradation in cells, tissue and whole animals. Figure 47C shows a fluorescence image (1000x) of mitochondria from the mucosal surface of an irradiated bladder sheet from a mt-keima reporter mouse that tracks mitophagy, showing cells with increased mitochondria trafficking to lysosomes.

2. REPEATABLE MEASUREMENTS OF LUT FUNCTION IN AWAKE ANIMALS.

Physiological comparison of animal LUT function to that of humans is challenging. Most animal studies use anaesthesia, decerebration or restraints to obtain bladder pressure and external urethral sphincter electromyograms (EUS-EMG) recordings. Cortical influences are removed using anaesthesia or decerebration, restrain methods can add psychological stress which would more than likely influence voiding behaviour. Thus, methodologies that can minimise stress/pain and facilitate conscious voiding behaviour would have the highest likelihood of obtaining relevant physiological responses.

2.1. Telemetric measurements of bladder pressure, voided volume and frequency in freely mobile mice to evaluate BOO.
Telemetric recordings of physiological parameters (*e.g.,* vessel pressure, electrical impulses, temperature, movement) are possible through commercially available telemetry systems designed specifically for animal research. Initial studies demonstrated the feasibility in rats where bladder pressure and voided volumes could be simultaneously recorded (804). These recordings are also feasible in mice where smaller implantable telemeters (HD-X10, Data Science International) may be used to record simultaneously bladder pressures and voided volumes and frequencies in freely mobile mice. Animals with subcutaneous telemeters (30-day battery life; activated only during recordings) can be housed for up to 72 hrs in modified metabolic cages where food and water consumption can also be accurately measured. In this way, data can be recorded over periods as long as six months. The pressure line is sutured into the bladder wall to record intravesical pressure. Urine output is measured simultaneously by highly sensitive load cells in the floor of the metabolic cages and used to estimate voided volume and frequency. Void spots can be collected by filter paper on the load cell to record changes in voiding behaviour (void spot tests). Recordings from an adult male mouse (9-months, Figure 48A) show a rise of bladder pressure followed by a single bladder emptying event after a 2-second delay. By contrast, an aged mouse (24-months, Figure 48B) showed a large rise in bladder pressure, followed by a much longer delay and multiple voiding attempts as evident from much smaller voided volumes dispersed over multiple locations. Overall, this bladder outflow obstruction phenotype, characterised by raised bladder pressures and reduced voided volumes as seen in Figure 48B, is measured in ~75% of aged animals (unpublished data, Kanai lab). In the remainder, greater bladder pressures and reduced voided volume are also recorded, but to a lesser extent. This innovative *in vivo* approach allows the diagnosis of severe (high bladder pressure/low urine flow) bladder outlet obstruction in aged animals and a lack of obstruction (low bladder pressure/high urine flow) in mature adult animals. Thus, it is possible to monitor the actions of daily treatment with potential therapeutic agents in freely mobile mice and to adjust the dosing regimen for optimal benefit and minimisation of potential side-effects. For example, telemetry combined with urine output analysis can follow progressive improvement in voided volumes, urine flow rates and characteristics of micturition contractions from an aged mouse before, and after two weeks of daily treatment with cinaciguat (10 $mg.kg^{-1}.day^{-1}$ over 2-weeks), an activator of soluble guanylate cyclase (sGC) to increase intracellu-

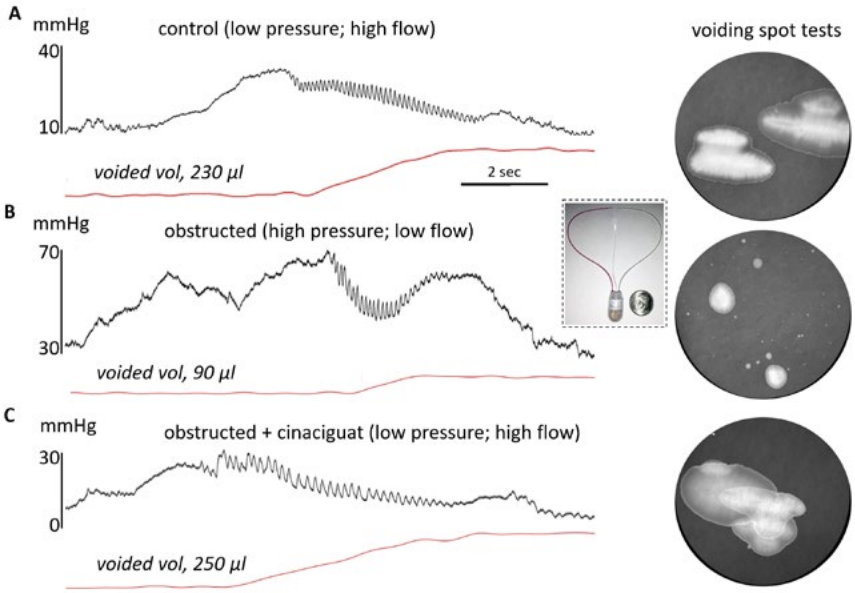

Figure 48. Telemetric recordings of bladder pressure, with void volumes and void spots. *A: Normal adult (12 weeks) male mouse. B: Aged (24 months) male mouse. C: Aged (24 months) male mouse 14 days after daily gavage with cinaciguat (10 mg.kg-1). Figures courtesy of Drs AJ Kanai, Y Ikeda and IV Zabbarova.*

lar cGMP levels (Figure 48C). This treatment normalised voided volume and flow rate as well as maximum voiding pressure and partially lowered micturition frequency. Thus, telemetric cystometric and voiding data in different age groups of mice can be used to test potential therapeutics to treat bladder outlet obstruction.

The recorded LUT variables, as described above, can be expanded to include electromyographic signals from the external urethral sphincter (EUS-EMG) through use of implantable telemeters with pressure sensors and electrical leads for biopotential recordings. As an example, Figure 49A,B shows bladder pressure, EUS-EMG, voided volume and void spot patterns recorded from normal and SCT mice implanted with HD-X11 telemetry units. The normal mouse shows a rise in bladder pressure and voiding corresponding to a decrease of EUS-EMG tonic activity. By contrast, an SCT mouse shows bladder pressure-transients without a decrease of EUS-EMG tonic activity, indicative of detrusor-sphincter dyssynergia. Accordingly, there were no void spots recorded on the load cells and the mouse showed signs of overflow incontinence. There are limitations to the use of telemetric recordings, including recording time constrained to battery life and inability for adjustment to probes following implantation. However, the advantages of achieving repeatable and near-physiological LUT recordings from awake unrestrained animals outweigh the limitations of such an approach.

2.2. Filling and non-filling cystometrograms and voided volumes in tethered mobile mice; the use of implantable access ports for long-term monitoring of bladder function.
Implantation of indwelling bladder catheters for pressure recordings is an established method for cystometrogram (CMG) recordings in awake rodents. In contrast to the telemetric methodology described earlier, catheter implant CMG recordings can only be performed once, as the catheter is placed subcutaneously on the animal and requires surgical externalisation after a recovery period. To achieve repeatable, filling and non-filling bladder pressure recordings, implantable vascular access ports (Instech, Inc) can be adapted for insertion of a pressure line into the bladder lumen and the access port placed on the back of the animal (Figure 49C). The access ports and check valve allow for measurements of bladder activity under continuous infusion (Figure 49D) or under physiological filling (Figure 49E) in freely mobile mice. Thus, multiple recordings can be performed over time in conjunction with metabolic cages with sensitive load cells to measure voided volumes. This technique facilitates repeatable recordings of both filling and ambient bladders pressure over a time course, allowing assessment of therapeutic agents and pathological processes. Theoretically, this methodology would also reduce the number of animals for CMG assessments as multiple evaluation time points can be derived from a single animal.

3. EX VIVO AND *IN SITU* BLADDER ASSESSMENTS

In the previous sections, the importance of assessing LUT function in awake, unrestrained animals was emphasised. *In vivo* assessments can be useful for characterising the pathophysiology or efficacy of treatment protocols but still need to be combined with information from *in vitro* or *in situ* methods to validate the modes/sites of action. The following sections will describe examples of *in situ*, tissue and cell-based recording techniques to assess various aspects of bladder function.

3.1. Stretch and micromotion-evoked bladder afferent firing: effect of cinaciguat on mouse bladders with irradiation-induced cystitis or following SCT.
A principal role for sensory dysfunction has been implicated in multiple LUT pathologies. This can be evaluated in animal models by direct measurement of sensory nerve activity in response to bladder stimulation using either *in vitro* (802) or *in vivo* (805) techniques. These methodologies allow afferent fibre subtypes to be categorised based on conduction velocity (Aδ- *vs* C-fibre) or their response to different stimuli (*e.g.* bladder distension, chemical irritants, tactile interventions). Single-unit *in vitro* bladder afferent recordings from irradiated mouse bladders (3- to 4-days post-irradia-

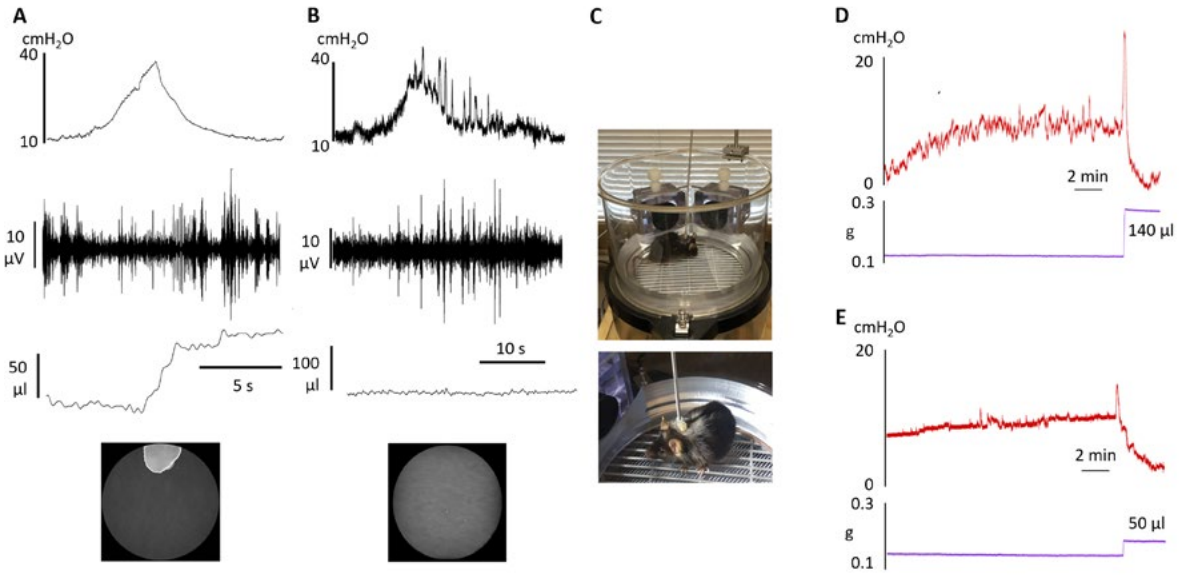

Figure 49. Assessment of LUT activity in awake mobile rodents. *A: Telemetric recordings from an adult male mouse of bladder pressure (upper) and EUS-EMG activity (lower). Also shown is voided volume and a corresponding spot test after three hours of activity. Note the phasic and more tonic EMG activity before and after voiding, respectively. B: Corresponding recordings from a mouse with spinal cord transection. Note the absence of voiding over the recording time. C: Metabolic cage with adult mouse. The mouse has an implanted bladder access port connected to a tethered catheter system for filling/non-filling mobile cystometry. D: Tethered filling cystometrogram (0.1 ml.min-1 at room temperature, upper) and voided volume (recorded by a sensitive (10μl detection) load cell, lower). The tether is magnetically attached to a check valve for easy attachment and detachment allowing multiple recordings. E: Natural fill cystometrogram with the same system as in D. Figures courtesy of Drs AJ Kanai, Y Ikeda and IV Zabbarova.*

tion, Figure 50B) exhibited spontaneous discharges not associated with changes in bladder tension, indicating increased sensitivity of afferent nerves in comparison to recordings from control preparations, Figure 50A: there was no indication of spontaneous detrusor contractions as a result of irradiation at the time when recordings were made. Cinaciguat decreased spontaneous and stretch-induced afferent firing as well as baseline tension *in vitro* demonstrating a direct action on afferent nerves (Figure 50B). Mechano-sensitive and spontaneous afferent firing rates were enhanced in SCT mouse bladders (Figure 50C). Furthermore, afferent firing in response to both stretch and micromotions observed in SCT mouse preparations were also dampened by cinaciguat (Figure 50C,D).

3.2. Optical mapping of SCT-induced bladder micromotions.
Detrusor micromotions are augmented in some bladder pathologies, specifically through enhanced gap junction coupling to coordinate greater activity of different contractile units in the bladder wall (526). Enhancement of autonomous bladder activity is most pronounced in models of bladder outflow obstruction such as physical outlet obstruction or due to spinal cord injury to produce DSD. Coordinated activity characteristic of SCT-induced micromotion can be evaluated using an optical mapping array system (Figure 51A,B**).** This system records fluorescent signals from a large surface area of tissues that are loaded with intracellular sensors that measure Ca^{2+} concentration changes or changes to membrane potential (E_m). Fluorescence sensors with comparable excitation wavelengths, but with different emission spectra may be used (*e.g.,* Rhod-2AM for Ca^{2+} and Di-4ANEPPS for E_m), allowing simultaneous recording of Ca^{2+} transients, E_m changes as well as isometric tension by attaching the preparation to a force transducer. In this example, when the bladder was relaxed, there were no recorded isometric micromotions. However, after an increase of baseline tension, large-amplitude, rhythmic micromotions developed. Cinaciguat reversibly inhibited micromotions (Figure 51C) and the clustering of Ca^{2+} transients (Figure 51D).

3.3. Optical mapping of isolated bladders to examine micromotion organisation.
Optical mapping of intracellular Ca^{2+} transients and E_m changes can be used, for example, to investigate the effect of cGMP signalling on bladder micromotions (Figure 52A-D). This technique may be used to show the organised nature of pathological bladder micromotions and uncover signalling mechanisms between the urothelium and underlying cells which could not otherwise be demonstrated (526,559,806-811). Thus, the system has been used to show propagation of Ca^{2+}/E_m activity in intact bladders, whole bladder sheets and across the different layers of the bladder wall (Figure 52A,B). The conduction velocity of activity propagation can be calculated from the magnitude of signal delays and may be represented as greyscale isochrone maps to visualise initiation sites (Figure 52C,D). An in-line laminar flow chamber (Figure 52E) holds three 12x12 mm plastic slides, each with primary cell cultures in free communication. The slides held urothelial, interstitial and detrusor smooth muscle cells to reproduce the structure of the bladder wall. Figure 52F,G shows schematics of the three adjacent and the traces above are actual recordings from the respective slides. Here, introduction of a superfusate of decreased osmolality generated Ca^{2+} transients in urothelial cells (UC) that spread to the interstitial cell layer and then to the detrusor smooth muscle layer. Figure 52F shows that removal of the slide holding interstitial cells abolished the spread of Ca^{2+} transients from the urothelial cell slide to that holding detrusor smooth muscle cells (Figure 52G). Figure 52H shows another phenomenon, namely that the interstitial cell layer can spontaneously generate intracellular Ca^{2+} transients. Ac-

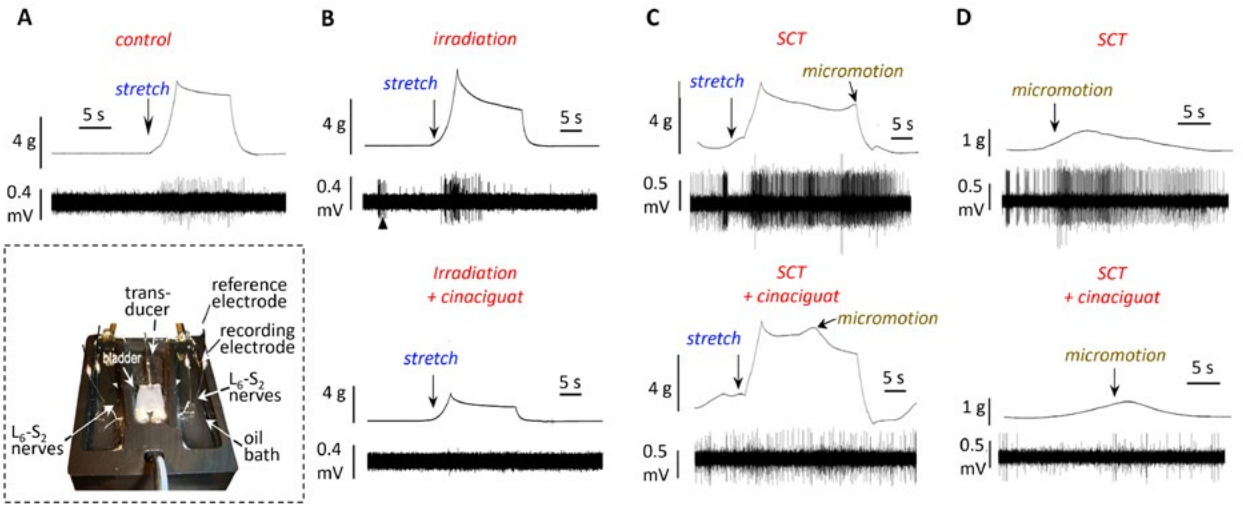

Figure 50. Recording of afferent activity from a bladder sheet with attached nerves. *A: Simultaneous recordings of isometric tension (upper trace) and single unit activity of lumbro-sacral spinal roots before, during and after a rapid stretch (1 mm, 100 µm.s-1, hold 20 s). An image of the recording chamber is shown below. B: Recordings from bladder irradiated three days previously, before (upper) and during (lower) superfusion with 1 µM cinaciguat. Note spontaneous activity before stretch (arrowhead, upper) and the increased compliance of the tissue and absence of nerve activity with cinaciguat (lower). C: Recordings from an SCT mouse preparation before and during exposure to cinaciguat. Note the small spontaneous contraction (micromotion) during the stretches. D: Recordings from an SCT mouse preparation showing larger micromotions, without stretch, before and during exposure to cinaciguat. Note that cinaciguat reduced both the micromotion and of afferent nerve activity. Figures courtesy of Drs AJ Kanai, Y Ikeda and IV Zabbarova.*

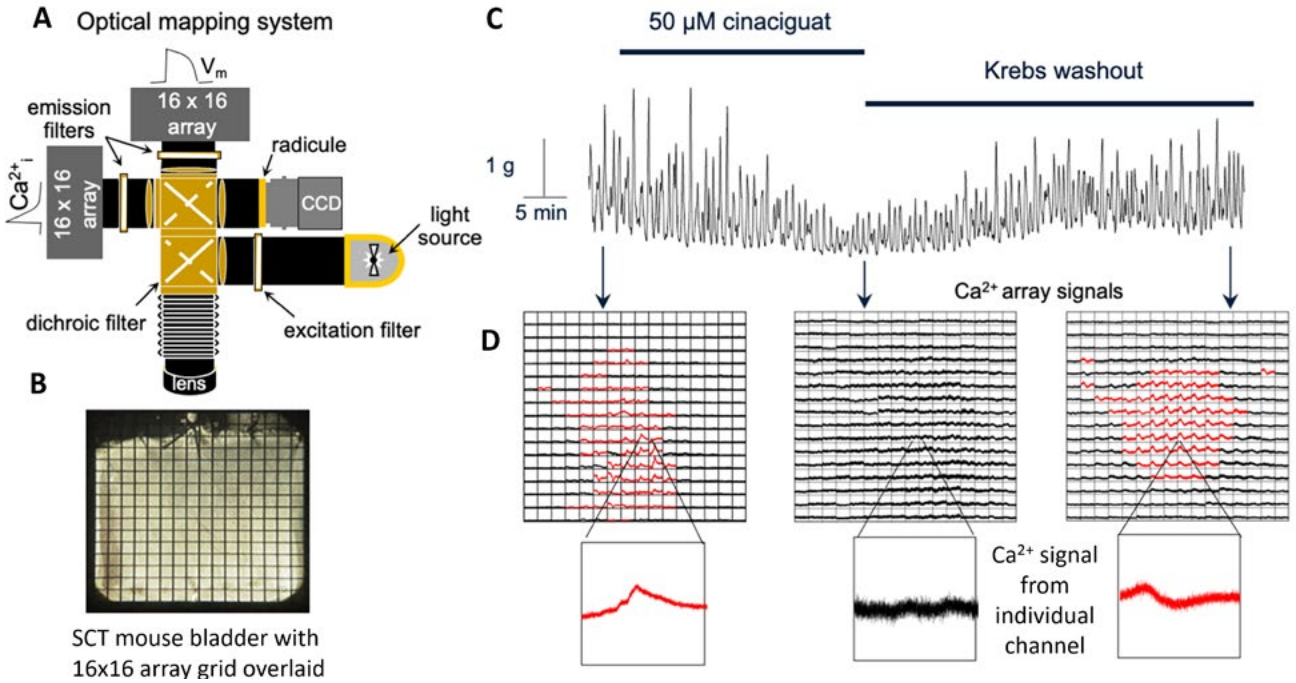

Figure 51. Simultaneous optical mapping and tension recording. *A: Schematic of the optical mapping system. B: Image of the mucosal surface of a SCT male mouse bladder sheet, with an overlaid 16x16 array grid. C: Isometric tension recording from the bladder sheet in the presence of 50 µM cinaciguat and following washout. D: Ca2+ trace map recordings at baseline, in the presence of cinaciguat and following washout. Note individual recordings from the same grid component, signals significantly above baseline shown in red. Figures courtesy of Drs AJ Kanai, Y Ikeda and IV Zabbarova.*

cordingly, this experimental model is one that may be used to test the action of agents designed to inhibit spontaneous interstitial cell activity that may underlie spontaneous activity of the bladder wall.

3.4. The decerebrate arterially perfused rodent (DAPR) model. The normal function of the lower urinary tract is based on coordinated responses from the cortical and autonomic nervous systems. The DAPR model (812-816) allows for recording of multiple physiological parameters while maintaining the brainstem and spinal control centres that control lower urinary tract function (Figure 53A). Rodents are heparinised and anesthetised with isoflurane. After a midline laparotomy, the vascular supply to the stomach, spleen, and free intestine are ligated and removed. The animals are immersed in artificial cerebrospinal fluid (CSF) at 4°C and decerebrated, by aspiration, at the pre-collicular level. After a midline sternotomy, the preparation is then transferred to a recording chamber and placed supine. A double-lumen cannula is inserted into the ascending aorta *via* the left ventricle and held in place by a ligature. The preparation can be arterially perfused with carbogenated artificial CSF at 32°C at a rate gradually increasing from 1 to 3 ml.min^{-1}. A 30G needle is inserted into the bladder dome to measure intravesical pressure and enable bladder filling. The left bladder afferent input to the pelvic nerve is used for afferent fibre recordings. EMG activity of the EUS is recorded with a glass suction electrode. Important simultaneous measurements that can be obtained include bladder intra-luminal pressure, EUS-EMG, pelvic nerve afferent nerve activity and pudendal motor nerve activity, along with recordings from respiratory nerves, electrocardiograms (ECG) and blood pressure (Figure 53B). This model has been used to demonstrate the effect of systemic sildenafil on both sensory and sphincter activity in normal male mice (813) where sildenafil increased pelvic nerve afferent firing, increased EUS activity while increasing bladder compliance. These unique findings suggest that PDE5 inhibitors may be elicit therapeutic effects through afferent regulation of EUS activity.

VIII. NEW DRUG TARGETS: MOLECULAR APPROACHES TO INVESTIGATE LUT DYSFUNCTION

1. INTRODUCTION

The control of bladder function is far more complex than previously believed and as illustrated by the previous sections. Prominent roles have emerged for afferent pathways, as well as the urothelium and suburothelium that line the muscular tissues of the urinary tract. Together this advancing knowledge of mechano-sensory control has consequences for improved understanding of the pathophysiology of lower urinary tract dysfunction (LUTD). This section will build on this knowledge to summarise some advances in drug development to manage different manifestations of LUTD. A con-

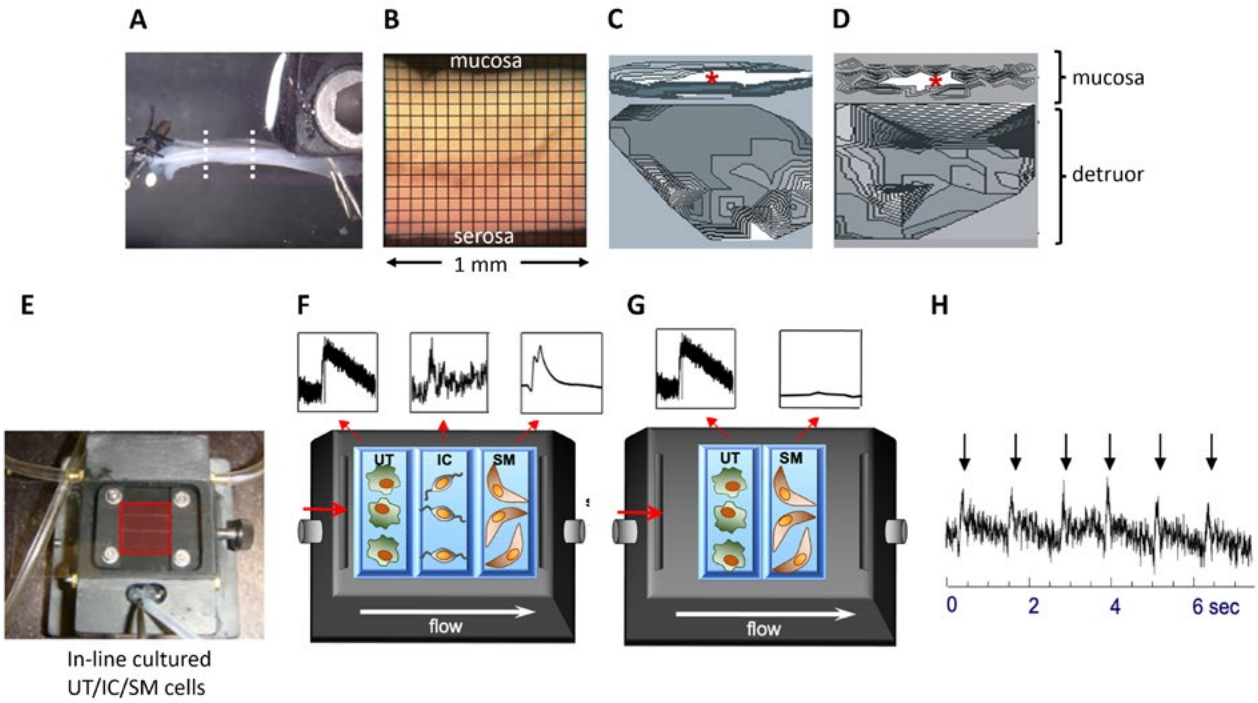

Figure 52. Optical mapping from bladder wall cross-sections and cultured primary cells. *A: Female adult rat bladder sheet shown in cross-section, stained with Rhod-2-AM for Ca2+ imaging. B: Photo image of the region denoted in A (white dotted lines) with 16x16 array grid overlay, mucosa and serosa surfaces labelled. C: Greyscale isochrone map of intracellular Ca2+ transients in response to focal tactile stimulation of the mucosa (red star). White regions indicate areas with earliest activation and progressively later time points as darker shades of grey, responses are confined to the mucosa. D: Preparation from an SCT rat with the same tactile stimulus. Note greater transmission of the signal to the detrusor layer. E: In-line laminar flow chamber. The chamber holds three 3x12 mm plastic slides with attached cells. F: Schematic of the chamber and cells with osmolality challenge added to the urothelial layer (UT; red arrow, left). Traces above are optical recordings of Ca2+ transients, showing spread to interstitial cell (IC) and detrusor smooth muscle (SM) layers. G: Similar experiment but with IC layer removed. H: Spontaneous Ca2+ transients from the IC layer. Figures courtesy of Drs AJ Kanai, Y Ikeda and IV Zabbarova.*

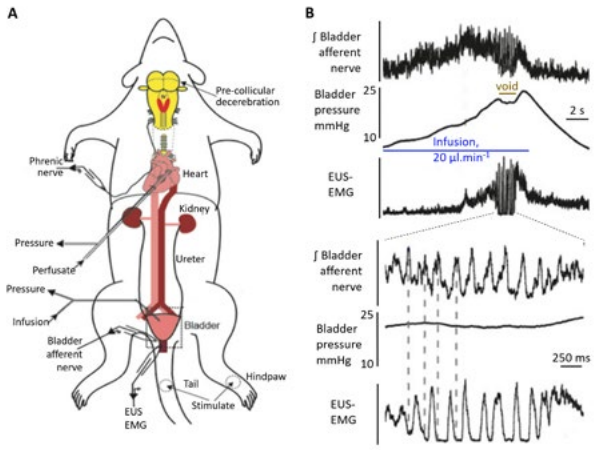

Figure 53. The decerebrate arterially perfused rodent (mice, rat) preparation. *A: Animals are decerebrated and arterially-perfused with artificial cerebral spinal fluid to maintain tissue viability and brainstem function. The preparation allows for multiple physiological variables to be recorded including bladder pressure, EUS activity, bladder afferent nerve firing, blood pressure and phrenic nerve activity. B: Recordings of integrated afferent nerve activity (upper), bladder pressure (middle) and integrated EUS-EMG (lower) activities during artificial filling of the bladder (20 µl.min-1). Part of the trace during a void is expanded below. Adapted from (807-811).*

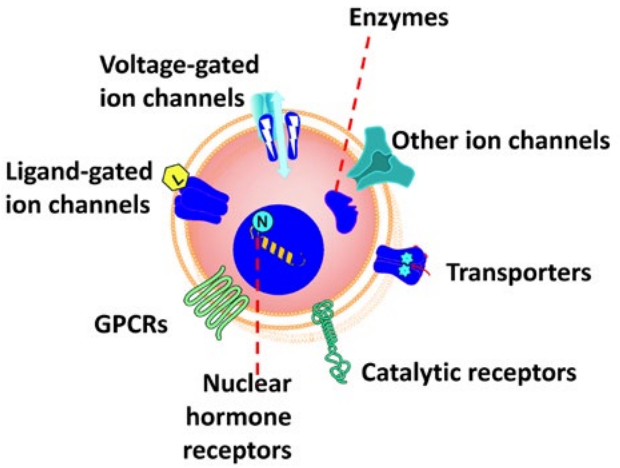

Figure 54. Schematic of the different signal transduction systems.

sideration of how different signalling mechanisms influence other tissue of the body will be included not only to gain more insight into their functions but also highlight potential side effects that must be considered in the development of any novel agent.

According to the most recent classification, signal transduction mechanisms as potential targets have been subclassified into a number of different categories. These are: G-protein coupled receptors; ligand-gated ion channels; other ion channels; nuclear (hormone) receptors; kinases and catalytic receptors; transporters; enzymes. In turn, ligands for the above mechanisms maybe subclassified for convenience and may be listed as: approved drugs; synthetic organics; metabolites; natural products; endogenous peptides; other peptides; inorganics; antibodies and labelled ligands. The terminology and definitions used are derived from the most recent classification “The Concise Guide to Pharmacology, 2019/20” [817] (Figure 54).

This section of potential novel molecular targets for managing LUTD will focus on the most currently relevant G-protein coupled receptors; promising ligand-gated and other ion channels; and briefly consider the role of vesicular nucleotide transporters. A n equally brief introduction to the function of clock genes will be described that may give insight into the design of therapies for cyclical LUT disorders such as nocturia. Finally, a section is devoted to the control of fibrosis, a connective tissue disorder that has profound implications for lower urinary tract function during paediatric and adult levels of development.

2. G-PROTEIN-COUPLED RECEPTOR (GPCR)S

G-protein coupled receptors are subclassified into 74 subfamilies, including orphans, and here, the nine pertinent receptor subfamilies will be described

2.1. Orphan GPCRs.

The nociceptin/orphanin FQ peptide (N/OFQ)[818,819]] is involved in a wide range of physiological responses with effects in the central and peripheral nervous systems, the cardiovascular system, airways, the gastrointestinal tract, the urogenital tract and the immune system [820,821] The N/OFQ receptor (NOP; also known as ORL1, OP4 or LC132) is a deorphanised member of the GPCR superfamily and is currently classified as a non-opioid member of the opioid receptor family. Although NOP shares considerable structural and localisation features with classical opioid receptors, NOP activity is insensitive to the opioid receptor antagonist naloxone.

In the rat, NOP receptors located on capsaicin-sensitive bladder primary afferent fibres inhibit the volume-evoked micturition reflex [822,823]. There are no studies detailing NOP expression in human bladder tissue. However, based on animal data a series of elegant clinical studies have been performed using intravesical N/OFQ. In a pilot study of 14 patients, intravesical instillation of N/OFQ increased bladder capacity and the volume required to elicit detrusor overactivity (DO). However, one patient had previously received intravesical capsaicin treatment and the effects of N/OFQ were minimal, indicating a capsaicin-sensitive target [824]. In a placebo-controlled study, N/OFQ was compared with the structurally similar but inactive [desPhe1]N/OFQ (a major metabolite of N/OFQ, which does not bind to NOP) in 14 patients with DO due to spinal-cord damage. Intravesical administration of N/OFQ, but not [desPhe1]N/OFQ, increased bladder capacity and volume required to elicit DO [825]. In a further study of 18 patients with incontinence from neurogenic DO, the number of daily urine leakage episodes was reduced in the N/OFQ (but not the control) group. There were no major practical problems and the effects of a single instillation in the morning lasted the whole day [826].

Collectively, these studies broadly agree with studies in rats that NOP is probably expressed on capsaicin-sensitive primary affer-

ents and their activation inhibits the micturition reflex. However, primary research has only been done in normal rats, and with humans N/OFQ is only effective in spinally injured patients where there may be afferent fibre switching [827]. However, N/OFQ and N/OFQ mimetics have a potential role in the treatment of OAB.

2.2. Acetylcholine-muscarinic receptors.
Molecular cloning studies have revealed five distinct genes for muscarinic ACh receptors in rats and humans, with five corresponding receptor subtypes. Muscarinic receptors are coupled to G-proteins; M1, M3, M5 are facilitatory (Gq) and M2, M4 are inhibitory (Gi) [828]. The signal transduction systems of M1, M3, and M5 preferentially couple to phosphoinositide hydrolysis leading to mobilisation of intracellular Ca^{2+}, whereas activation of muscarinic M2 and M4 receptors inhibits adenylate cyclase activity. Detrusor smooth muscle expresses both M2 and M3 receptors [829] and activation of either subtype elicits contraction. Although M2 receptors predominate in receptor binding studies, the M3 receptor mediates contraction in normal detrusor.

Desensitisation of muscarinic receptors is one mechanism whereby detrusor smooth muscle becomes less sensitive to incoming stimuli. This is mediated by phosphorylation of muscarinic receptors by guanosine phosphate binding (G) protein-coupled receptor kinase (GRK)[830]; all m2, m3, and GRK2 mRNAs have been isolated. However, protein expression of GRK2 in normal detrusor is significantly higher than in tissue from obstructed bladders in patients with benign prostatic hyperplasia [831] and failure of this desensitising mechanism may contribute to DO in BPH patients.

Currently, the principal treatment for OAB is with anticholinergic drugs that initially were believed to act by reducing the action of acetylcholine on the detrusor as released by parasympathetic nerves. However, there is now considerable evidence to suggest that anticholinergic drugs also interact with sensory pathways. Stimulation of muscarinic receptor pathways depresses sensory transduction by a mechanism independent of changes to bladder tone [832]. The density and binding affinity profile of the muscarinic receptor population in human bladder mucosa, by radioligand binding assay, is similar to that of detrusor muscle. Moreover, the density of the M3 subtype in mucosa is similar to that in detrusor muscle, but lower than that in the parotid gland [833]. Finally, clinically effective muscarinic receptor antagonists bind to receptors on both the bladder mucosa and the detrusor. Thus, there is experimental support for the hypothesis that muscarinic receptors in the mucosa may represent an important site of action for these agents in OAB [834], but there is at present no compelling evidence in the clinical setting.

2.3. Adrenergic b-receptors.
There are three adrenergic β-receptor subtypes ($\beta1$,$\beta2$,$\beta3$) and relaxation of detrusor smooth muscle was regarded as mediated by $\beta2$-receptors [835]. The $\beta3$-receptor was considered to be related only to fat metabolism, but gene expression of the β3-adrenergic receptor in human detrusor and relaxation of isolated human detrusor preparations was reported [836-839]. Now, the role of adrenergic $\beta3$-receptors in determining the contractile state of detrusor is regarded as significant. Consequently, several β3-agonists (KUC-7483, YM-178, FK-175) were developed in Japan and YM-178 (mirabegron) has been launched to manage OAB in in Japan, USA and European Countries. Vibegron, another β3-agonist, is now also used to treat OAB.

The $\beta3$-receptor is Gs protein-coupled, and its activation increases intracellular cAMP and this is believed to be the key pathway that elicits detrusor relaxation. Downstream effectors activated by cAMP-dependent mechanism(s) include membrane K^+ channels, such as BK channels, and (de)phosphorylation pathways that directly regulate the Ca^{2+}-sensitivity of the contractile proteins. However, there may also be cAMP-independent signalling pathways, as evidenced in airway smooth muscle where activation of BK channels, independent of cAMP elevation, causes relaxation [840].

The $\beta3$-receptor is an attractive target for drug discovery, but selectivity is important, as activation of $\beta1$- or $\beta2$-ARs will cause undesirable side-effects. The $\beta3$-receptor agonist GW427353 evokes bladder relaxation and facilitates bladder storage mechanisms in the dog [841] and another agonist, CL-316243, increases urine storage in spontaneously hypertensive rats [842]. In addition to direct detrusor relaxant effects, $\beta3$-receptor agonists have been reported to inhibit cholinergic neurotransmission through adenosine release and prejunctional A1 receptor stimulation in the human and rat bladder [843] and also reduce postjunctional purinergic receptor-mediated contractions of mouse detrusor [844].

A further potential site of action is the urothelium and $\beta3$-receptor agonists mediate reduction of pig detrusor contractions via the urothelium (mucosa) [845]. The isolation of $\beta3$-receptor mRNA from the urothelium as well as detrusor muscle suggest multiple sites of action in the lower urinary tract [846]. In addition, β-receptor agonists, including $\beta3$-agonists, promote expression of matrix metalloproteinases (MMPs) in human urothelial cells, which may have a pivotal part in structural remodelling and fibrosis, as may occur under pathological increases of hydrostatic pressure [847]. Because MMP expression is regulated by the PKA/CREB pathway, this may also be an attractive target for $\beta3$-receptor agonists in OAB patients.

2.4. Cannabinoid receptors.
Cannabinoids, the active components of *Cannabis sativa linnaeus* (marijuana) and their derivatives, are drawing renewed attention because of their diverse pharmacological activities such as cell growth inhibition, anti-inflammatory effects, and tumour regression [848-850]. The cannabinoid receptor has two subtypes, CB1 and CB2, both of which are GPCRs [851] and are activated by endogenous ligands such as N-arachidonoyl-ethanolamine (anandamide), N-homo-γ-linolenoyl-ethanolamine, N-docosatetra-7,10,13,16-enoylethanolamine and 2-arachidonoylglycerol [852].

CB1 is expressed in urinary bladder hypersensitivity and overactivity disorders and correlates with symptom changes in human and animals. In rats with bladder outlet obstruction, immuno-fluorescence labelling and protein expression of CB1 and CB2 receptors were increased, and receptor agonists improved contraction interval and contraction pressure [853]. Also, CB2 agonists selectively inhibit the mechano-sensitivity of capsaicin-sensitive mucosal bladder afferents, but not muscular-mucosal afferents. This indicates endocannabinoids may modulate bladder function though sensory pathways in pathological states [854].

CB1-immunoreative suburothelium nerve fibres were significantly increased in the suburothelium of tissue from painful bladder syndrome (PBS) and idiopathic DO (IDO) patients, and also in the detrusor layer from IDO patients. Suburothelial nerve fibre density correlated significantly with pain scores in PBS and urgency scores in IDO patients [588]. A *Cannabis sativa* extract enriched in cannabidiol (CBD) botanic drug substance (BDS) and pure CBD reduced cholinergic-mediated contractility. If confirmed *in vivo*, such results could provide a pharmacological basis to explain, at least in part, the efficacy of Cannabis medicines in reducing incontinence episodes in patients with multiple sclerosis [855].

Amplification of endocannabinoid activity by fatty acid amide hydrolase (FAAH) inhibitors may be an attractive drug target in specific pathways involved in LUTS [856]. FAAH degrades endocannabinoids and is expressed in human, rat, and mouse bladder mucosa. The FAAH inhibitor oleoyl ethyl amide (OEtA) altered urodynamic parameters that reflect sensory functions of micturition in rats, suggesting a role for the endocannabinoid system in bladder mechano-afferent functions of rats [857]. FAAH inhibition in the sacral spinal cord by OEtA also modulated urodynamic activity of normal and obstructed rat bladders, which also suggests involvement of a spinal endo-cannabinoid system in micturition control [858,859].

The endocannabinoid system may also be involved in physiological control of micturition through regulation of afferent signals [592]. CP55,940 is a synthetic analogue of tetrahydrocannabidiol, a psychoactive ingredient of the Cannabis plant. It decreases normal rat bladder activity and urinary frequency induced by nociceptive stimuli, probably by suppression of bladder afferent activity and are abolished by both CB1 and CB2 antagonists. However, the role of the two CB subtypes in micturition is yet to be established [860]. The endocannabinoid system is a potential drug target for pharmacological management of LUTS, with a more favourable adverse event profile than antimuscarinic agents [861].

2.5. $GABA_B$ receptors.

Functional $GABA_B$ receptors are formed from the heterodimerisation of two similar subunits: $GABA_{B1}$ and $GABA_{B2}$. Stimulation of spinal GABAergic mechanisms by intrathecal application of $GABA_A$ and $GABA_B$ receptor agonists could be effective for the treatment of neuropathic DO as determined in spinal cord injured rats [862]. ADX71441, a novel positive allosteric modulator of the $GABA_B$ receptor, also has a potential to modulate bladder nociception through supra-spinal sites from rat studies but did not affect normal bladder contractions and micturition [863].

DO may also be controlled by modulating afferent input from the bladder as well as the excitability of the sacral reflex centre. This suggests a novel method to treat OAB patients with oral gabapentin, as it reduced urinary frequency in a lipopolysaccharide-induced chronic cystitis model [864]. This was corroborated in a clinical trial where gabapentin improved OAB symptoms with an acceptable safety profile, [865].

2.6. Glutamate metabotropic receptors.

Glutamate receptors consist of two major classes, ionotropic receptors that form ligand-gated cation channels and metabotropic receptors (mGluRs) that are a family of GPCRs. The former includes NMDA, AMPA and kainite receptors which have essential roles in the control of micturition reflexes [866,867]. mGluRs have eight subtypes (mGluR1 - mGluR8) and are placed into three subgroups (groups I-III) based on sequence homology, transduction mechanism and agonist pharmacology. Less is yet known about their functional roles in the LUT.

Wild-type and mGluR1 knockout mice were used for *in vivo* cystometry with a selective mGluR5 antagonist 6-methyl-2-(phenylethynyl) pyridine. Loss of function of both receptors increased bladder capacity and reduced afferent signal transmission from the bladder [868]. Thus, blockade of both mGluR1 and mGluR5, could have a beneficial effect to manage storage dysfunctions including OAB and urgency urinary incontinence. Similar data suggests glutamic acid has a transmitter function in somato-bladder reflex mechanisms and raises the potential for mGluR5 as a target for LUTD [869]

2.7. Prostanoid receptors.

Prostanoid actions are mediated by specific membrane receptors: DP, EP, FP, IP and TP that respond to PGD_2, PGE_2, PGF_2, PGI_2 and thromboxane, respectively. EP itself is subdivided into EP1, EP2, EP3 and EP4 receptors [870].

EP1 receptor-knockout mice have normal cystometry but do not react to intravesical PGE2 instillation which causes bladder overactivity in wild-type controls. Obstruction of EP1 receptor-knockout mice still increases bladder weight but prevents the increase of non-voiding contractions seen in the wild-type controls [871]. PGE_2 enhances the micturition reflex through C-fibre afferents via EP1, so that selective antagonists may improve bladder storage function [872]. However, the EP1 receptor antagonist ONO-8359 had no significant effect on patients with non-neurogenic OAB [9][72]. A recent study showed that the main contractile effects of PGE_2 on both mucosa and detrusor contractions is mediated by the FP receptor. Thus, there is significant interaction between different prostanoids and their receptors [873].

For EP2 receptors, there is little information on their role in the normal micturition cycle, even though receptor expression has been demonstrated on the urethra and bladder of animals [874]. EP3 receptor knockout mice show an enhanced bladder capacity and implicates their contribution to bladder overactivity when PGE_2 production is enhanced [875]. The EP4 receptor antagonist AH23848 reduces cyclophosphamide-induced OAB in rats [876].

Contrary to antagonists, potent agonists for EP2 and EP3 have been developed as potential treatments for detrusor underactivity, e.g. from diabetes [877]. A highly potent and selective agonist for EP2 and EP3 receptors, ONO-8055, contracted bladder strips and relaxed urethral strips, and decreased post-void residual urine. Thus, the beneficial effects may be a dual action on bladder and outflow tract [877,878]. Finally, the EP4 agonist ONO-AE1-32p reduces detrusor muscle contraction and afferent activity [879].

2.8. Tachykinin receptors.

Tachykinin receptors are activated by the endogenous peptides substance P (SP), neurokinin A (NKA), neurokinin B (NKB), neuropeptide K and neuropeptide G. NKA and NKB are mammalian members of the tachykinin family, which includes peptides of mammalian and non-mammalian origin containing the consensus sequence, Phe-x-Gly-Leu-Met. Several neurokinin-1 receptor antagonists or SP-reducing agents has been tested for efficacy in reducing OAB, including aprepitant, cizolirtine citrate and netupitant [880-882] and have provided clinical evidence that modulation of tachykinin pathways could be an effective way to treat OAB.

2.9. Taste receptors.

Expression of a functional sweet taste receptor has been reported in numerous extragustatory tissues [883]. Artificial sweeteners may activate sweet taste receptors in the bladder, resulting in OAB symptoms. $T1R_{2/3}$ sweet taste receptors are expressed in human and rat bladder urothelium and their activation by artificial sweeteners may result in augmented bladder contractions [884].

The family of bitter taste receptors (TAS_2Rs) also perform non-gustatory functions outside the mouth and mRNA expression of various TAS_2R subtypes has been shown in both human and mouse detrusor smooth muscle. Chloroquine, a TAS_2R agonist, relaxed carbachol- and KCl-induced contractions of human detrusor smooth muscle strips in a concentration-dependent manner and treatment significantly suppressed OAB symptoms of mice with partial BOO [885].

3. ION-CHANNELS

Ion channels are pore-forming proteins that allow the flow of ions across cell or organelle membranes. Many ion channels (e.g. most Na^+, K^+, Ca^{2+}, TRP channels, and some Cl^- channels) are voltage-gated and others (e.g. certain K^+ and Cl^- channels, ryanodine receptors and IP_3 receptors) are relatively voltage-insensitive and are gated by extracellular or intracellular mediators. Ligand-gated ion channels are integral membrane proteins that contain a pore which allows the regulated flow of selected ions across the plasma membrane. Ion flux is passive and driven by the electrochemical gradient for permeant ions. The channels are opened, or gated, by the binding of a neurotransmitter to an orthosteric site to trigger a conformational change that results in the conducting state. Ion channels represent the second largest target for existing drugs after G protein-coupled receptors. However, the advent of novel, faster screening techniques for compounds acting on ion channels suggests that these proteins represent promising targets for the development of additional, novel therapeutic agents. This section will summarise selected channel targets.

3.1. P2X receptors.

Purinergic receptors form two main classes, P1 and P2, and P2 receptors are further divided into ionotropic P2X and metabotropic P2Y receptors. Their role in normal and pathological lower urinary tract function has been described extensively [886]. ATP is released from parasympathetic post-ganglionic fibres where it can activate $P2X_1$ receptors and contribute to contractile activation. In the normal human bladder, the purinergic component of parasympathetic contractile generation is very small, but in pathological conditions, such as interstitial cystitis, obstructed and neuropathic bladder, or in the paediatric bladder (see later) the purinergic component is substantial. ATP is also released from the urothelium of the bladder and ureter under conditions of physical or chemical stresses to act on $P2X_3$ and $P2X_{2/3}$ receptors on suburothelial sensory nerves to initiate the voiding reflex, via low threshold fibres, and nociception, via high threshold fibres, as discussed previously. Purinergic therapeutic strategies are being explored to bring benefit and relief to many patients with urinary tract disorders [886].

Functional P2X receptors exist as polymeric transmitter-gated channels; the native receptors may occur as either homopolymers (e.g. $P2X_1$ in smooth muscle) or heteropolymers (e.g. $P2X_{2/3}$ in the sensory nerve terminals and the nodose ganglion and $P2X_{1/5}$ in cortical astrocytes). $P2X_2$, $P2X_4$ and $P2X_7$ receptors also form functional homopolymers which, in turn, activate pores permeable to low molecular weight solutes. The hemi-channel pannexin-1 has been implicated in the pore formation induced by $P2X_7$, but not $P2X_2$ receptor activation [852].

Several $P2X_3$/$P2X_{2/3}$ receptor antagonists have been developed in the light of this mapping of P2X receptors in the urinary tract. AF-792 ([5-(5-ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine]) is a novel selective $P2X_3$/$P2X_{2/3}$ antagonist which significantly inhibited micturition reflex activity. Afferent signals originating from the bladder are regulated by spinal $P2X_3$/$P2X_{2/3}$ receptors and establish directly an endogenous central presynaptic purinergic mechanism to regulate visceral sensory transmission. Thus, $P2X_3$/$P2X_{2/3}$ receptors are promising agents to treat not only urological dysfunction, such as overactive bladder but also sensory disorders, including chronic pain states [887]. After bladder outlet obstruction in rats, $P2X_3$ receptor expression, as well as of M2 and M3 receptors, is increased along with bladder overactivity, consistent with changes in urothelium purinergic, and muscarinic, receptor expression having a role in mediating bladder afferent sensory responses [888]. Furthermore, the $P2X_3$/$P2X_{2/3}$ receptor antagonist A-317491 improves signs of cyclophosphamide-induced cystitis in the rat [889].

3.2. Acid-sensing (H^+-gated) ion channels (ASICs).

Acid-sensing ion channels (ASICs) are members of a Na^+ channel superfamily that includes the epithelial Na^+ channel (ENaC), the FMRF-amide activated channel (FaNaC) of invertebrates, the degenerins (DEG) of *Caenorhabitis elegans*, channels in *Drosophila melanogaster* and 'orphan' channels. ASIC subunits contain two transmembrane domains and assemble as homo- or hetero-trimers to form H^+-gated, voltage-insensitive, Na^+ permeable channels.

A number of subtypes have been reported: ASIC1 is the dominant subunit expressed in urothelium, whereas both ASIC1 and ASIC2 are expressed in detrusor smooth muscle. ASIC3 expression is less abundant but is localised to the suburothelial region. In the mucosa overall, the ASIC1 gene is more highly expressed in male mice, whereas ASIC2 expression in detrusor is greater in females.

For comparison $TRPA_1$ and $TRPM_8$ expression are not different between sexes. Thus, the sex difference in the bladder responses to acidic irritation may in part be attributed to variation of ASIC subtype expression [890].

H^+ (acting via both ASIC and $TRPV_1$ channels) and capsaicin (via $TRPV_1$ channels) both induce ATP release from the rat bladder mucosa, that is principally of urothelial origin and mediated by a rise of the intracellular [Ca^{2+}]. This highlights the role of H^+ (or as H_3O^+) as a signalling moiety, and the potential involvement of ASIC channels, to modulate bladder function [571,891]. This ASIC system may be upregulated by bladder inflammation. Cyclophosphamide treatment increases expression of two ASIC subtypes (ASIC2a and ASIC3), although ASIC1 expression is unaltered [892], and may contribute to increased pain and hyperalgesia in patients with bladder pain syndrome [893].

Systemic administration of A-317567, a potent, non-amiloride ASIC blocker, increased inter-contraction interval during instillation of both saline and acetic acid in decerebrated, un-anaesthetised female mice. However, intravesical perfusion of A-317567 (100 μM) had no effect on bladder activity under the same conditions. Thus, blockade of ASIC signal transduction may increase bladder capacity under normal conditions and when intravesical pH is decreased, but possibly through effects distant from the bladder itself, such as via dorsal root ganglia [894].

3.3. Epithelial sodium channels (ENaC).

ENaCs have a role in Na^+ reabsorption by epithelium lining the distal part of the kidney tubule and fulfil similar functional roles in some other tissues such as the alveolar epithelium and the distal colon. This reabsorption of Na^+ is regulated by aldosterone, vasopressin (ADH) and glucocorticoids, and is one of the essential mechanisms in the regulation of sodium balance, blood volume and blood pressure. The degenerin epithelial Na^+ channel (ENaC) family has been proposed as mechano-sensitive transducers in several species [895,896]. In rabbit bladder, ENaCs alter their Na^+ transporter properties after changes to transmural hydrostatic pressure [896]. This is mirrored in rat renal pelvic epithelium where ENaC participate in the activation of afferent renal mechano-sensitive neurons by increased renal pelvic pressure [897].

The significance of ENaC in mediating normal and pathological sensory function is implied by several human and animal studies. ENaC mRNA and protein expression in human bladder urothelium correlates significantly with storage symptom scores [898] and

ENaC (γ-subunit) expression is increased in urothelium from patients with neuropathic DO [899]. With rats, intravesical infusion with 1mM amiloride (an ENaC inhibitor) significantly reduced the frequency of reflex voiding during bladder filling and increased bladder capacity, but without effect on the amplitude of micturition pressure. These findings were mirrored by a suppression of stretch-induced ATP release in mucosa-intact isolated preparations [900].

3.4. Potassium (K^+) channels.

Potassium channels are fundamental regulators of cell excitability and control the cell membrane potential, action potential frequency and waveform as well as secretion of hormones and neurotransmitters. Their activity may be regulated by transmembrane potential difference, [Ca^{2+}] or neurotransmitters. They consist of a primary pore-forming α-subunit, often associated with auxiliary regulatory subunits.

The 2TM (two transmembrane) and 6TM families of K^+ channels. This domain family of K^+ channels, also known as the inward-rectifier K^+ channel family includes the strong inward-rectifier K^+ channels (KIR2.x), G-protein-activated inward-rectifier K^+ channels (KIR3.x) and the ATP-sensitive K^+ channels (KIR6.x, which combine with sulphonylurea receptors). The pore-forming α-subunits form tetramers and heteromeric channels may be formed within subfamilies (e.g. KIR3.2 with KIR3.3). The 6TM family of K^+ channels comprises: voltage-gated K_V subfamilies; the KCNQ subfamily; the EAG subfamily (including HERG channels); the Ca^{2+}-activated, large conductance Slo subfamily (BK_{Ca} channels; actually with 7TM); and the Ca^{2+}-activated SK subfamily. Similar to the 2TM family, pore-forming α-subunits form tetramers and heteromeric channels may be formed within subfamilies (e.g. K_V1.1 with K_V1.2; KCNQ2 with KCNQ3). Considerable attention has been directed to modulation of BK_{Ca} channel activity, as outlined below and as highlighted also in section 6.

BK_{Ca} and SK_{Ca} channels play an important role in controlling membrane potential, cellular excitability and contractile function of urinary bladder smooth muscle [733,734,901,902]. Ca^{2+} entry through voltage-dependent Ca^{2+} channels activates both BK_{Ca} and SK_{Ca} channels, but Ca^{2+} release through ryanodine receptors also activates BK_{Ca} channels. Because phasic contractions depend on Ca^{2+} entry into the detrusor myocyte, BK_{Ca} and SK_{Ca} channels represent attractive pharmacological targets to modulate contractile function in OAB [691,719]. The importance of the BK_{Ca} channel as a potential target was demonstrated when local hSlo cDNA (i.e. BK_{Ca} channel) injection ameliorated detrusor overactivity in a rat model of partial urinary outlet obstruction [731]. It was suggested that expression of hSlo in the bladder functionally antagonised the increased contractile function normally observed in obstructed animals and thereby improved detrusor overactivity and form the basis of a gene therapy for urinary incontinence. This is consistent with increased frequency in Slo(-/-) mice and provides further evidence that BK channel dysfunction can lead to OAB [903].

Several BK_{Ca} channel modulators have been tested on bladder function. NS-8 increases Ca^{2+}-sensitive K^+-channel opening activity in rats and during bladder filling decreased pelvic nerve afferent discharge rate [904]. Kurarinone, a flavanone from *Sophora flavescens*, is a strong potentiator of BK_{Ca} channel activity, identified from screening a library of natural compounds, and relaxes detrusor muscle [905]. Finally, 4-(4-(4-chlorophenyl)-3-(trifluoromethyl) isoxazol-5-yl)benzene-1,3-diol (CTIBD), is another potent BK_{Ca} channel activator, on rat detrusor where a significant relaxation was measured [906]. By contrast, a non-peptidergic BK_{Ca} channel blocker, A-272651, enhanced field stimulated contractions in pig detrusor and spontaneous contractions in guinea-pig detrusor, as well as increasing the excitability of capsaicin-sensitive DRG neurons [907]. Overall, up- or down-regulation of BK_{Ca} channel activity have predictable effects on detrusor function. The translation of this research to human trials is awaited however, the safety and tolerability of escalating doses of hMaxi-K, a gene transfer product of human BK_{Ca}, were confirmed in a small patient cohort with moderate to severe erectile dysfunction [908].

Indirect modulation of BK_{Ca} channel activity is another feasible approach to achieve detrusor relaxation. Relaxation of pig and human bladder neck smooth muscle is greater with rolipram, a phosphodiesterase type 4 inhibitor that will increase cAMP activity, than by phospho-diesterase type 5 inhibitors, that will increase cGMP activity. This enhanced activity by rolipram was explained in part by PKA-dependent activation of BK_{Ca} [909].

3.5. Transient receptor potential (TRP) cation channels.

The TRP superfamily of cation channels, whose founder member is the *Drosophila* Trp channel, is divided in mammals into six families; TRPC, TRPM, TRPV, TRPA, TRPP and TRPML based on amino acid homologies. TRP subunits contain six putative transmembrane domains and assemble as homo- or hetero-tetramers to form cation selective channels with varied permeation properties (Figure 55). The TRPC ('Canonical') and TRPM ('Melastatin') subfamilies consist of seven and eight different channels, respectively (*i.e.*, $TRPC_1$-$TRPC_7$ and $TRPM_1$-$TRPM_8$). The TRPV ('Vanilloid') subfamily comprises six members ($TRPV_1$-$TRPV_6$) whereas the TRPA (Ankyrin) subfamily has only one mammalian member ($TRPA_1$). The involvement of TRP channels in disease is reviewed in [910,911]. Several TRP channels have mechano- or thermo-sensitive properties and are potential molecular targets for treatments of LUTD. However, knowledge of the mechanisms by which TRP channel function is still limited and in consequence few medical treatments have emerged based on targeting these channels. Several that were considered useful but not used for various reasons, however, may still be used to probe channel function so that more useful agents may be developed. Four TRP channels will be considered below; $TRPV_1$, $TRPV_4$, $TRPA_1$ and $TRPM_8$.

$TRPV_1$. $TRPV_1$ is an ion channel activated by capsaicin, heat, H^+ and endogenous ligands such as anandamide and receptor expression are prominent in sensory fibres and urothelial cells. Nociception was the first role attributed to $TRPV_1$ in the urinary tract. However, $TRPV_1$ also regulates the frequency of bladder contractions, either through direct excitation of sensory fibres or through urothelial-sensory fibre cross-talk involving the release of neuromodulators from epithelial cells. Capsaicin and resiniferatoxin (RTX) are agonists for $TRPV_1$ and their desensitisation of the receptor was investigated for therapeutic purposes for painful bladder syndrome and OAB of neurogenic and non-neurogenic origin. However, non-toxic, potent $TRPV_1$ antagonists are available [912] and may be used to ameliorate chronic pain, whereas $TRPV_1$ agonists that induce desensitisation may be used to treat diseases in which channel overexpression occurs [911]. A splice variant of $TRPV_1$, $TRPV_{1b}$, in which 60 amino acids are deleted in the intracellular N-terminal region, forms capsaicin-insensitive and stretch-inhibited cation channels [913]. This channel is activated by hypertonic cell shrinkage and mediates osmo-sensitivity in the supraoptic nucleus [914]. Such $TRPV_1$ variants might explain partly why a mechano-sensory function for $TRPV_1$ has been suggested in the bladder.

Patients with neurogenic detrusor overactivity (NDO) have increased immunoreactivity of $TRPV_1$ in the suburothelium and the basal layers of the urothelium compared to control patients. This

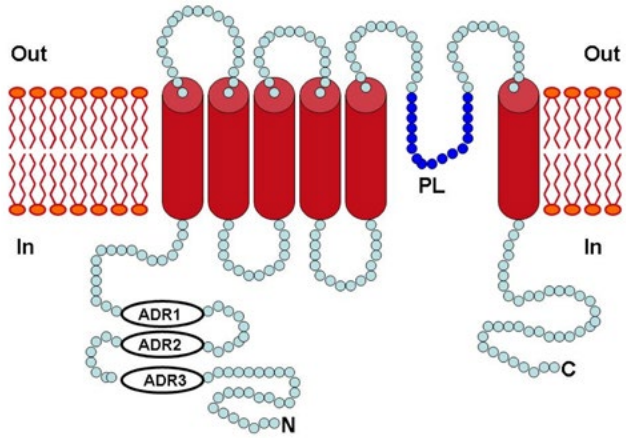

Figure 55. Molecular structure of TRP channels. *Most TRP channels are composed of six membrane-spanning helices with intracellular N- and C-termini. Ankyrin-repeat domains (ADRs), as the sensor, are in the C-termini. Mammalian TRP channels are activated by a wide variety of stimuli: e.g. osmotic pressure, volume, stretch, vibration, and regulated by post-transcriptional mechanisms like phosphorylation, G-protein receptor coupling, ligand-gating, and ubiquitination. Receptors are found in almost all cell types and largely localised in the cell membrane, modulating ion entry. PL, pore-forming loop; ADR, ankyrin-repeat domain.*

was reduced in patients who clinically responded to intravesical resiniferatoxin instillations to suggest a role for $TRPV_1$ in the pathophysiology of NDO [521]. The effects of GRC-6211, an orally active $TRPV_1$ antagonist, on the function and noxious input of normal and inflamed bladders has been evaluated in the rat and reduces bladder hyperactivity and noxious sensations induced by cystitis [915]. XEN-D0501, another $TRPV_1$ antagonist, has also been evaluated for use to manage OAB symptoms [916]. The effects of botulinum toxin A (BoNT/A) BoNT/A on the expression of nerve growth factor (NGF) and $TRPV_1$ in the urothelium and detrusor muscle of rats with detrusor overactivity due to partial bladder outlet obstruction have been investigated. Although BoNT/A reduced NGF expression, $TRPV_1$ expression, particularly in the urothelium, was not changed [917].

$TRPV_4$. $TRPV_4$ was originally postulated to act as a mechano- or osmo-sensor [918]. Studies with $TRPV_4$ knock-out mice revealed involvement in sensing mechanical pressure, osmolality and warmth *in vivo* [919,920]. $TRPV_4$ is abundantly expressed in rodent bladder epithelium and knockout mice manifest an incontinence phenotype with a spontaneous voiding pattern, a lower frequency of voiding contractions and increased bladder volume [519,574]. $TRPV_4$ agonists promote Ca^{2+} influx and enhance ATP release in cultured rat urothelial cells [519]. These studies indicate that $TRPV_4$ receptors sense distension of the urothelium.

Development of cystitis-induced bladder dysfunction is strongly impaired in $TRPV_4$ knock-out mice HC-067047, a previously uncharacterised, potent, and selective $TRPV_4$ antagonist increases functional bladder capacity and reduces micturition frequency in wild-type mice and rats with cystitis. However, it had no effect on bladder function in knock-out animals and indicate that $TRPV_4$ antagonists provide a potential treatment for such bladder dysfunction [921]. $TRPV_4$ expression may be regulated by NGF in LUT tissues. In transgenic mice with chronic urothelial overexpression of nerve growth factor HC-067047 increased inter-contraction interval (ICI) and void volume and decreased non-voiding contractions (NVCs) with reduced pelvic sensitivity and luminal ATP release [922,923]. $TRPV_4$ agonists may also have a role in detrusor underactivity. In rat models intravesical GSK1016790A, significantly decreased ICI, bladder capacity, voided volume, and post-void residual volume without increasing non-voiding contractions [924,925]. Finally, $TRPV_4$ receptors may also have functional roles in the sensory limb of the micturition reflex. An animal model of stress in rats showed increased urothelial $TRPV_4$ expression and $TRPV_4$ blockade ameliorated lower urinary tract dysfunction associated with this model [926].

It should be noted that $TRPV_4$ and $TRPV_1$ are present in different bladder afferent populations and the synergistic activity of antagonists for these receptors in very low doses may offer the opportunity to treat LUTS while minimising the potential side-effects of each drug [927,928]. Evaluation of $TRPV_4$ antagonists in larger trials across several indications is warranted given the availability of high-quality candidates and the promise of therapeutic benefit based on pre-clinical evidence [929].

$TRPA_1$. $TRPA_1$ is the only mammalian member of the Ankyrin TRP subfamily and is a potential mechano-sensor and nociceptor, responding to allyl isothiocyanate (in mustard oil), allicin (in garlic) and cinnamaldehyde (in cinnamon), as well as low temperature [797,919]. $TRPA_1$ is localised in the urothelial cells of the bladder and the prostate gland, as well as sensory C-fibres beneath the urothelium [930].

$TRPA_1$ receptors are proposed to play a role in the sensory responses and urinary frequency to inflammatory conditions, and up-regulation of c-fos mRNA in the spinal cord with such mediators is not observed in $TRPA_1$ knock-out mice [931,932]. Blockade of $TRPA_1$ receptors alleviates cyclophosphamide-induced bladder hyperalgesia [799]. In this context, the role of hydrogen sulphide (H_2S) as a $TRPA_1$ activator may be an intermediate in inflammatory bladder disorders [760]. Blockade of $TRPA_1$ receptors by antagonists, such as HC-030031 and A-967079, in a similar rat model of cystitis decreased afferent nerve activity and attenuated consequent detrusor overactivity induced by inflammation [933]. In addition, $TRPA_1$ activation induces bladder contractions, mediated by sensory afferent stimulation and release of neuropeptides and prostanoids. $TRPA_1$ activation is also proposed to contribute to LUT dysfunction in bladder outflow obstruction and spinal cord injury [563,934].

$TRPM_8$. $TRPM_8$ is also mechano-sensitive and cold-sensitive: and a bladder cooling reflex can be elicited by treatment with the $TRPM_8$ agonist, menthol. This reflex is sensitive to ganglion blockade or capsaicin-sensitive C-fibre deafferentation [935]. The $TRPM_8$ channel blocker, N-(3-aminopropyl)-2-[192]-N- (2-thienylmethyl) benzamide hydrochloride salt (AMTB), acts on bladder afferent pathways to attenuate the micturition reflex and nociceptive reflex responses in rats [936]. In addition, KPR-5714 (N-[(R)-3,3-difluoro-4-hydroxy-1-(2H-1,2,3-triazol-2-yl) butan-2-yl]-3-fluoro-2-[5-(4-fluorophenyl)-1H-pyrazol-3-yl] benzamide), a novel and selective $TRPM_8$ antagonist, has been shown to improve urinary frequency with inhibition mechano-sensitive C-fibres of bladder afferents after intravesical instillation of acetic acid [937].

Brief cold stimuli applied to the skin can evoke a sudden desire to urinate, which can be highly bothersome in patients with overactive bladder, but there is no clear explanation for such acute cold-induced urinary urgency. Cold and menthol stimuli to the skin generate bladder nerve responses conducted through dichotomising axons, which are significantly decreased in the presence of the

$TRPM_8$ blocker BCTC. $TRPM_8$-expressing sensory neurons with dichotomising axons projecting to the skin and bladder may therefore be responsible for the urinary urgency evoked by cold sensation [938]. The $TRPM_8$-selective antagonist DFL23448 [5-(2-ethyl-2H-tetrazol-5-yl)-2-(3-fluorophenyl)-1,3-thiazol-4-ol] has been shown to reduce cold-induced bladder overactivity. induced was tested and evaluated in cold-induced behavioural tests and tests on bladder function and experimental bladder overactivity *in vivo* in rats. According to the results, a role for bladder $TRPM_8$-mediated signals is present in experimental bladder overactivity [939].

3.6. Piezo channels.

Piezo1 and its close homologue Piezo2 are mechano-sensitive ion channels that in humans are encoded by the gene PIEZO1 and are predicted to have 24-36 transmembrane domains [940,941]. Piezo1 is expressed in the kidney, ureter, bladder, and urethra as well as organs in close proximity, including the prostate, seminal vesicles and ducts, ejaculatory ducts and the vagina [321]. Unlike Piezo2 which is highly expressed in sensory dorsal root ganglia, piezo1 is not expressed in sensory neurons [941].

Mouse urothelial cells exhibited a Piezo1-dependent increase of cytosolic Ca^{2+} concentration in response to mechanical stretch stimuli, leading to ATP release but Piezo1 and $TRPV_4$ respond to different intensities of mechanical stimulus. GsMTx4, an inhibitor of stretch-activated channels, attenuated Ca^{2+} into urothelial cells and decreased ATP release upon stretch stimulation. Hence, Piezo1 senses extension of the urothelium, leading to ATP release, and inhibition of Piezo1 might provide a potential target for treatment of bladder dysfunction [942,943] (Figure 56).

4. TRANSPORTERS

Membrane transporters carry solutes across cell membranes, which would otherwise be impermeable to them. The energy required for active transport processes is obtained from ATP turnover or by exploiting ion gradients. ATP-driven transporters can be divided into three major classes: P-type ATPases; F-type or V-type ATPases; and ATP-binding cassette transporters. P-type ATPases, are multimeric proteins, which transport (primarily) inorganic cations. F-type or V-type ATPases, are proton-coupled motors, which can function either as transporters or as motors. ATP-binding cassette transporters are importantly involved in drug disposition as well as transporting endogenous solutes.

The second largest family of membrane proteins in the human genome, after the G protein-coupled receptors, is the SLC solute carrier superfamily which transport a great variety of solutes, from simple inorganic ions to amino acids and sugars to more complex organic molecules like haem. SLC transporters include secondary active transporters that function as antiporters (counter-transporters) or symports (co-transporters). A third, relatively small group are equilibrative transporters, that allow solutes to travel across membranes down their concentration gradients. A more complex family of transporters, the SLC27 fatty acid transporters also ex-

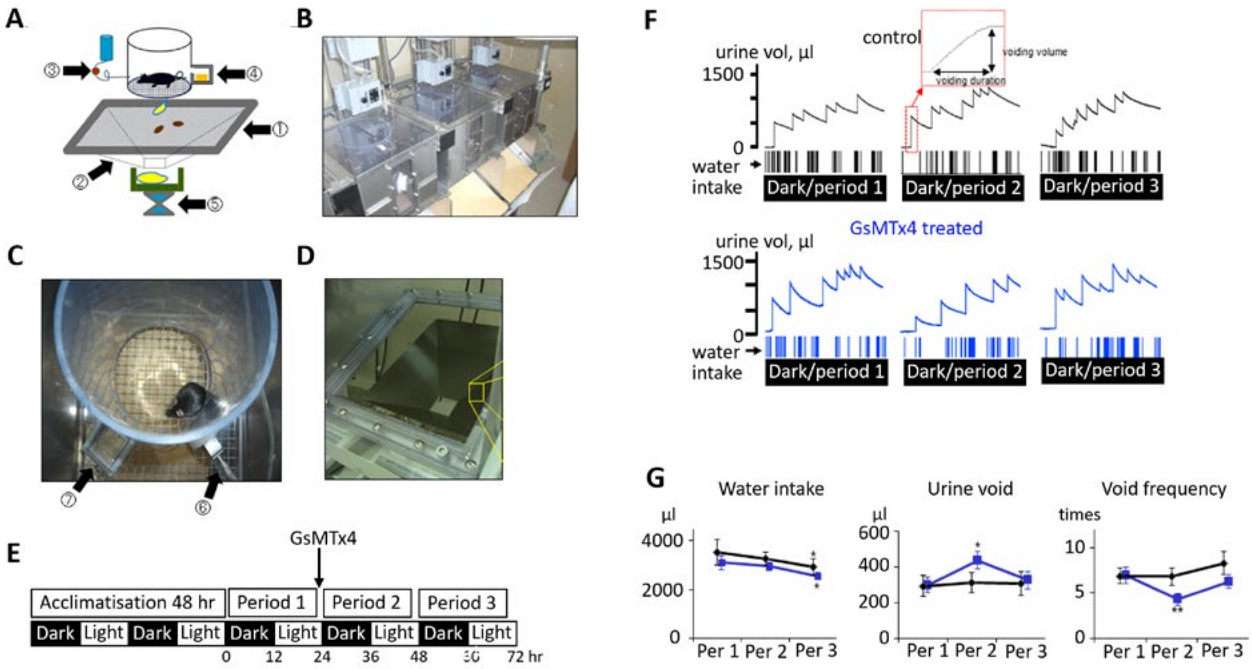

Figure 56. Metabolic cage system for micturition behaviour in mice, effect of GsMTx4. *A: Metabolic cage schema for collection of voided urine in a sound-proof wind-break room at 25°C. The mesh (patent licence no. 2009-187420, Mitsubishi Kumamoto Japan) that forms the floor allows passage of urine, weighed below, but catches faeces and food. Mice are provided with free access to food and water and housed with a 12/12 h dark/light period. Water intake is measured by a sensor. After two days acclimatisation, voiding frequency and voided urine are recorded continuously for 72 hours. The following are recorded: water intake (µl/12 h in dark period); urine volume (µl/12 h in dark period); voiding frequency (times/12 h In dark period). B: photograph of three cage systems. C: Top view of one cage showing he mesh floor. D: urine collection unit under the floor. E: Schematic of acclimatisation and collection periods. F: water intake and urine volume recordings in three dark periods; control (top) and with GsMTx4 (1350 µg/kg, i.p.). G: Calculated water intake and urine volume/ frequency under control conditions (black) and with GsMTx4 (blue); *p<0.05; **p<0.01 vs per 1. Unpublished data; courtesy of T Mitsui.*

press enzymatic function. Many transporters also express electrogenic properties of ion channels [944].

The vesicular nucleotide transporter (VNUT), SLC17A9, is the most recent member of the SLC17 family to have an assigned function. Uptake of ATP is independent of pH, but dependent on Cl^- and membrane potential and endogenous substrates ATP, GDP and GTP. VNUT is inhibited by DIDS and Evans blue dye [945]. VNUT is abundantly expressed in the bladder urothelium and releases ATP by exocytosis. During the initial stages of bladder filling ATP is released by vesicular exocytosis and VNUT-deficient mice showed reduced bladder compliance and urinary frequency. From this, it has been concluded that VNUT-dependent ATP exocytosis is involved in urine storage that promote the relaxation of the bladder during this phase of bladder filling (Figure 57) [946].

5. CLOCK GENES

Clock genes exist in most cells and organs, and their products regulate oscillations in the sleep-awake rhythm and gene expression rhythms of various metabolic enzymes, channels, and receptors. Of more than 10 types of clock genes that have been identified, Per, Cry, Bmal, and Clock play the most important role in regulation of circadian rhythm. Exact circadian rhythms are driven by the formation of a large number of complex feedback loops under the control of the master clock in the suprachiasmatic nucleus (SCN) (Figure 58) [947].

The pathophysiological conditions of nocturia and nocturnal polyuria are multifactorial and complex, and their aetiologies remain unclear in many patients, but LUT functions are regulated by clock genes [948,949]. Moreover, melatonin secretion, which has a circadian rhythm that is regulated by clock genes in the SCN and affects circadian rhythms in peripheral tissues by controlling hormonal activities influences the onset of nocturia in patients [950]. A novel hypothesis has been proposed regarding the relationship between abnormalities in clock genes and LUT function.

The voiding behaviour of Clock-mutant (ClockΔ19/Δ19) mice over 24 hours has been measured to investigate the effect of clock genes on LUT function. Although no significant differences were observed in behaviour patterns between ClockΔ19/Δ19 and wild-type mice, ClockΔ19/Δ19 mice showed the phenotype of nocturia and nocturnal polyuria [951]. In primary cultured urothelial cells

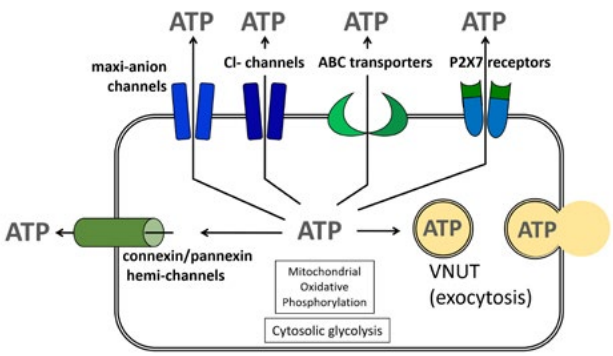

Figure 57. Schematic of the different ATP-transport modalities. *Three classes of routes for ATP release. 1, diffusion through large channels composed of connexin or pannexin proteins: 2, flux through ion channels or transporters; 3, vesicular exocytosis.*

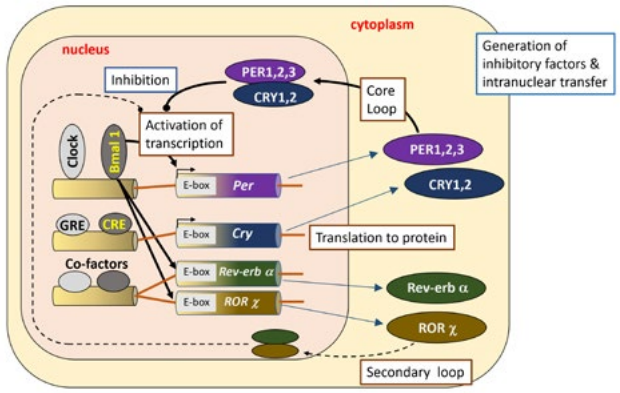

Figure 58. Schematic of the cellular clock cycle. *The clock cycle is maintained by protein expression of Per and Cry families from respective genes that form a negative feedback loop to transcription of the same genes to form a cyclical process.*

from ClockΔ19/Δ19 mice expression of clock genes, mechano-sensors such as Piezo1 and ATP release mediators such as VNUT and connexins showed desynchronised circadian rhythms, with ATP release remained high in both the sleep and awake phases and providing a cellular basis for nocturia [952-954].

6. FIBROSIS AND THE URINARY TRACT: A TARGET FOR DRUG DEVELOPMENT

Fibrosis is a thickening of tissue associated with an excessive deposition of connective tissue, as part of a natural healing process or of a pathological development. Connective tissue itself, one of the four basic tissue types, is of mesodermal origin, has a supportive role for other tissue types and has three principal components: protein fibres of collagen and elastin; cells (including fibroblasts, macrophages, leucocytes and mast cells); both embedded in a ground substance of glycosaminoglycans and proteoglycans. Considerable variation and specialisation of connective tissue occurs throughout the body (e.g., to bone, cartilage, adipose tissue and blood) but this basic description is applicable to connective tissue in the urinary tract. The relative ratios of the principal components can vary, even in different manifestations of urinary tract tissues, that have a bearing on its supportive functions. Different proportions of protein fibres and ground substance will determine the biomechanical properties of connective tissue, as collagen and elastin offer a considerable stiffness compared to ground substance. Of relevance also is that of mesenchyme, a form of connective tissue in the developing embryo that contains cells capable of differentiating into other cells of matured connective tissue.

6.1. Fibrosis: cellular pathways and biomechanical consequences.

Tissue damage from chemical or mechanical injury, or an autoimmune reaction results in a shorter-term wound-healing phase that may lead to a fibrotic, chronic inflammatory phase (955). Important in the process is the recruitment of collagen-producing myofibroblasts from local fibroblasts, epithelial cells by a process of epithelial-mesenchymal transition, or even from a similar endothelial cell transition (956-958). If accumulation of extracellular collagen is eventually reversed then a wound-healing process can be achieved, but if dysregulated and allowed to accumulate fibrosis will ensue. Crucial to this is a balance or otherwise between activities

of matrix metalloproteinases (MMPs), that will degrade collagen, and various tissue inhibitors of MMPs (TIMPs) (959,960). Initiation of fibrosis is mediated by a number of soluble factors released by immune cells, such as macrophages. The best characterised is of transforming growth factor-β (TGF-β) through activation of an intracellular SMAD transcription factor pathway (961), although other mediators such as connective tissue growth factor (CTGF) and platelet-derived growth factor (PDGF) and interleukins such as IL-10 are also important (962-964). Associated pathways that may regulate the above include *wnt*-like signal transduction, also important in regulating tissue proliferation and development, to prevent degradation of the transcription factor β-catenin that in turn acts in a similar way to TGF-β/ SMAD pathways (965,966). Of relevance, inhibition of these pathways offers routes for antifibrosis strategies. An example is to increase intracellular cGMP concentrations, as this cyclic nucleotide will inhibit both Smad-dependent and -independent fibrotic pathways (967).

Fibrosis can influence the passive mechanical and active contractile properties of muscular tissues in several ways.

i. Passive mechanical stiffness will be altered dependent on the relative amounts of collagen/elastin or ground substance deposited, as the former is stiffer than contractile muscle and the latter less stiff. Note: an increase of mechanical stiffness is equivalent to a decrease of tissue compliance or distensibility.
ii. Replacement of muscular tissue by connective tissue will reduce overall muscle tissue contractility, simply by reducing the number of contractile units in a given volume of tissue. Reduction of tissue integrity may also permit less alignment of individual muscle fibres further reducing muscle force in a particular vector.
iii. Some of the cytokines released by inflammatory or other cells in a tissue mass undergoing fibrosis may have direct effects on muscle contractility. For example, histamine generates transient increases of detrusor contractile tone, through an HI-receptor action (968) and IL-6 enhances contractile responses to muscarinic agonists (969).

With respect to biomechanical integrity, collagen is deposited as two major subtypes, as collagen type-I and collagen type-III, the former increasing in proportion in hypertrophied bladders induced by say spinal cord injury (970). Measurement of tissue stiffness or elasticity modulus (inverse compliance) is measured as the slope of a linear stress(tension)/ strain(stretch) relationship with units of Pascals (Pa, or usefully MPa – 10^6 Pa). The elasticity of different isolated collagen subtypes has probably less meaning that how variation of type-I/type-III proportions has on mixed gels as the overall elastic properties of will depend on the relative orientation of different fibrils and their absolute size. However, for reference pure type-I fibrils, about 325 nm diameter, have an elasticity modulus of 100-360 MPa (971). Mixed gels of type-I and type-III collagen showed that maximum elasticity occurred with a type-1/ type-III ratio of 80% declining by more than 50% as the ratio either increased to 100% type-1 or decreased to 20% (972). Another confounding aspect is that stress-strain relationships for biological tissues with significant extracellular matrix are generally not linear but increasingly exponential with greater strains (513), reflecting additional re-orientation of collagen fibrils and other tissue components. Thus, most useful is to gauge how elasticity alters as tissue composition varies within a complex structure. This has not been as comprehensively investigated in urinary tract tissue as it has in blood vessels where for example in the ferret aorta elasticity is greatest (35 MPa) in the outer adventitia, rich in extracellular matrix, through to the innermost intima (8 MPa) (973). Thus, whilst there is still considerable required research with urinary tract tissue, it may be concluded that increased collagen-rich extracellular matrix deposition increases tissue stiffness (decreases distensibility) and variation of collagen subtype will alter this relationship. In the case where excess extracellular matrix deposition occurs with a greater proportion of ground substance it may be expected that a more floppy, less elastic tissue will result, as observed in models of excessive deposition (613,974).

6.2. Fibrosis: the adult and pediatric urinary tract.

Fibrosis is a feature of normal ageing in the human and animal bladders (975-977). The former study found fibrosis in both male and female subjects and concluded that it occurred independently of outflow tract obstruction, as may occur with benign prostate enlargement in men. However, fibrosis is also associated with a number of pathologies. With spinal cord injury in human and animal models, bladder tissue re-modelling is associated with fibrosis (978-980) and additionally associated with up-regulation of TGF-β1 levels (981). Equally, fibrosis is a consequence of the hypertrophied bladder following partial outflow obstruction, also with an increase of TGF-β1 and connective tissue growth factor (982-985). MicroRNAs, non-coding single-strands of RNA, have been proposed to regulate not only the hyperplastic and hypertrophic growth of the bladder, but also the increased deposition of extracellular matrix. This offers a potential range of targets not only to understand more about the process of bladder growth and remodelling, but also to control and even reverse these processes (986).

Fibrosis also occurs in bladders subjected to chronic ischaemia, the magnitude of which is related to the extent by which blood flow is reduced but sufficient to decrease filling compliance (987,988). A role for hypoxia inducible factors (HIFs) has been implicated, not only in metabolic adaptation to a more anaerobic metabolism, but to a more fibrotic phenotype (989). For example, fibrosis induced by bladder obstruction of young male mice was accompanied by up-regulation of genes associated with fibrosis and increased epithelial-mesenchymal transition the extent of which could be regulated by controlling HIF activity (990,991).

Fibrosis may also be induced by iatrogenic means. For example, radiation therapy that can significantly impact on bladder contractile function (992,993), most likely as a result of inflammation generated by the treatment and may be ameliorated by basic fibroblast growth factor (994). However, genetic predisposition may influence the extent of radiation-induced damage and dysfunction as shown by comparing data from different strains of mice (995).

Fibrosis is also a feature of the foetal and paediatric bladder. The proportion of smooth muscle compared to connective tissue increases with age in both the human and animal bladders (996,997). However, the extent of fibrosis is much greater in the bladder wall of children with a range of congenital anomalies including: exstrophy-epispadias complex, bladder obstruction in boys with posterior urethral valves (PUV); and neuropathic bladders through spinal cord defects (998-1000). This increase of connective was generally associated with increased passive stiffness of isolated tissue and would translate to reduced filling bladder compliance. This increased connective tissue content showed a significant association with reduced contractile ability of isolated detrusor preparations, whether evaluated with agonist- or nerve-mediated contractions, and a trend that is continued with adult human preparations (Figure 59). Parallel experiments with isolated smooth muscle cells showed no evidence of intracellular Ca^{2+} metabolism when exposed to contractile agonists (998). The figure also shows that tissue from one congenital, cloacal anomaly, showed contractile function and connective tissue content comparable with tissue from children with functionally normal bladders. These data were mirrored in experi-

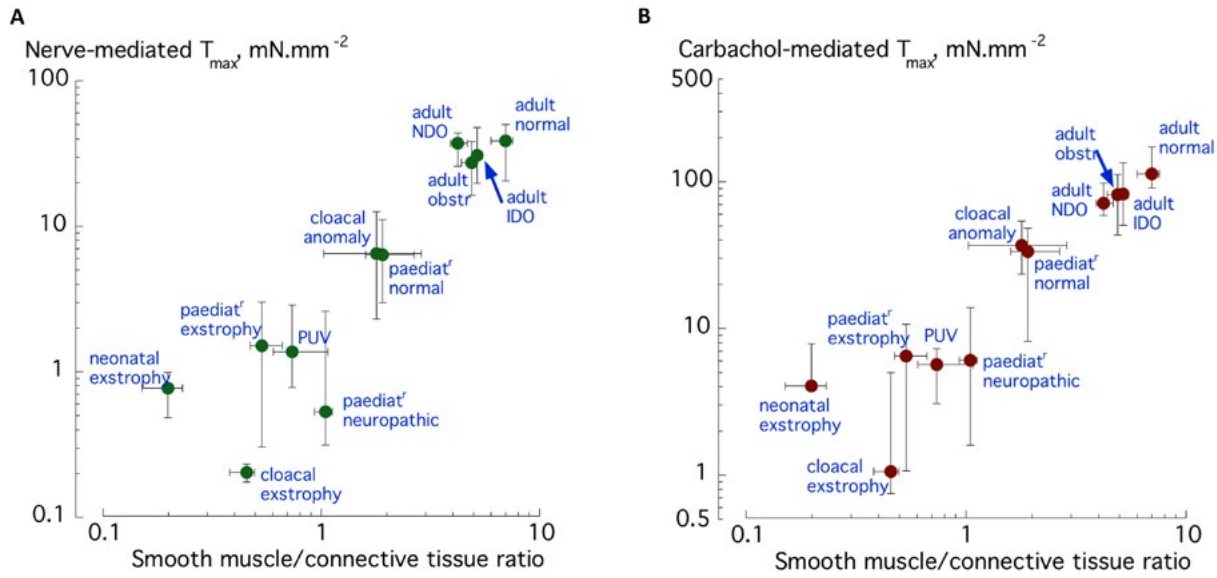

Figure 59. The relationship between human detrusor contractile performance and smooth muscle content. *A: In vitro maximum nerve-mediated contraction magnitude as a function of the smooth muscle/connective tissue ratio, note the logarithmic axes to express the wide range of both variables. B: A similar relationship for maximum carbachol contractions as a function of the smooth muscle/ connective tissue ratio. The close relationships indicate the predominant dependence of contraction magnitude as a function of smooth muscle content in tissue from a wide range of age and pathological conditions. Key: IDO, NDO; idiopathic and neurogenic detrusor overactivity in adult preparations. 'obstr'; obstructed bladder. 'paediatr' paediatric patients. 'neonatal exstrophy; samples obtained at first-stage repair. 'paediatr exstrophy; samples obtained at second-stage repair. PUV; posterior urethral valves. Data, unpublished and from (977,998-1000).*

ments with foetal sheep that were obstructed in the second trimester, as an experimental model for PUV (974,1001-1003). Further experiments showed that the duration of obstruction required to produce a phenotype of reduced contractility and fibrosis was only a few days (1004,1005) and raised the question of the desirability of *in utero* bladder decompression to prevent more severe bladder damage at birth. Overall, the data with human tissue specimens shows that reduction of smooth muscle mass, and consequent increase of connective tissue content, is the most important factor that determines detrusor contractile function. Reversal or reduction of connective tissue content is therefore a primary goal to restore near normal bladder contractile function in children with several important congenital anomalies of the lower urinary tract.

6.3. Strategies for reversal of fibrosis in the bladder wall.
A number of paradigms have been examined that may reduce the extent of fibrosis, whether by: inhibiting the intracellular pathways that regulate transcription of genes that regulate extracellular matrix generation; reduce epithelial-mesenchymal transition; or increase breakdown of extracellular matrix components. It is important to emphasise that approaches that may be successful in some fibrosis pathologies may not be successful in others. For example, fibrosis associated with paediatric congenital anomalies such as exstrophy, posterior urethral valves (PUV) or spinal cord defects can show variations in expression of proteins associated with cell cycle regulation (e.g. cyclin-D1), cell proliferation (c-Myc) or collagen degradation (MMP-7). Thus, whilst cMyc expression is reduced in all three conditions (compared to tissue from normally functioning bladders), cyclin-D1 expression is increased only in PUV bladders and MMP-7 expression whilst decreased in exstrophy bladders, in increased in PUV tissue and unaltered in neuropathic bladders (998-1000). This just highlights the complexity of regulatory pathways associated with one pathological feature (fibrosis) and their potential variability in different conditions.

Perhaps the most-studied fibrosis pathway is the TGF-β pathway whereby these ligands, released from cells under a number of chemical and mechanical stresses, bind to TGF-β receptor type-2 (TGFBR2). This initiates phosphorylation of intracellular SMAD proteins (SMAD2 and SMAD3) which in turn form a complex with SMAD4 to regulate transcription of genes including those involved in expression of extracellular matrix proteins and differentiation of collagen-producing myofibroblasts (1006). Manipulation of this pathway is a target for anti-fibrotic approaches. For example, original work has shown the effectiveness of cAMP analogues, prostaglandin (PGE2) and prostacyclin (PGI2) in reducing fibrosis (1007-1009) and interferon-γ (1010,1011) and PPAR-γ (1012) are effective in a number of tissues.

More recently agents that increase cGMP levels have been shown to exert antifibrotic action, potentially through the ability of cGMP-dependent protein kinase G to inhibit the TGFBR2:SMAD pathway by sequestration of SMAD3 (1013,1014). This may underlie the action of the endogenous antifibrotic hormone relaxin, a peptide hormone that is part of the insulin superfamily. The best characterised form, relaxin-2 binds to its receptor (RXFP1) to enhance NO-dependent generation of cGMP, through activation of soluble guanylate cyclase, and PKG activation (1015). Final actions are likely to be manifold but epithelial-mesenchymal transition and MMP expression are down-regulated and TIMP expression increased. Relaxin is effective in the bladder to reduce fibrosis after X-ray irradiation and reverses the overactive phenotype induced by this insult (992) and mirrors its success as an antifibrotic agent in pulmonary and renal fibrosis (1016,1017). The expense in manufacturing relaxin may limit it potential usefulness and so other means to increase

cGMP levels in LUT tissues should be sought. One possibility is the use of phosphodiesterase type-5 inhibitors (PDE5I) such as sildenafil and tadalafil. Sildenafil is effective in mice to prevent detrusor hypertrophy, collagen deposition and bladder overactivity that occurs after outflow tract obstruction, without affecting voiding function (1018). Tadalafil alone, or in combination with a PDE4I (roflimilast; to enhance cAMP levels), also reduced fibrosis and an overactive bladder phenotype in obstructed and ageing animal models (1019,1020).

Research to reduce fibrosis in lower urinary tract tissues lags equivalent work with other tissues, in particular with fibrosis in lungs, liver, heart and skin. But general principles gained from these tissues may be applied to LUT fibrosis, with the above caveat that information may not be wholly translated.

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COMMITTEE 3

PATHOPHYSIOLOGY OF URINARY INCONTINENCE, PELVIC ORGAN PROLAPSE AND FAECAL INCONTINENCE

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COMMITTEE 3

PATHOPHYSIOLOGY OF URINARY INCONTINENCE, PELVIC ORGAN PROLAPSE AND FAECAL INCONTINENCE

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LIST OF ABBREVIATIONS

ACS	American College of Surgeons
ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
AD	Autonomic Dyreflexia
ADMS	Cs adipose-derived mesenchymal stem cells
AF	Autonomic Failure
ANLUTD	Adult Neurogenic Low Urinary tract Disease
ANS	Autonomic Nervous System
ASIA	American Spinal Injury Association
ASR	Anal Sphincter Rupture
ATP	Adenosine Triphosphate
AUA	American Urology Association
BMI	BODY Mass Index
BOO	Bladder Outlet Obstruction
BOLD	Blood Oxygen Level – Dependent
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostatic Obstruction
cAMP	Cyclic Adenosine Monophosphate
CD	Crohn's Disease
CI	Confidence Interval
CNS	Central Nervous System
CPPS	Chronic Pelvic Pain Syndrome
CPT	Current Perception Threshold
CRADI	Colorectal-Anal Distress Inventory
CRAIQ	Colorectal-Anal Impact Questionnaire
CRP	C – Reactive Protein
CS	Cesarean Section
CSCI	Clean Intermittent Self – Catheterization
CSF	Cerebrospinal Fluid
CXS	Connexins
DIB	Dementia with Lewy – Bodies
DO	Detrusor Overactivity
DM	Diabetes Mellitus
DRA	Diastasis Rectus Abdominus
DSD	Detrusor Sphincter Dyssynergia
EAS	External Anal Sphincter
ECM	Extra-Cellular Matrix
EMG	Electromyography
ENAC	Epithelial Na – Channel
EQD	Equivalent Dose
EPC	Evoked Pressure Curves
ER	Oestrogen Receptor
EUS	External Urethral Sphincter
FI	Faecal Incontonence
FTD	Fronto Temporal Dementia
FUS	Fused Sarcoma
GCI	Glial Cytoplasmatic Inclusions
HIFU	High – Intensity Focused Ultrasound
HOLEP	Holmium Laser Enuclation of the Prostate
HOLRP	Holmium Laser Resection
IAS	Internal Anal Sphincter
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IC	Interstitial Cystitis
ICI	International Consultation on Incontinence
ICIq – SF	International Consultation on Incontinence Questionnaire – Short Form)
ICS	International Continence Society
IDO	Idiopatic Detrusor Overactivity
ILC	Interstitial Laser Coagulation
IPSS	International Prostate Symptom Score
ISAFSCI	International Standards to Document Remaining Autonomic Function after Spinal Cord Injury
ISD	Intrinsic Sphincter Deficiency
IT	Integral Theory
IUS	Internal Urethral Sphincter
KPT	Potassium Titanyl Phosphate
KUCP	Urethral Closure Pressure With A Pelvic Floor Contraction Or Kegel
LAM	Levator Ani Muscle
LBT	Lower Bowel Tract
LMNL	Lower Motor Neuron Lesion
LUT	Lower Urinary Tract
LUTS	Lower Urinary Tract Symptoms
MAPT	Microtubule – Associated Protein Tau
MCA	Muscle Contractile Activity
MCP	Monocyte Chemotatic Protein
MEP	Motor Evoked Potential
MMC	Mielomeningocele
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSA	Multiple System Atrophy
M – TURP	Monopolar Transurethral Resection of the Prostate
MUCP	Maximal Urethral Closure Pressure
MUL	Mid Urethral Length
MUS	Mid-Urethral Sling
NANC	Non-Adrenergic, Non-Cholinergic
NDO	Neurogenic Detrusor Overactivity
NE	Norepinephrine
NGF	Nerve Growth Factor
NMDA	N – Methil – D - Aspartate
NLUTD	Neurologic Lower Urinary Tract
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NUBs	Neurovascular Bundles
OAB	Overactive Bladder
OASI	Obstetric Anal Sphincter Injury
OR	Odds Ratio
PAF	Pure Autonomic Failure
PBS	Painful Bladder Syndrome
PD	Parkinson's Disease
PDD	Parkinson's Disease Dementia
PFD	Pelvic Floor Dysfunction
PFM	Pelvic Floor Muscle
PFME	Pelvic Floor Muscle Execise
PG	Prostaglandine
PGRN	Progranulin
PKEP	Plasmakinetic Enucleation of the Prostate
PKRP	Plasmakinetic Resection of the Prostate
PMC	Pontine Micturition Center
PNTML	Pudendal Nerve Terminal Motor Latency
PNTML	Pudendal Nerve Motor Terminal Motor Latency
POP	Pelvic Organ Prolapse
POPQ	Pelvic Organ Prolapse Quantitation
PPI	Postprostatectomy Incontinence
PPL	Puboprostatic Ligament
PR	Progesterone Receptor
PUL	Pubo-Urethral Ligament
PVL	Pubovesical Ligament
PVP	Photoselective Vaporization of the Prostate
RAIR	Rectoanal inhibitory reflex
RARP	Robot – Assisted Radical Prostathectomy
RRP	Radical Retropubic Prostatectomy
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomized Controlled Trial
RR	Relative Risk

SALE ..... Stratify by Anatomic Location and Etiology
SCI ..... Spinal Cord Injury
SNCA ..... Sinuclein Alpha – Protein
SSRI ..... Selective Serotonin Re-uptake Inhibitor
SSRS ..... Skin Sympathetic Responses
SUI ..... Stress Urinary Incontinence
SUS ..... Striated uUrethral Sphincter
TGF ..... Transforming Growth Factor
THULEP ..... Thulium Laser Enucleation of the prostate
THULRP ..... Thulium Laser Resection of the Prostate
TRP ..... Transient Receptor Potential
TTX ..... Tetrodotoxin
TUIP ..... Transurethral Incision of the Prostate
TURP ..... Transurethral Prostatectomy
TURS ..... Transurethral Resection Syndrome
TUVP ..... Transurethral Electrovaporization of the Prosate
UC ..... Ulcerative Colitis
UCM ..... Urethral Compressive Musculature
UDI ..... Urodynamic Investigation
UDS ..... Urodynamic Studies
UHT ..... Urethral Hanging Theory
UI ..... Urinary Incontinence
UMNL ..... Upper Motor Neuron Lesions
UUI ..... Urgency Urinary Incontinence
USI ..... Urodynamic Stress Incontinence
UTI ..... Urinary Tract Infection
VD ..... Vaginal Delivery
VIP ..... Vasoactive Intestinal Polypeptide
VLPP ..... Valsalva Leak Point Pressure
YAG ..... Laser Yttrium – Aluminium – Garnet Laser

I. PATHOPHYSIOLOGY OF STRESS URINARY INCONTINENCE IN MEN

1. INTRODUCTION

Urinary incontinence (UI) in men is defined as an involuntary loss of urine experienced during the bladder storage phase [1]. UI is subdivided into three major groups [1-3]:

- Urgency urinary incontinence (UUI) defined as complaint of involuntary loss of urine associated with urgency,
- Stress urinary incontinence (SUI) defined as complaint of involuntary loss of urine on effort or physical exertion such as sporting activities, or on sneezing or coughing.
- Mixed urinary incontinence (MUI) is defined as the complaint of both stress and urgency urinary incontinence, that is, involuntary loss of urine associated with urgency as well as with effort or physical exertion.

Adult LUTD are classified as neurogenic (ANLUTD) only in the presence of a relevant neurological disease [5]. Changes in bladder ultrastructure and function can occur as a result of neurological diseases or associated with ageing [4]. Several changes may be related to benign and/or malignant diseases of the prostate and their treatment. [5,6]. Also, sphincter insufficiency resulting in SUI does not generally occur as a result of male ageing, but rather secondary to surgery or irradiation of the prostate leading to neurological injury [7].

Extra-urethral incontinence in men, defined as urine leakage through channels other than the urethral meatus [1] is only known as a result of a fistula. Fistulae in men are most often iatrogenic (surgery, radiotherapy, cryotherapy, HIFU (High-intensity focused ultrasound)) or inflammatory (diverticulitis) [1-3].

This section focuses on the pathophysiology of stress incontinence in men.

2. CONTINENCE MECHANISM IN THE MALE

According to Latini *et al.* [8], the continence mechanism in the male is related to three anatomical properties of the urethra: the bladder neck, the prostatic urethra and the membranous urethra.

The smooth muscle of the bladder neck is histologically, histochemically and pharmacologically distinct from the vesical detrusor muscle. In the male, the bladder neck is completely surrounded by a circular collar of smooth muscle which extends distally to surround the prostatic portion of the urethra. Because of the location and orientation of its constituent fibres, the term preprostatic sphincter is suitable for this particular component of urinary tract smooth muscle. This is a genital sphincter mechanism with an autonomic parasympathetic and sympathetic fibres from the inferior hypogastric plexus. Distally, this muscle merges with and becomes indistinguishable from the musculature in the stroma and capsule of the prostate gland.

The prostatic urethra extends from the proximal edge of the membranous urethra or the proximal verumontanum to the distal bladder neck. It is surrounded by the prostate. The prostatic urethra is c.3-4 cm in length and tunnels through the substance of the prostate closer to the anterior than the posterior surface of the gland. It is continuous above with the preprostatic part and emerges from the prostate slightly anterior to its apex (the most inferior point of the prostate). An elevation, the verumontanum (colliculus seminalis), at about the middle of the length of the urethral crest, contains the slit-like orifice of the prostatic utricle. On both sides of, or just within, this orifice are the two small openings of the ejaculatory ducts. Its walls are composed of fibrous tissue, muscular fibres and mucous membrane; the latter is pitted by the openings of numerous small glands. The lowermost part of the prostatic urethra is fixed by the puboprostatic ligaments and is therefore immobile.

The membranous urethra extends from the proximal bulbar urethra to the distal verumontanum. It is surrounded by the voluntary external sphincter mechanism, both the smooth muscle external sphincter and the striated/rhabdosphincter. The membranous urethra is unattached to any fixed structure and is the only segment of the male urethra not surrounded by any other structure. It descends with a slight ventral concavity from the prostate to the bulb of the penis, passing through the perineal membrane, c.2.5 cm posteroinferior to the pubic symphysis. The wall of the membranous urethra consists of a muscle coat, separated from the epithelial lining by a narrow layer of fibroelastic connective tissue. The muscle coat consists of a relatively thin layer of bundles of smooth muscle, which are continuous proximally with those of the prostatic urethra, and a prominent outer layer of circularly orientated striated muscle fibres, which form the external urethral sphincter (EUS), as it is commonly known. The bladder neck is sometimes called the internal urethral sphincter (IUS) mechanism, to distinguish it from the distal sphincter mechanism. This latter term has con-

siderable value because it recognises that the sphincter-active membranous urethra consists of several components, namely, urethral smooth muscle (lissosphincter); urethral striated muscle (rhabdosphincter), which is the most important component; and the periurethral part of levator ani, which is important to resist surges of intra-abdominal pressure (e.g. on coughing or exercise). The EUS represents the point of highest intraurethral pressure in the normal, contracted state. The intrinsic striated muscle component is devoid of muscle spindles. The striated muscle fibres themselves are unusually small in cross-section (15-20 µm diameter), and are physiologically of the slow twitch type, unlike the pelvic floor musculature, which is a heterogeneous mixture of slow and fast twitch fibres of larger diameter.

At the boundary between the IUS and EUS, the striated and smooth muscle fibres intertwine to some extent. The EUS extends from the prostatic urethra below the verumontanum through the membranous urethra. Hence, EUS includes the rhabdosphincter (intrinsic skeletal and smooth muscle) and extrinsic paraurethral skeletal muscle. At the prostate level, the superior part of the striated EUS is largely confined to the anterior side of the urethra and prostate. Inferior to the prostate, the EUS is horseshoe-shaped (although named as the rhabdosphincter, omega shaped) with the opening on the dorsal side. The dorsal muscle fibres of the left and right sides approach the midline and sometimes cross the prostate [14-16].

The rhabdosphincter has longitudinal smooth muscle and slowtwitch (type I) skeletal muscle fibres. The lissosphincter forms a complete cylinder of circular muscle fibres around the urethra can maintain resting tone and preserve continence [14,17-19] (Figure 1). The rhabdosphincter is invested in a facial framework and supported below by a musculofascial plate that fuses with the midline raphe, which is also a point of origin for the rectourethralis muscle [20]. Superiorly, the fascial investments of the rhabdosphincter fuse with the puboprostatic ligaments [21]. This dorsal and ventral support probably contributes to the competence of the sphincter. The striated fibres of the extrinsic paraurethral muscle (levator ani complex), on the other hand, are of the fast-twitch (type II) variety [17]. During sudden increases in abdominal pressure, these fibres can contract rapidly and forcefully to provide continence.

It is known that during radical prostatectomy the smooth muscle fibres of the bladder neck (IUS) are resected, which interrupted innervation. Furthermore, it is worth noting that impaired detrusor contractile function seems to be frequently associated with intrinsic sphincter deficiency. With the increasing knowledge of the periprostatic nerves and the improvement of the preservation of the bladder neck the functional outcome improved even further [22].

The EUS is innervated by the autonomic (via the pelvic nerve) and somatic (by the pudendal nerve) nervous systems. Nerve fibres are seen proximally in a dorsolateral position (5 to 7 o'clock), while more distally, they are located primarily laterally [20, 23]. The rhabdosphincter may also receive somatic innervation. Hollabaugh *et al.* described the so-called "putative continence nerves" as branches of the pelvic nerve travelling under the endopelvic fascia picking up intrapelvic branches of the pudendal nerve, given off before it enters the pudendal canal, which was further verified by Castello *et al*. [23,24].

It has also been proposed that somatic innervation is primarily sensory in origin, facilitating reflex contraction of the sphincter complex to maintain the continence [25].

A histological and immuno-histochemical study with 3-D reconstruction in the male fetus has confirmed mixed autonomic and somatic innervation (Figure 2) [14]. Unmyelinated (autonomic) nerve fibres destined for smooth muscle fibres run alongside of the myelinated (somatic) fibres. The majority of the unmyelinated fibres approach the smooth muscle layers at 5 and 7 o'clock while the majority of myelinated fibres penetrate the striated sphincter at 3 and 9 o'clock.

Tuygun *et al* have found a much higher incidence of periurethral (or perisphincter) fibrosis in incontinent vs. continent men after prostatectomy [26-28]. This might lead to the importance of the corpus spongiosum, which surrounds the bulbar urethra and supports with its blood filling in addition to its sphincteric function.

2.1. Supporting Structures Of The Membranous Urethra [29]

The supporting structures of the male urethra can be divided into the anterior and posterior support structures and the pelvic floor. The anterior urethral support structures contain the pubourethral ligaments, comprising the pubovesical ligament (PVL), the puboprostatic ligament (PLL), and the tendinous arch of the pelvic fascia. These ligaments stabilize the position of the bladder neck as well as the external sphincter complex and help to secure the membranous urethra to the pubic bone [30].

The posterior support consists of the perineal body (central perineal tendon), Denonvillier's fascia, the rectourethralis muscle, and the levator ani complex [31,32]. The third support structure is the pelvic floor, composed of the levator ani muscle and the surrounding fascia [33]. The pelvic floor is not directly connected to the urethra [33] but plays a role in continence by providing an additional occlusive force on the urethra via increased intraabdominal pressure [34].

It is postulated that the overall role of the support structures is to provide all-round stability and suspensory support for the urethral sphincter complex [35]. Normally the omega-shaped urethral rhabdosphincter has its anchoring points dorsally at the so-called conjoined fibrous tissue [36]. This conjoined fibrous tissue acts like a fulcrum for the anterior forces exerted by the rhabdosphincter. It compresses the urethra in an anteroposterior direction.

In summary, continence depends on the integrity of the IUS and/or EUS, on its support structures and on neural innervation and probably on the prostate. The IUS could be damaged during radical prostatectomy and continence seems to be maintained by the EUS mechanism. Thus, preservation of the IUS is important. The smooth muscle and slow twitch striated muscle of the rhabdosphincter (EUS) are probably majorly responsible for the sphincter continence; however, striated muscle contractions of the periurethral and paraurethral muscles are likely assist. Damage to the innervation (parasympathetic and somatic) of the smooth and striated muscle may indirectly contribute to post-prostatectomy incontinence. In addition, compromise of the sphincter support mechanism or post-operative changes such as fibrosis can compromise the sphincter function (Figure 1, Figure 2).

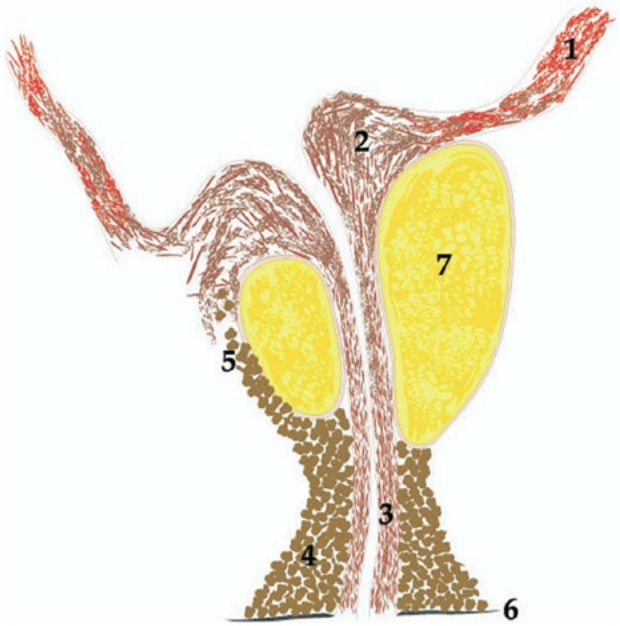

Figure 1: Revised concept of male urethral sphincter complex. 1, bladder musculature. 2, proximal part of lissosphincter internal sphincter. 3, distal part of lissosphincter smooth circular muscle layer of urethra. 4, rhabdosphincter. 5, prostatic part of rhabdosphincter. 6, perineal membrane. 7, prostate. The urethral sphincter complex extends in the form of a cylinder around the urethra from the vesical orifice to the distal end of the membranous urethra. While the outer component of skeletal muscle (rhabdosphincter) is most marked and thickest around the membranous urethra, and becomes gradually less distinct toward the bladder, in contrast, the inner component of smooth muscle (lissosphincter) has its main part at the vesical orifice and is thinner in its further course in the urethra. Also, whereas the lissosphincter forms a complete cylinder of circular muscle fibers around the urethra, the rhabdosphincter does not.
From Koraitim MM. J Urol. 2008 May;179(5):1683-9 [19] chiedere autorizzazione

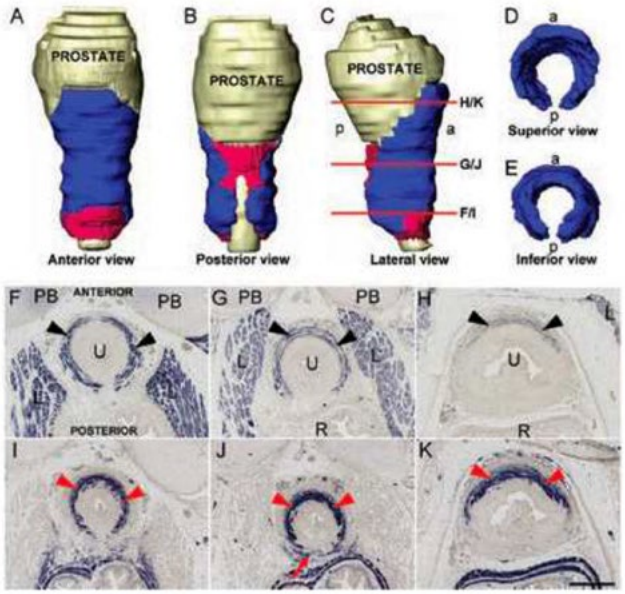

Figure 2: The external urethral sphincter (EUS) and internal urethral sphincter (IUS) in a male fetus (12 wk of gestation). Three- dimensional reconstruction in (A) anterior view, (B) posterior view, (C) right-lateral view, (D) superior view, and (E) inferior view. The EUS is shown in blue, and the IUS is shown in pink. The urethra and prostate are shown in light grey. Anterior and posterior directions are represented by the letters "a" and "p." Immunohistochemically stained sections: Sections from inferior (F) to superior (H) stained immunohistochemically for striated muscle, showing the EUS (black arrowheads). Panels (I) through (K) are from same level as sections (F) through (H), stained immunohistochemically for smooth muscle, showing the IUS (red arrowheads). Note the smooth muscle tissue at the dorsal side of the urethra, where the striated muscle of the external sphincter is lacking; see red arrow in (J). Red lines in (C) illustrate the level of the sections as seen in (F) through (H). L = levator ani muscle; PB = pubic bone; R = rectum; U = urethra; bar = 0.5 mm. From Wallner et al, Eur Urol 55(4):932-944, 2009 [14]

3. INCONTINENCE ASSOCIATED WITH BPH AND ITS TREATMENT

Benign prostatic hyperplasia (BPH) and benign prostatic obstruction (BPO) and their treatments have been widely associated with incontinence in men. Detrusor Overactivity (DO), impaired compliance and UUI are prevalent in men with BPO.

In adult males the prevalence of OAB ranges from 10% to 26% [37]. It increases with age and often is associated with other LUTS [37]. In men undergoing urodynamic investigation (UDI), DO is present in 40-80% of patients with obstruction [38-40]. In addition, impaired compliance, another potential cause of incontinence, has been shown to have a high correlation with outlet obstruction in men [41,42]. Thus, even before treatment of BPH and BPO there is a notable incidence of bladder dysfunction and incontinence.

Incontinence after the treatment of BPH may be related to 1. sphincter dysfunction (injury), 2. persistent bladder dysfunction or, 3. new onset bladder dysfunction. In 2015, Parker *et al.* reported an incidence of early incontinence of 30–40% and attributed this to UUI related to what was then termed detrusor instability. The authors reported an incidence of 0.5% for late incontinence, which was likely related to external sphincter damage, manifesting as SUI. [43]

In 2007, Han *et al* identified a cohort of men with BPH. From a total of over 12 million men, 411,658 men with BPH (3.3%) were identified. Most of these men (87.5%) did not have prior BPH surgery, but in those who did have surgery, 12.5% were diagnosed with incontinence [44]. The rates were almost identical whether the procedure was transurethral resection or incision, laser, transurethral needle ablation or transurethral microwave therapy [45].

Most studies evaluating post TURP and open prostatectomy incontinence from the past have found a significant incidence of sphincter and bladder dysfunction. The incidence of sphincter dysfunction ranges from 20-92% and bladder dysfunction from 56-97% [46-51].

3.1. Sphincter dysfunction (Injury)

According to Koraitim [19], urine is normally held at the level of the vesical orifice, which is a smooth muscle function. Also, after transurethral prostatectomy (TURP) urine is held at the lower limit of the prostatic cavity, where the lissosphincter is intact, and proximal to the membranous urethra, where the main part of the rhabdosphincter is located. Post-TUR incontinence may result from resecting a few mm in depth distal to the verumontanum, which obviously injures the lissosphincter but leaves the more distal rhabdosphincter intact. The presence of the whole length of the lissosphincter is not essential to maintain continence. However, a minimal length of lissosphincter is crucial below which incontinence is inevitable [19,52].

Causes of sphincter damage related to transurethral or open prostatectomy include direct damage due to poor surgical performance, electrocautery or thermal injury to the sphincter [53].

As mentioned above, incidence of sphincter dysfunction variesfrom 20-92%. The relatively high incidence of sphincter dysfunction may seem surprising as the incidence of DO before treatment is high and it persists in 18- 59% after surgery [38-42]. Therefore, one might expect that many patients would have persistent DO and UUI. However, in large series, sphincter dysfunction appears to be the main cause of incontinence. The high incidence of sphincter dysfunction is likely to represent a selection bias given that many patients are referred to tertiary centers for treatment of stress incontinence. Indeed, Nitti *et al.,* evaluating patients with voiding dysfunction after TURP, found that of those who had incontinence 75% had bladder dysfunction, while only 20% had sphincter dysfunction (the cause of incontinence could not be identified in 5%) [54].

3.2. Bladder Dysfunction (Persistent or new onset)

Turner-Warwick *et al*. first directed attention to the relationship of BOO, the symptoms of frequency, urgency and UUI and the correlation of these symptoms with DO seen on cystometry [55]. They noted that in 75% of men, symptoms were relieved by de-obstruction.

Several contemporary explanations for the cause of persistent overactivity after obstruction endure. These include denervation super-sensitivity of the bladder muscle [56,57], alterations in collagen composition of the obstructed bladder [58], emergence of altered and increased sensory reflexes mediating the micturition reflex [59,60] and physical changes in detrusor myocytes affecting electrical transmission [61] or even the the remaining influence of CRP as investigated by Kupelian *et al* [62]. In addition, the bladder itself,and particularly the trigone may be inadvertently resected during surgery, causing bladder dysfunction or even without prior surgical treatment.

3.3. Different Techniques

Monopolar TURP (M-TURP) has been considered as “gold standard” for the treatment of BPH in the past decades, although it is associated with complications such as transurethral resection syndrome (TURS) and blood loss [63]. Until theearly 2000s, M-TURP and open prostatectomy accounted for the majority of surgical procedures to treat BPO. In 1989, the American Urological Association published two major series on M-TURP and its complications [64,65]. Rates of post-TURP incontinence requiring a pad or collection device were 0.4% in the first and 3.3% in the second study. The AUA Cooperative study also reported mild stress incontinence in 1.2% [65]. In 1994, the Agency for Health Care Policy and Research reviewed the role of M-TURP vs open prostatectomy to analyze treatment outcomes. The panel ranked total incontinence of urine as the fourth most important outcome influencing a treatment decision. After M-TURP, 2.1% of patients experienced stress incontinence, 1.9 % had urgency incontinence, and 1.0% reported total incontinence. For open prostatectomy stress incontinence occurred in 1.9%, urgency incontinence in 0.5% and total incontinence in 0.5% of patients [66].

With the progress of surgical techniques and development of instruments, many transurethral procedures have been invented to overcome the faults of M-TURP. These alternative transurethral procedures include bipolar plasmakinetic, electrovaporization, and various lasers [67]. The modalities of prostate tissue ablation include enucleation, resection, and vaporisation [68].

All available surgical treatments are currently widely used, and each surgical procedure has its own advantages or disadvantages. However, the efficacy and safety of different transurethral procedures for the treatment of BPH are still undefined. Hundreds of randomized controlled trials have compared different types of transurethral procedures. However, most have only compared 2 or 3 types of procedures. The comparative efficacy and safety of different surgical procedures are therefore difficult to estimate [69].

Studies that have evaluated holmium laser resection (HoLRP) and potassium titanyl phosphate (KTP) laser vaporisation of the prostate have shown a similar incidence of incontinence. Two randomized controlled trials of HoLRP versus TURP have shown rates of stress incontinence to be very similar. Westenberg *et al* showed the incidence of stress incontinence with or without urgency incontinence to be 7% for HoLRP versus 6.7% for TURP at a minimum of 4 years follow-up [70]. Kuntz and colleagues found just 1% stress incontinence in each group at 12 months [71]. They also showed a similar rate of resolution of preoperative urgency incontinence for both groups (81% versus 85%). Two other prospective non-randomised trials of HoLEP found 0.6% -2.5% incidence of stress [72]. Two randomised controlled trials of KTP (green light) laser versus TURP reported 0% and 1% stress incontinence in each group respectively [73,74] while a third randomised trial did not mention incontinence [75]. A recent study comparing green light with TURP showed a comparable 24-month outcome and safety profile [76]. Retrospective studies on green light showed a 2- 3.3% incidence of stress incontinence [77,78]. Te *et al.* [79] reported 1-year results of Green Light in the first US multicentre prospective trial. At 12 months 2 of 139 men had persistent new onset UUI And reported no stress incontinence. Others report no superiority outcome for any standard approaches except for hospitalisation time [80].

Recently Sun *et al.* reviewed 88 random controlled trials utilisong fifteen procedures in a network meta-analysis. Procedures included were: DiLEP=diode laser enucleation of prostate, HoLEP=holmium laser enucleation of prostate, HoLRP=holmium laser resection of prostate, ILC= intrestitial laser coagulation, M-TURP=monopolar transurethral resection of prostate, PKEP=plasmakinetic enucleation of prostate, PKRP=plasmakinetic resection of prostate, PVP=photoselective vaporization of prostate, TmLRP=thulium laser resection of prostate, TmLEP=thulium laser enucleation of prostate, TURis=bipolar transurethral resection in saline, TUVP= transurethral electrovaporization of prostate. Stress urinary incontinence frequently occurred in KTP/Nd:YAG laser.HoLEP was the best choice to

reduce the incidence of stress urinary incontinence and retrograde ejaculation even though it demonstrated a potential damage of prostate capsule because of its pulse work mode and requirement of tissue morcellation [81-92]. In general, thulium laser, diode laser, and holmium laser showed equally high efficacy and safety [69].

In 2019, Huang *et al* reviewed 109 trials with a total of 13 676 participants. SUI was reported in 83 trials. The authors saw no significant difference between the new methods and M-TURP for this complication. However, the risk of short-term transient incontinence was higher in enucleation than in resection methods [93].

Recently, new minimally invasive treatment options entered the market. Besides theprostatic urethral lift (Urolift®) none has been compared to TURP. Although the rate of postoperative incontinence did not differ significant after one year (Urolift 85% vs. TURP 75%, p=0.4 patients recovered significantly faster from the minimally invasive procedure [94]. Results of a crossover study (LIFT®) with a two-year follow-up were similar [95]. In the initial published data, Roehrborn reported that UI after Urolift was moderate to mild [96].

In 2015, Aquablation (water ablation) was described as a novel minimally invasive therapy combining image guidance and robotics. In the preliminary study, no cases of urinary incontinence were reported [97]. The same authors reported results at 12 months and confirmed the absence of SUI cases [98]. In 2019, Bhojani *et al* reported a 2% *de novo* incontinence rate at 12 months in patients with large (80-150 cc) prostates [99].

In addition to surgical treatment, males with urinary tract infections had higher adjusted rates of UI with a pooled odds ratio of 3.5 (95% CI: 2.3 -5.2) [100-104].

Acute genitourinary toxicity, enuresis, incomplete urination (residual), and other urological conditions were associated with higher adjusted odds of UI in all studies that examined the relationship [100,105-107].

4. INCONTINENCE ASSOCIATED WITH RADICAL PROSTATECTOMY

4.1. Incidence

The incidence of incontinence after radical prostatectomy, commonly referred to as postprostatectomy incontinence (PPI), has been a source of controversy over the past several decades as reported rates have varied greatly depending on the definition and method of data collection. While multiple factors are associated with the development of PPI, surgical modifications also play a role. The incidence has probably declined over the past two decades, owing to advances in surgical technique and to earlier recognition of lower stage disease in younger patients, however the prevalence of PPI has risen [108].

About 30 years ago, Foote *et al* tabulated data from series published between 1977 and 1990 and reported incontinence rates ranging from 2.5% to 87% after retropubic radical prostatectomy [109]. In general, older single-institution studies utilizing physician assessments to determine incontinence rates reported relatively low rates (5-8%) [110-114]. Another study with a follow-up of up to 5 years reported frequent leakage in 14% or no urinary control men 60 months after diagnosis [115]. A variety of definitions of incontinence were used, making comparison of data difficult. Since then, validated patient questionnaires have helped to standardize definitions of incontinence, allow easier comparison between institutions, and assess of the impact of incontinence on quality of life. This eliminates physician bias, perhaps improving accuracy [116-118]. As expected, these studies show the incidence of incontinence to be significantly higher, 13-65%, depending upon the definition.

There appear to be differences in physician vs. patient reported outcomes and centres of excellence versus community surgeons' outcomes [119]. When trying to interpret all the data, it is clear that the varying definitions of incontinence make comparisons impossible. Even using the definition of pad free, totally continent has its limitations. As in earlier open and laparoscopic prostatectomy series, robotic series tend to be single institution studies with physician reported outcomes and continence status based on no or 0-1 pads. In the meantime, more robust data, comparing open vs. RARP demonstrate that RARP is more likely to result in continence post-operatively [120,121]. Others report this for the early post-operative phase but this seems to equalise after one year [122].

In a systematic review of more than 8000 men who underwent RARP, laparoscopic prostatectomy, or retropubic prostatectomy, Ficarra *et al*. found that for a ''no pad'' definition of UI, rates ranged from 4% to 31%, with a mean of 16%. Considering a "no pad" or "safety pad" definition, the incidence ranged from 8% to 11%, with a mean of 9%. Few comparative studies have evaluated the impact of different surgical techniques on urinary continence recovery after RARP. Posterior musculofascial reconstruction with or without anterior reconstruction was associated with a small advantage in urinary continence recovery 1 month after RARP. Only complete reconstruction was associated with a significant advantage in urinary continence 3 mnthso after RARP (odds ratio [OR]: 0.76; p = 0.04) [121]. Age, body mass index (BMI), comorbidity index, pre-existing lower urinary tract symptoms (LUTS), and prostate volume were preoperative predictors of UI after RARP. The authors concluded that the prevalence of UI after RARP is influenced by preoperative patient characteristics, surgeon experience, surgical technique, and methods used to collect and report data. The techniques purported to provide better functional results were nerve-sparing procedures, bladder neck preservation, preservation of anterior urethral ligaments, and proper urethrovesical reconstruction. RARP appeared to have better continence rates compared to open prostatectomy, whereas bladder neck preservation resulted in better continence rates compared to bladder neck reconstruction.

4.2. Recovery Of Continence After Radical Prostatectomy

While the majority of patients experience incontinence immediately following RRP, in most this is transient with a gradual improvement over time. It is important to consider that there is also a group of incontinent men who might not consider themselves as incontinent [123]. Most studies report progressive return of continence up to one year after surgery and, in general, intervention for incontinence is usually delayed until one year after surgery unless absolutely no improvement is seen. Thus, most prostatectomy series report continence rates at 1 year. Lepor and Kaci [124] showed that, based on objective and subjective measures, continence may continue to improve up to 24

months. They showed modest improvements in bother (UCLA RAND questionnaire), pad usage and rates of total control between 12 and 24 months. Pad weights were not determined so it is possible that some “improvements” could have been related to a change of patient tolerance and expectations over time. Smither *et al*. objectively assessed the natural history of post radical prostatectomy incontinence using a standardised I hour pad test [125]. This study showed a rapid improvement in urinary control during the first 18 weeks post-RRP with a flattening of the recovery curve beyond that point. Minimal incontinence, defined as < 1 g on a 1-hour pad test was as demonstrated in 3,37,66, 85, 87 and 91% of patients at 2, 6, 18, 30, 42, and 54 weeks. They concluded that the 18-week marker appears to be the time point atwhich the majority of patients achieve urinary control, although a small percentage will have continued objective improvement. This estimation is shaired by Sacco *et al.* reporting progressive improvement of continence until two years after RRP, but some patients may become continent even later [126] whereas others report that maximum continence was reached after three months [123].

4.3. Risk Factors

4.3.1. Age

An increased risk of PPI in older men is supported in theory by anatomical observations [108]. With advancing age, there is evidence of atrophy [20] and neural degeneration of the rhabdosphincter [127]. Several studies have shown advancing age to be a risk factor for postoperative incontinence [110,111, 114, 128-130]. Steiner *et al.* [113] found no correlation between age and continence status, but only 21 of the 593 patients were 70 years or older. Catalona *et al.* [110] reported that recovery of urinary continence occurred in 92% (1,223 of 1,325 men) and was associated with younger age (p<0.0001) which might be related to surgical approach (nerve sparing), perhaps performed more often in the younger than in the older patient, although they ultimately reached a similar outcome [131]. Khoder *et al*. noted that a nerve sparing procedure makes sense for older adults (>70y of age); this is of particular importance giventhat this patient group increased significantly over the recent years [132]. In a study that included 308 patients who underwent RARP, Novara *et al.* [133] found that patients who recovered their continence 1 yr after surgery were significantly younger than patients in the incontinent group. Karakiewicz *et al.* [134] reported that age was predictive of urinary functional outcomes among 2415 patients after RP. In an analysis of 2849 patients, Matsushita *et al* [135] confirmed that greater age was an independent predictor of worse continence outcomes at 6 and 12 months after prostatectomy. Conversely, univariate and multivariate analyses of data for 111 patients by Kadono *et al* [136] found no effect of age in continence recovery.

4.3.2. Body Mass Index [108]

A recent metanalysis performed by Wei *et al.* explored 6 trials with 2890 participants. The authors indicated that obesity (BMI ≥ 30) may increase the UI risk at 12 and 24 months after laparoscopic and RARP [137]. Previously, Wiltz *et al.* found that, among 945 patients who underwent RARP, urinary continence outcomes were significantly poorerfor patients with BMI >30 kg/m^2 at 1 and 2-yr follow-up [138]. Conversely, univariate and multivariate analyses of data from 111 patients by Kadono *et al*. revealed that BMI did not predict the post-RP continence outcome [136]. Hsu *et al.* observed no statistically significant relation between body weight and postoperative continence [139]. In one of the larger series evaluating preoperative predictors of urinary continence, Matsushita *et al*. reported that among 2849 patients who underwent prostatectomy, higher BMI was an independent predictor of worse continence outcomes at 6and 12-month follow-up [135].

4.3.3. Prostate size and Membranous Urethral Length (MUL) [108]

Urethral length preservation during RP improves continence outcomes [140]. Cambio *et al.* reported that in patients with a large prostate, RP is theoretically associated with excision of relatively longer parts of the urethra, which might impair continence outcomes in such patients [141]. Hsu *et al.* also assumed that PPI may be explained by pre-existing LUTS among men with a large prostate [139]. In a retrospective analysis of data from 355 patients who underwent extraperitoneal RARP, *Boczko et al.* explored the role of prostate size and found that the 6-months post-RP continence rate was significantly lower for men with prostate size >75 cm^3 than for men with a prostate <75 cm^3 [142]. Konety *et al.* from a group of 2097 patients reported that men with prostate size >50 cm^3 had lower rates of continence at 6 and 12 months after RP. Continence rates equalized across all prostate size categories at 24-mo follow-up [143].

Conversely, univariate and multivariate analyses by Kadono *et al.* [136] using data from 111 patients found that prostate size did not predict post-RP continence outcome. This data aligned with an evaluation of 3067 men performed by Pettus *et al*. who found that prostate size did not appear to have any effect on functional outcomes, includingUI , at 12 months after prostatectomy [144].

Nguyen *et al*. observed that preoperative urethral sphincter length (measured from the prostatic apex to the penile bulb) was approximately 14 mm. Continence recovery at 1 yr was 89% among patients with length >12 mm postoperatively, compared to 77% for patients with length <12 mm. This group also observed that urethral sphincter length was significantly associated with quicker postoperative recovery of continence. Longer preoperative and postoperative length was also associated with higher continence rates [145]. Indeed, Paparel *et al.* noted that preoperative and postoperative mid urethral length (MUL) and the MUL loss ratio were related to recovery time and the degree of urinary continence [146]. Matsushita *et al.* evaluated 2849 men and confirmed that longer MUL was strongly associated with improved continence rates at 6 and 12 months after prostatectomy [135].However, Borin *et al* did not find any difference in continence rates or in the time to achieve continence when dissecting more heavily at the apical borders to achieve less positive surgical margins. The continence rates were similar when the dissection was performed 1 cm below, 0 cm or 1 cm above the urogenital diaphragm. No correlation between continence rates and preoperative or intraoperative urethral stump length was observed [147].

4.3.4. Stage Of Disease

Most large series have found no correlation between the stage of disease and incontinence rates, whereas Loeb reported the importance of aiming to maintain continence in youngers patient in the high-risk group [148]. However, in certain cases, the stage of disease may influence the surgical technique (i.e. nerve sparing), but the effect appears to be related to surgical technique rather than disease stage [111].

4.3.5. Pre-Existing LUTS And TURP before RP [108]

Rodriguez *at al.* investigated the role of pre-existing LUTS in a cohort of 106 patients. They reported that 74 of 106 patients reporting occasional leakage after RP had significantly more noticeable LUTS compared to the 32 patients who were completely dry before surgery [149]. Multivariate analysis by Wei *et al.*, using data from 482 RP patients revealed that pre-RP baseline continence was a significant predictor of post-RP continence [150].

Pompe *et al.* analyzed a group of 470 patients who underwent TURP before RP. TURP patients exhibited a higher risk for urinary incontinence at the third post operative month (OR:1.47; 95% confidence interval [CI]1.01−2.12, P=0.04) and after the first year (OR: 2.06; 95% CI1.23−3.42, P=0.006) [151]. Conversely, in a controlled trial involving 124 patients, Palisaar *et al*. reported no significant difference in PPI rate between patients with and without TURP before RP [152].

4.3.6. Salvage RP Following Radiation Therapy (RT)

Patients who have undergone prior radiation for prostate cancer are at high risk of developing incontinence after RP with the possible need of postoperative RT [148]. In the past, some authors reported rates of incontinence after salvage prostatectomy ranging from 57-64% [153, 154]. In 2006, Sanderson and colleagues reported that 45% of men underwent artificial urinary sphincter placement after salvage prostatectomy and another 31% without an artificial sphincter had incontinence greater than occasional dribbling [155].

In a more recent systematic review, Chade *et al.* reported continence rates — defined as using no pads — ranging from 21% to 90% for open surgery, from 67% to 78% for laparoscopic surgery, and from 33% to 80% for robotic surgery [156].

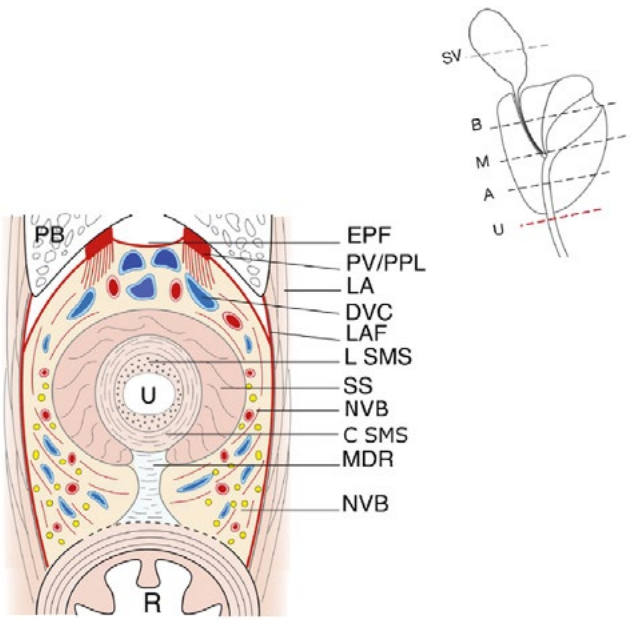

Figure 3: Axial section of the sphincteric urethra.
A = apex; B = bladder; C SMS = circular smooth muscle sphincter; DVC = dorsal vascular complex; EPF = endoplevic fascia; LA = levator ani muscle; LAF = levator ani fascia; L SMS = longitudinal smooth muscle sphincter; M = midprostate; MDR = median dorsal raphe; NVB = neurovascular bundle; PB = pubic bone; PV/PPL = pubovesical/puboprostatic ligament; R = rectum; SS = striated sphincter; SV = seminal vesicle; U = urethra.

Walz J, Epstein JI, Ganzer R, Graefen M, Guazzoni G, Kaouk J, et al. A Critical Analysis of the Current Knowledge of Surgical Anatomy of the Prostate Related to Optimisation of Cancer Control and Preservation of Continence and Erection in Candidates for Radical Prostatectomy: An Update. Eur Urol 2016.

4.4. Etiology nd Pathophysiology of Post Radical Prostatectomy Incontinence: Sphincter Vs. Bladder Dysfunction

There is extensive literature on urodynamic investigation of post prostatectomy incontinence. While it is well established that both bladder and sphincter dysfunction may be present after RP, most studies agree that sphincter dysfunction (stress incontinence) is the main cause.

As described by Walz *et al*., the trigone may play a role in the maintenance of continence given that is formed by fibres of the vesical sphincter, which is an elliptic structure formed by circular smooth muscle fibres arranged circumferentially around the urethral opening. This muscular structure is part of the vesical sphincter that assures continuous urinary continence as well as bladder neck closure. Inferiorly, circular fibres of this muscle surround the proximal prostatic urethra down to the colliculus seminalis. This part of the sphincter is modified by and interspersed with the development of BPH, and the intravesical part may be displaced upwardsinto the bladder lumen [157]. The so-called bladder neck–sparing technique is performed in this anatomical area with the aim of improving postoperative continence. To date, the effect of bladder neck sparing on urinary continence, is unclear and no clear conclusion for or against the technique can be drawn [121,157-160]. Multiple studies have shown this to be a contributing factor [161-163]. However, Marien and Lepor showed that sparing of the bladder neck has no effect on continence rates [164].

Some have suggested that denervation of the urethra or the bladder may occur during radical prostatectomy. John *et al.* [165] studied trigonal innervation by biochemical markers and found that urinary incontinence was associated with decreased trigonal innervation, a high sensory threshold and low maximal urethral closure pressure which was evaluated differently by the same author in different reports [166].

Heesakkers *et al.* reported that there is some evidence that neurovascular bundles (NVBs) may play a role in PPI [108]. There is debate about the role and extent of the contribution of the NVB in the innervation of the external urethral rhabdosphincter [167,168]. Moreover, Strasser and Bartsch [169] found that the NVB directly innervates the membranous urethra leading to the thought that damage to the NVB does affect the continence mechanism and preservation does lead to at least earlier recovery of continence after RP. This has been shown by many good quality studies [126, 161, 170-174]. However, it has also been questioned by others who saw no difference in continence rates between nerve-sparing and non–nerve-sparing techniques [164].

Supporting structures of the membranous urethra may also play a role. Several studies have shown that preservation of the puboprostatic ligament and pubo-vesical ligament to allow proper sphincter functioning improves PPI [175-178]. Reconstruction of the posterior musculofascial plate of Denonvilliers or the

posterior fibrous raphe, a technique also known as the Rocco stitch, seems to improve PPI, as shown by multiple studies [175,179,180], although some surgeons did not note a similar improvement in continence after RP [181]. Total pelvic reconstruction with fixation and anchoring of the sphincteric complex and the bladder urethra anastomosis anteriorly and posteriorly has several biomechanical advantages and also seems to result in earlier return to continence [175].

Bladder dysfunction has been explored as a cause of PPI. Ficazzola and Nitti found that although 46% of patients reported bladder dysfunction, incontinence on UDS was demonstrated in only 27% in the context of an overwhelming majority of sphincter dysfunction [182]. Groutz and colleagues found a 33% incidence of bladder dysfunction but found that thiswas the main cause of incontinence in only 7.25% [183]. Some authors argue that in some patients with severe intrinsic sphincter deficiency, bladder dysfunction may occur as a result of filling the bladder to volumes to whichit is unaccustomed to holding [182].

Giannantoni *et al.* reported that after RRP a high proportion of patients (70.3%) were affected by DO. About half of these patients complained of overactive bladder (OAB) symptoms, in whom DO was observed in 61.2% before surgery. This suggested that DO may be attributed to surgical damage in a small percentage of patients [184]. At the 36-month follow-up, the dysfunction persisted in 56.3% of 32 men, and about 40% of these presented with OAB symptoms. At the three-year follow-up, the dysfunction persisted in 25% of cases [184]. Recently, Matsukawa *et al.* reported that *de novo* OAB was observed in 37.8% (87/230) of patients and that post-operative continence was significantly more likely in the OAB-free group (79.7%) than in the *de novo* OAB group (8.0%) [185].

Filling to capacity during cystometry may induce DO or give the impression of compliance. Thus, bladder dysfunction could be interpreted as an artefact, but could also demonstrate a partial decentralization of the bladder combined with somatic denervation, as a result of bladder mobilization during prostatectomy [182]. The branches of the pudendal nerves innervating the pelvic floor muscles and the striated urethral sphincter split before reaching the urogenital diaphragm. In addition, bladder dysfunction may stem from obstructive uropathology present before prostatectomy. For the placement of an artificial sphincter, the 2015 consensus conference suggested waiting at least 6 months following prostatectomy \ [186]. Recently a network metanalysis failed to reach consensus regarding the definition of severity of incontinence and found no statistically differences in continence rates when AUS versus adjustable sling were compared, with an RR of 0.78 (95% CI: 0.09-6.56) [187]. Machioka *et al*. recently suggested the use of the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) and 24-h pad weight test to compare UI status pre- and post-RP [188].

Post prostatectomy bladder dysfunction may have been present preoperatively, for example due to pre-existing outflow obstruction, may be caused by the operation itself, or may be due to age related changes in bladder function. Indeed, Juszczak *et al.* suggested that bladder hypertrophy could be identified as a predictor of OAB and/or UUI in the general population, as well as in patients after radical prostatectomy [189] and argued that preoperative OAB patients are at a higher risk of developing more severe UI after RP [190]. There are currently no data on how preoperative management or surgical technique may prevent post-prostatectomy OAB [191]. However, Yamada *et al.* reported that baseline OAB seemed to represent an independent negative predictor for recovery of continence within 12 months after RALP (p = 0.019) [192].

5. INCONTINENCE RELATED TO RADIATION THERAPY FOR PROSTATE CANCER

Radiation therapy, whether external beam or brachytherapy, can be a cause of voiding dysfunction and incontinence [7, 193]. Sometimes this is a direct effect of the radiation or it can be related to the treatment of other sequelae such as urinary retention. The initial response is primarily oedema and then gradual degeneration, fibrosis and disorganization of the bladder musculature. While radiation is primarily delivered to the prostate, portions of the bladder may also be affected [7]. Perivascular fibrosis of blood vessels may then cause vascular occlusion followed by ischaemia of the bladder wall, which can then progress to fibrosis within 6 to 12 months [194].

Symptom-specific associations to dose distribution have been demonstrated for urinary symptoms [195]. Global symptoms, like increased urinary frequency, are likely associated with the dose distribution across the whole bladder (i.e. mean dose) while associations with dysuria, haematuria and incontinence were shown to be more localized, dependent on the area of the bladder receiving a high dose [193,196].

A recent prospective study by Mylona *et al.* analyzed 272 patients with prostate cancer treated with intensity-modulated radiation therapy/image-guided radiation therapy. The authors observed that a local dose-effect relationship was found in the bladder and the urethra. Symptom-related subregions were identified for 5 symptoms: acute incontinence in the urethra, acute retention in the bladder trigone, late retention and dysuria in the posterior part of the bladder, and late haematuria in the superior part of the bladder, with significant dose differences between patients with and without toxicity, ranging from 1.2 to 9.3 Gy. This led to the conclusion that the dose delivered to the urethra and the posterior and superior parts of the bladder was predictive of acute incontinence and retention and of late retention, dysuria, and haematuria [197].

The rate of severe late incontinence ranges between 1 and 5% at 3–5 years after RT end, although higher incidences were reported with ultra-high doses and in the post-operative setting [198,199]. Moreover, Corazzini *et al.* reported that the risk of late patient-reported urinary incontinence markedly increased for 2Gy equivalent dose (EQD2) > 80 Gy. Previous abdominal/pelvic surgery and previous TURP were significantly predictive of late patient-reported urinary incontinence [200].

Choo *et al.* found that urodynamic bladder capacity decreased by an average of 54 ml, 18 months after radiation therapy [201]. Blaivas *et al.* evaluated 47 men with symptomatic LUTS after brachytherapy and found that 71% were incontinent and 85% had detrusor overactivity [202]. Similarly, radiation can cause damage to the distal urinary sphincter, which can result in incontinence.

Urinary retention and increased obstructive LUTS are other common problems particularly following brachytherapy. The

incidence of retention reportedly ranges from 2% to 30% after brachytherapy [203-205]. Most patients with retention will have resolution within weeks while others may require surgical procedures. Flam *et al*. reported that 19 of 600 (3.1%) patients receiving brachytherapy required TURP [206]. Kollmeier and colleagues reported a similar rate of 2% in 2050 men [207]. Incontinence following TURP after brachytherapy has been reported in 0-70% and is often severe [206-208]. External beam radiation is also a risk factor; Green *et al*. reported a 33% incidence of incontinence following TURP in patients post-irradiation for prostate cancer [209]. Some authors have emphasized that incontinence can be minimised by performing a limited resection [210] or by performing TURP within 2 years of brachytherapy [207]. However, others suggest that delaying TURP until 5 years after radiation can actually reduce the risk of incontinence [210].

6. CONCLUSIONS

Incontinence in the male can be broadly divided into causes related to bladder and/or sphincter dysfunction. The pathophysiology of incontinence is fairly well described; however, advances in science and anatomy will undoubtedly provide better understanding in the future. Although the causes of sphincter insufficiency are known (i.e. damage to muscle, nerve and/or supporting structures), sometimes clinicians are not able to accurately assess the exact cause. Therefore, much of our understanding of post treatment incontinence "pathophysiology" is derived from reports of incontinence (incidence/prevalence) after surgery or radiation. Following the AUA/SUFU guidelines, the time of incontinence after any procedures may vary; although non-surgical options, such as pelvic floor muscle exercises (PFME), can hasten continence recovery, patients who remain incontinent at one-year post-procedure, or have severe incontinence at six months, may elect to undergo surgical treatment [211].

In addition, the incidence of incontinence related to interventions for prostatic disease is still difficult to determine. Two future directions are important: a better standardization of pre and after treatment incontinence evaluation and a more accurate reporting data. New technologies for the treatment of BPH have been largely described and will provide additional evidence in the future.

Data regarding the incidence of post-radical prostatectomy incontinence is increasing due to the use of metanalysis.

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II. PATHOPHYSIOLOGY OF STRESS URINARY INCONTINENCE, FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE IN WOMEN

1. ANATOMY AND PHYSIOLOGY OF THE FEMALE UROGENITAL DIAPHRAGM

The factors necessary for the urethra to remain closed at rest and during increased abdominal pressure have been well characterized, but their functional inter-relationships are still not fully understood. These factors include: 1) a healthy, functioning striated sphincter controlled by pudendal innervation, 2) well vascularised urethral mucosa and sub- mucosa, 3) a properly aligned and functioning intrinsic urethral smooth muscle, and 4) intact urethro-vaginal support.

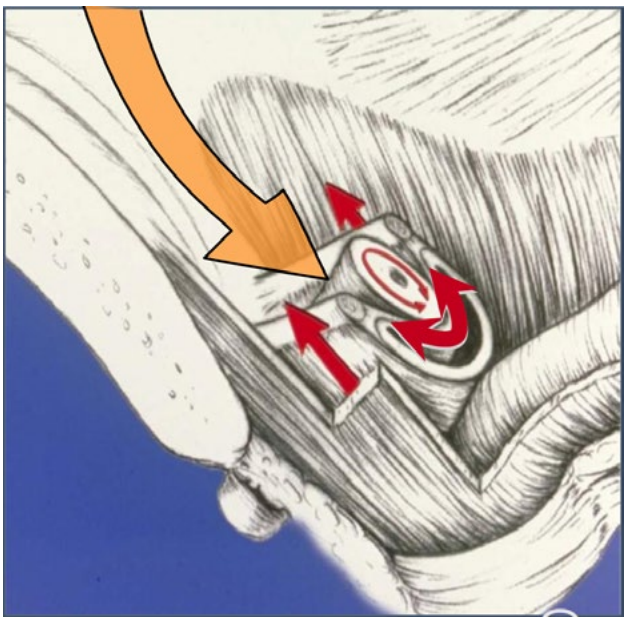

Figure 1: Schematic view of the continence mechanism seen from the right side after removal of near-side structures. The upward red arrows indicate the effect of levator ani muscles; the upward curving arrow, the fascial layer under the urethra; and the circular arrow, the spincter's action. The orange downward arrow, the effect of abdominal pressure on the system. © DeLancey

There are many historical theories proposed to explain stress incontinence. More recently, scientific studies have been conducted comparing objective measurements between stress incontinent and continent women that provide data against which these theories can be tested. Current data indicate that a combination of a weak urethral sphincter and disruption in the supportive mechanism of the bladder and urethra are both involved. [1; 2] and weakening of the muscular structures of the pelvic floor, bladder neck and urethral sphincters [3] can cause SUI. A view of the aspects involved in continence is seen in Figure X. Unfortunately, considering the complex interactions among tissue morphology, mechanical properties, perfusion, innervation and motor control, several factors may contribute to the pathophysiology of SUI, yet the evidence for some of these factorsis lacking, and their relative importance is largely unknown [1].

"The Integral Theory" (IT) [4] stated that stress urinary incontinence is mainly caused by connective tissue laxity in the vagina or its supporting ligaments. However, the "Urethral Hanging Theory" (UHT), hasquestioned the rationale of the IT. This theory states that is proximal urethral funneling also contributes to SUI and failure of sling procedures, [5]. IT and UHT both emphasize Pubo-urethral ligaments (PUL) as important structures, but are principally different [6]. IT postulates that the pathophysiology of SUI is multifactorial and that no single method can be expected to cure all patients. UHT postulates that the pathophysiology of SUI is unifactorial and that the cure is to "stop urethral hanging." Preventin the urethra from descending downward. Another recent theory suggests that continence is a result of defects in passive as well as active urethral closure mechanisms. The smooth muscles of the urethra, the vascular bed, and the oestrogen influenced urethral mucosa, combined with striated muscle tone, contribute to the intra-urethral pressure. A passive transmission of force to the urethra exists only in the abdominal proximal third of the urethra. In the distal two thirds of the urethra an active closure mechanism is present, dependent on sufficient urethral support in the proper anatomical position. This active closure mechanism is generated by reflex contraction of striated muscles of the urethra and the pelvic floor, milliseconds before abdominal pressure increases. [7].

1.1. The Female Urethral Sphincter and Perineal Membrane

Because failure of the urethral sphincter is a key factor in causing stress incontinence, an understanding of its structure and function is necessary. Detailed descriptions of the striated urogenital sphincter muscle have been made by Max Brodel working with Howard Kelly [8], Oelrich [9] and further expanded by DeLancey [10]. These reports have provided clear descriptions of the urethral rhabdosphincter. The location of the sphincter elements can be understood by dividing the urethral lumen into 5 equal segments. The first 20% is surrounded by the bladder muscle and detrusor loop, the next 40% surrounded by a sleeve of striated muscle that forms the sphincteric portion of the striated sphincter. Next, from 60 to 80% two arch shaped bands of muscle diverge from the wall of the urethra to surround the vagina (urethrovaginal sphincter) and perineal membrane (compressor urethrae). Manometric and electrophysiological recordings from the mid urethra have shown that it generates the highest level of resting pressure and electromyographic activity. This portion of the urethra is an intra-pelvic structure located immediately posterior to the pubic bone. In the past, much has been made of the loss of this intra-pelvic position in stress incontinence. It had been suggested that when the urethra descends away from its intra-abdominal position, intra-abdominal forces no longer constrict it during straining. This concept has survived and been modified into the "hammock hypothesis" [11] which suggests that the anterior vaginal wallprovides a backboard against which increasing intra-abdominal forces compress the urethra. The anterior vaginal wall is stabilized by its lateral attachments to the arcus tendineus fascia pelvis and levator ani muscle. Data supporting this hypothesis are drawn from urethral pressure transmission studies showing that continent patients experience an increase in intra-urethral pressures during coughing. This pressure increase is reduced in stress incontinence and may be restored following successful surgical

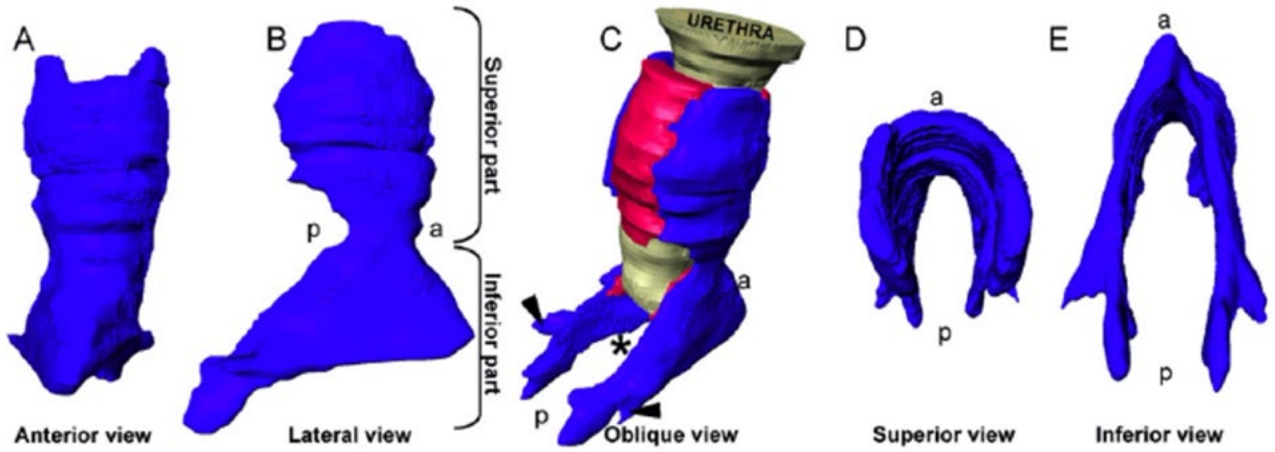

Figure 2: EUS in 18 weeks female foetus: A anterior view, B lateral view, C oblique view, D superior view, E inferior view - From Wallner et al., Eur Urol 2009 [222].

interventions designed to stabilize or elevate the sub-urethral vaginal wall [12-21].

The urethra is supported by the anterior vaginal wall. The superior vaginal sulcus, most clearly found in nullipara, exists at this junction of the lower and middle third of the vaginal wall. This point represents the two lateral insertion points of the vaginal "hammock ". Portions of the pubococcygeus muscle attach to these to sulci within the pelvis and can produce elevation during voluntary contraction.

Immediately anterior to the proximal urethra are found the reflections of the endopelvic fascia. The most prominent of these, the attachments of the arcus tendineus fascia pelvis (sometimes referred to clinically as "pubo-urethral ligaments", are sufficiently condensed to form distinct and recognizable ligaments on either side of the pubis where they attach to the pubic bone about 1 cm from the midline and 1 cm above the bottom of the pubis. These structures are continuous with a complex of tissues including the perineal membrane and levator ani. The arcus tendineus fascia pelvis, which can be seen at the time of retropubic surgery, are the more familiar of these. These are strong fascial condensations which most likely maintain their characteristics throughout life. Previous investigators have suggested that elongation of these structures may be responsible for the loss of urethral support seen in stress incontinence, yet objective evidence for this is lacking.

Different authors have described the striated urogenital sphincter (SUS) that has also been called the external urethral sphincter (EUS) by some authors, both in fetuses [22, 23] and adults [24] as a superior horseshoe structure covering the urethra and an inferior one surrounding the anterolateral aspect of the urethra and the lateral part of the vagina.

The Levator Ani Muscle (LAM) is involved in urethral support. Wallner *et al.* [25] investigated the topographical relationship between the SUS and the LAM (Figure 8.9), showing that in female fetuses, but not in male, the inferior part of the EUS is firmly attached to the LAM by a tendinous connection. This determines an anterior bending of the midurethral zone when a simultaneous contraction of the LAM and EUS occurs, closing the urethral lumen and maintaining continence. The functional

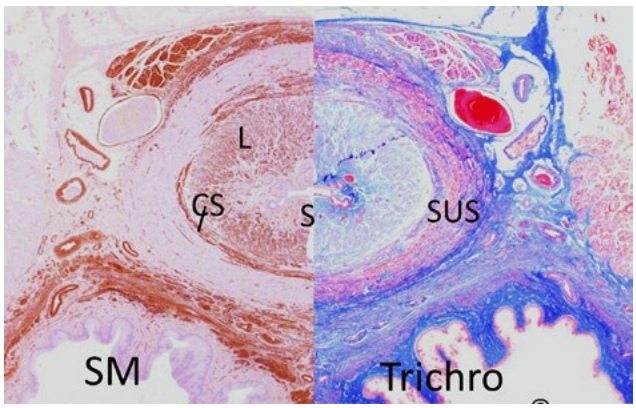

Figure 3: Axial midurethral actin immunoperoxidase histological section for smooth muscle (SMA) (a) and mirrored Mallory trichrome histological section (b) from the same specimen. A few small spots are identified in the submucosa (SM). The longitudinal (LMU) and circular (CMU) smooth muscle of the urethra, the pubovesical muscle (PVeM), and the smooth muscle layer of the anterior vaginal wall (AV) are easily identified on the actin-stained immunoperoxidase preparation, whereas the striated urogenital sphincter muscle (SUS) does not stain with actin. Abbreviations: ATFP, arcus tendineus fasciae pelvis; LA, levator ani muscles.

integrity of this connection between the EUS and the LAM is therefore crucial to avoid urinary incontinence.

The striated external urethral sphincter (EUS), both in fetuses and adults, has a superior horseshoe structure covering the urethra and an inferior one surrounding the anterolateral aspect of the urethra and the lateral part of the vagina.

Moreover, while the lower one-third of the vagina is orientated more vertically in nullipara, the upper two-thirds of the vagina deviate horizontally ~~[Iuo 2016].~~ This orientation is dueto the posterior attachments of the cervix by the cardinal and utero-sacral ligaments and to the anterior position of the levator hiatus.

Modifications of the genital hiatus determining an increase in the genitohiatal distance can be associated with urodynamic

stress incontinence. In a retrospective study of 396 women with urodynamic stress incontinence [26], pelvic floor ultrasound revealed a small but statistically significant negative association of the genitohiatal distance to urodynamic functional urethral parameters such as the functional profile length, the maximum urethral closure pressure and a low Valsalva leak-point pressure ($r = -0.148$, $P = 0.018$ and $r = -0.227$, $P = 0.009$, $r = -0.199$, $P = 0.02$ respectively) that would explain about 5% of the observed variation.

2. EFFECT OF CHILDBIRTH, VAGINAL PROLAPSE AND URETHRAL POSITION ON URINARY CONTINENCE

2.1. Introduction

Labour and delivery alter vaginal and pelvic anatomy and innervation in several ways as has been discussed in other sections of this chapter. Each of these may contribute to the eventual development of urinary incontinence:Direct crushing or traction on the pudendal nerve has previously been suggested as a primary cause of sphincter incompetence in stress incontinence. The pudendal nerve, which projects from Onuf's nucleus and traverses Alcock's canal before entering the ischiorectal fossa and innervating the EUS, can be injured during vaginal delivery, particularly in the area between the sacrospinous and sacrotuberous ligaments. Two different mechanisms of pudendal nerve damage during delivery have been described: 1) nerve compression and stretching which may cause an elongation of the 13% of its motor branch innervating the EUS [27]; 2) reduced at8% stretch and complete ischaemia at 15% stretch of the nerve in a tibial nerve rat model [28]. Thus, pudendal nerve ischaemia could occur during vaginal delivery as a result of both stretch and compression [29]. However, evidence of denervation associated with childbirth has been extensively evaluated in the literature, yet longitudinal studies [30] fail to correlate such changes to urinary incontinence symptoms later in life, leaving their role in the childbirth-related stress incontinence somewhat unclear.

Birth damage to the innervation of the pelvic floor might also be an important factor in the aetiology of SUI. Neuropeptides, which are considered a marker of nerve damage, are well-represented in the innervation of the human female reproductive tract. Neurons that contain vasoactive intestinal polypeptide (VIP) are abundant in the vagina, where they innervate blood vessels and smooth muscle in the vaginal wall and form a plexus beneath the epithelial layer. Previous studies have shown that VIP levels were significantly decreased in the anterior vaginal wall in premenopausal and postmenopausal SUI patients. Also, neuronal Nitric oxide (nNO), an anorganic free-radical gas that stimulates soluble guanylyl cyclase activity and creates smooth muscle relaxation, decreased significantly in the anterior vaginal epithelium of the patients with SUI [31]. Although visible damage to the levator ani is more common in stress incontinent women soon after birth [32], they are not more common in women presenting for treatment of SUI later in life [33]

Some authors have suggested that cardinal and utero-sacral ligaments may be stretched or torn, resulting in anterior displacement of the uterus during straining or under the influence of gravity. Lepage *et al.*, [34] using a computerized pelvic model of the pregnant woman at term during a simulated delivery, showed that utero-sacral ligaments undergo a displacement depending on the size of fetal head. When a fetal head at the 50th percentile for the term goes through the pelvic system, uterosacral ligaments undergo a deformation of around 30%. Another computerized analysis [35] revealed an increase in the length of utero-sacral ligaments during the pregnancy. Shortening occurs during the postpartum period but the ligaments do not return to their initial length. These results confirmed that lesions of utero-sacral ligaments, which are the major pelvic sustaining structures, may be a potential cause of pelvic floor disorders. These observations require validation in clinical testing to see whether these simulations correspond to what is seen during human birth.

The vagina itself may be torn away from its intrapelvic attachments with subsequent loss of the superior vaginal sulcus. There may be direct attenuation of the vaginal wall itself, manifested by loss of vaginal rugae and a thin appearance. Cullen-Richardson has suggested four distinct kinds of vaginal injuries: paravaginal, central, distal, and cervical, the first two being the most commonly seen in women with stress incontinence. These defects have been identified by sonographic examination [36]. Finally, detachment of the pubococcygeal (sometimes called pubovisceral) portion of the levator ani muscle occurs during birth and results in a longer and wider levator hiatus and reduced force of contraction [37, 38]. This is not due to nerve injury or muscle compression as sometimes suggested. Here, the perineum is displaced anteriorly and posteriorly under stress and temporarily fails to support the pelvic organs. These changes in the levator hiatus with or without associated relaxation of cervical support result in chronic anterior displacement of pelvic organs with a loss of both active and passive organ support during rest and especially during straining. In the patient with stress urinary incontinence these changes typically give rise to a rotational descent of the proximal urethra away from its retropubic position.

A direct comparison of 80 primiparous women with de novo stress incontinence that persisted 9 months after vaginal birth to 80 women who did not develop incontinence and 80 nulliparous women of the same age allows urethral function and support to be evaluated [32]. Urethral closure pressure was 25% lower in primiparous incontinent women compared to continent women, who were similar to nulliparous women. Vesical neck movement measured during cough with ultrasonography was 5 mm more in stress incontinent women than the other two groups. In logistic regression, urethral closure pressure explained 25% of incontinence while support explained 16%. Levator injuries were twice as common in the incontinent group. Studies on passive and active material parameters of the pubovisceralis muscle using an inverse numerical method, showed as incontinent women have a lower passive parameters as consequence of softer muscles. This may be explained by a significant reduction of type III collagen, due to increased degradation of nascent collagen rather than decreased production. Thus, incontinent women have decreased active force and stiffness that can be associated with muscular weakness. Furthermore, also showed that incontinent women have an increased number of fibres, but these are significantly narrower than that of the asymptomatic women [39].

Mechanical injury of the pelvic floor (such as childbirth) may disrupt the supportive tissues and connections via the remodeling of Extra Cellular Matrix (ECM). Then, the urethra will lose the hammock-like support and result in SUI. The metabolism of

ECM shows an increase of matrix synthesis in response to suitable mechanical strain, while excessive force would reduce the production of ECM, which may be one of the main pathological mechanisms underlying childbirth trauma-induced SUI.

Tang *et al.* suggest that mechanical strain induced ECM remodeling of L929 fibroblasts might be associated with Nrf2/ARE signaling suppression mediating TGF-β1/Smad3 signaling inhibition, which might be the pathomechanism of mechanical trauma-induced SUI. This might reflect a new molecular target for SUI research. [40]

Perineal sonographic studies of urethrovesical angle found differences in women with stress incontinence compared to women with other urologic disorders have found excellent correlation between the angle and degree of incontinence, supporting these original observations [41].

Although we have considerable knowledge about anatomical defects in most patients with urodynamic stress incontinence (USI), less is understood about the effect of these defects and the vaginal position itself, on urethral closure. Early experience with operations for stress incontinence showed that not all women with stress urinary incontinence had vaginal prolapse, that correction of vaginal relaxation did not always correct stress incontinence, and that women who developed recurrent stress incontinence symptoms after apparently successful surgery did not necessarily show a recurrence of their prolapse [42].

In animal models, the effect of anatomical defects in the urethral mechanism induced by vaginal delivery has been investigated. A rat model of birth trauma has been simulated inducing vaginal distension by balloon catheter inflation [43]. Sneeze induced stress urinary incontinence was caused by decreased active closure mechanisms at the mid urethra without affecting the passive transmission of abdominal pressure in the proximal urethra. The greater involvement of the urethral mechanism in the occurrence of post-partum stress incontinence was confirmed in a case control study evaluating urethral closure pressure and bladder neck movement assessed with ultrasound [32]. Eighty primiparous women complaining of de-novo stress incontinence 9-12 months after delivery were compared with 80 primiparous continent and 80 nulliparous continent women. Lower maximal urethral closure pressure followed by vesical neck mobility was most likely to be associated with de novo stress incontinence after first vaginal birth.

2.2. Role of childbirth, vaginal prolapse and urethral position

2.2.1. Role of childbirth

Childbearing is an established risk factor UI among young and middle-aged women. It has been suggested that vaginal delivery is the main contributing factor, possibly because of damage to important muscle tissue or nerves. However, pregnancy itself may cause mechanical changes, hormonal changes, or both that can lead to UI.

The Swedish Pregnancy, Obesity and Pelvic Floor (SWEPOP) study demonstrated that 20 years after one birth, vaginal delivery was associated with a 67% increased risk of urinary incontinence (UI), and UI > 10 years increased by 275% compared with caesarean section. [44] These data showed also that the prevalence of all three subtypes of UI (stress urinary incontinence (SUI); urgency urinary incontinence (UUI) and mixed urinary incontinence (MUI)) 20 years after one delivery was higher after vaginal delivery (VD) compared with caesarean section (CS). This was also the case for the prevalence of bothersome UI, the severity of UI and the severity of each subtype of UI. Moderate to severe incontinence occurred in two-thirds of women with MUI, in every second woman with UUI, whereas two-thirds of women with SUI had mild symptoms. [45] LEVEL OF EVIDENCE: II

The largest community-based study (EPICONT study) [46] evaluated the risk of incontinence associated with CS and VD on the 15,307 women < 65 years and who either were nulliparous or had only caesarean deliveries or only vaginal deliveries. The prevalence of any incontinence was 10.1% in the nulliparous group; age standardized prevalences were 15.9% in the CS group and 21.0% in the VD group. As compared with nulliparous women, women who had CS had an adjusted OR for any incontinence of 1.5 (95 % CI, 1.2 to 1.9) and an adjusted OR for moderate or severe incontinence of 1.4 (95 % CI, 1.0 to 2.1). Only SUI and MUI were significantly associated with CS. The adjusted OR for any incontinence associated with VD as compared with CS was 1.7 (95 % CI, 1.3 to 2.1), and the adjusted OR for moderate or severe incontinence was 2.2 (95 % CI, 1.5 to 3.1). Only SUI (adjusted OR, 2.4; 95% CI, 1.7 to 3.2) was associated with the mode of delivery. The authors concluded that the risk of UI is higher among women who have had CS than among nulliparous women and is even higher among women who have had vaginal deliveries. CS seems to decrease the postpartum UI, but its protective effect seems to diminish over time and disappears after multiple deliveries. [46,47] LEVEL OF EVIDENCE: II

In a systematic review and metanalysis Tahtinen *et al.* [48] looked for the long-term effects of childbirth on urinary leakage. From 15 eligible studies, they found that compared with CS, VD was associated with an almost twofold increase in the risk of long-term SUI, with an absolute increase of 8%, and the effect is largest in younger women. LEVEL OF EVIDENCE: II

In the cohort study extracted from national Swedish Medical Birth Registry between 1973 and 1982 [49], two groups were identified: 30,880 women who had their first and all subsequent deliveries by CS vs. an age-matched sample of 60,122 women who delivered vaginally only. SUI surgery was observed in 0.4% of the CS group and 1.2% of the VD group (follow-up time 26.9 years), and the risk of SUI was estimated to be 2.9 times higher after VD compared with women after CS. Among women with VD, rates of SUI surgery increased with the number of births, whereas in the CS cohort it slightly decreased. Compared with CS, the risk of SUI was more than doubled for VD with vacuum extraction and tripled for a vaginal non-instrumental delivery. After VD, the incidence rates for SUI surgery steadily increased, reaching a peak close to 3 decades after the first delivery. For CS, the incidence of SUI increased more slowly and started to diverge from the curve for vaginal delivery very early (Figure 1). LEVEL OF EVIDENCE: III

The group of Tähtinen [50] recruited 13,694 women > 20 years after a VD for two surveys addressing SUI and UUI: of these 12.7% reported SUI. Among women <50 years, there was a statistically significant difference in the risk of SUI for forceps delivery (OR 1.42, 95% CI) but not for vacuum (OR 0.80, 95% CI) when compared with spontaneous VD. Among women <50 years, forceps also had increased risk for SUI (OR 1.76, 95% CI) when compared with vacuum. In this large population-based study of women across a wide age range, forceps delivery was associated with a significantly increased long-term risk of SUI among women <50 years, but there was no longer a measurable impact for women >50 years. LEVEL OF EVIDENCE: III

In a prospective study, Hansen *et al.* [51] investigated the impact of the first pregnancy and delivery on the prevalence and types

of UI during pregnancy and 1 year after delivery. The prevalence of SUI during pregnancy was 3.3 times higher compared with a control group of nulliparous women. After 1 year, the difference was reduced, but still 2.5 times higher in the primiparous group. LEVEL OF EVIDENCE: II

Twelve risk factors associated with postpartum SUI have been identified: vaginal delivery (OR 2.08, 95% CI 1.72–2.52), advanced age at gestation (OR 1.06, 95% CI 1.04–1.08), advanced maternal BMI (OR 1.04, 95% CI 1.03–1.06), excess weight gain during pregnancy (OR 1.13, 95% CI 1.00–1.26), advanced current BMI (OR 1.32, 95% CI 1.02–1.70), diabetes (OR 1.91,95% CI 1.53–2.38), episiotomy (OR 1.76, 95% CI 1.06–2.94), forceps delivery (OR 2.69, 95% CI 1.25–5.76), gestational UI(OR 5.04, 95% CI 2.07–12.28), gestational SUI (OR 4.28, 95% CI 2.61–7.01), prenatal UI (OR 8.54, 95% CI 3.52–20.70), and early postpartum UI (OR 3.52, 95% CI 1.61–7.69). [56] LEVEL OF EVIDENCE: II

Although most women with postpartum SUI regain continence within 1 year but they have a greater predisposition to develop recurrent SUI years later: among women with postpartum SUI, 92% had recurrent SUI 5 years later. [52] Indeed, trauma to the pelvic floor nerves, muscles, and connective tissue during pregnancy and vaginal delivery may persist even in the absence of SUI symptoms and could become an underlying risk factor for later development of SUI. [29] That is demonstrated by the fact that transient antepartum or postpartum SUI is predictive of later development of recurrent SUI. [53]

These findings suggest that even with functional recovery from postpartum SUI, there are latent pathophysiologic changes in the continence mechanism, which could lead to later development of recurrent SUI. LEVEL OF EVIDENCE:III

In a multicentre trial including 2305 twin pregnancies without history of SUI, women in the planned caesarean group had lower SUI rates compared with women in the planned vaginal birth group [8.11% versus 12.25%; OR, 0.63; 95%CI, 0.47–0.83; P = 0.001]. However, among those with problematic SUI, quality of life was not different for planned caesarean vs planned vaginal birth groups. The authors concluded that among women with a twin pregnancy and no prior history of SUI, a management strategy of planned CS compared with planned VD reduces the risk of problematic SUI at 2 years postpartum. These findings show that the likelihood but not the severity of SUI was associated with mode of birth. [54] LEVEL OF EVIDENCE: II

Data for the rates of incontinence after elective and emergency CS areinconsistent and it remains unclearwhether caesarean performed before labour confers greater protection than caesarean performed after labuor.

To understand the true impact of CS on UI, future studies must compare incontinence by planned delivery modes, consider a woman's entire reproductive career, focus on urinary leakage severe enough to be problematic or bothersome, consider other bladder symptoms in addition to incontinence, and take into account other risk factors, particularly antepartum UI. [55] GRADE OF RECOMMENDATION C

2.2.1.1. Pathophysiologic mechanism of birth injury to UI

During the process of childbirth, the vaginal wall and muscles, ligaments and connective tissue of the pelvic floor can be compressed and overstretched. [57] In addition, the pudendal nerve in Alcock's canal is vulnerable to trauma during delivery, particularly with associated increased duration of second stage of labour, forceps delivery, or a large birthweight baby.[58] LEVEL OF EVIDENCE: III

The major mechanism by which vaginal delivery might contribute to pelvic floor trauma are muscle trauma, nerve injury, connective tissue damage and vascular damage.

Muscle trauma

The pelvic floor muscles (PFMs), including the levator ani muscles (LAMs), coccygeus muscle, perineal muscles, striated urethral sphincter and external anal sphincter, form the base of the abdominal-pelvic cavity and contribute to the support of the pelvic contents and continence control. The LAMs are considered a functional unit which provides support to the pelvic organs in the transverse plane (lifting) and compresses the urethra against the anterior vagina in the mid-sagittal plane (squeezing). Damage to, or dysfunction of the LAMs is thought to be a contributor to SUI. [1] LEVEL OF EVIDENCE: II

A computer model quantified the pelvic floor muscle stretch induced during the second stage of labour as a model in which the fetal head progressively engaged and then stretched the iliococcygeus, pubococcygeus and puborectalis muscles. The authors demonstrated that the medial pubococcygeus muscles undergo the largest stretch of any LAMs during vaginal birth and it is therefore at the greatest risk of stretch-related injury. [59] LEVEL OF EVIDENCE: II

The occurrence rate of postpartum levator injuries in primiparae after VD is reported between 15-39.5%. [60-69] LEVEL OF EVIDENCE: III

The aetiological role of LAM integrity in bladder dysfunction is still not completely clear. A weakly significant association between levator avulsion and worsening or de novo UI has been reported 3 months postpartum. [70] LEVEL OF EVIDENCE: III

However, recent evidence questions this link, reporting that women with a major levator defect are less likely to experience SUI [71], and that puborectalis trauma is not associated with an increased risk of SUI or urodynamic stress incontinence [72]. Brincat et al [73], found no significant association between maximal urethral closure pressure (MUCP) and urethral closure pressure with a pelvic floor contraction or Kegel (KUCP) in women with or without LA defects, illustrating the involvement in urethral functon in the generation of SUI. Additionally, there was no correlation between MUCP and vaginal closure force ($r = 0.06$, $p = 0.41$), and only a weak correlation between KUCP and vaginal closure force ($r = 0.20$, $p = 0.01$). The authors concluded that urethral pressure profiles are unrelated to LAM defect status after vaginal birth, indicating that the mechanism responsible for LAM damage spares the urethra. Also, Shek *et al*. [70] demonstrated that except at the bladder neck, there was no significant association between urethral mobility and levator avulsion. LEVEL OF EVIDENCE: III

However, it has been showed that stress-incontinent women had less skeletal muscle content, fewer muscle fibres in each LAM fascicle and higher connective tissue content in their LAMs than were observed in continent women. [74, 75] LEVEL OF EVIDENCE: III

On study showed also that asymmetry of the puborectalis muscles was more common in stress incontinent women. [76] Li *et al.* [77] recently demonstrated that there were no differences between women with and without SUI in terms of overall levator defects (asymmetry, hypertrophy or disruption) but in the study of Stock-

er *et al.* [78] a significantly greater percentage of pubococcygeal muscle defects was found in stress incontinent women (45–66%) than in their continent counterparts (10–28%). During maximal effort pelvic floor muscle (PFM) contraction, one study showed greater elevation of the proximal urethra in incontinent women versus continent controls [33] while another showed the opposite [79]. In one study, the midurethra rose higher in women without than with SUI when performing a PFM contraction [80] but in another study there was no difference in bladder neck elevation between groups performing the same task [81]. These conflicting results, as well as the detection bias associated with LAM strength measurement and an overall lack of assessor blinding in studies comparing LAM strength between women with and without SUI, lead us to conclude that there is limited evidence for the integrity and strength of the LAM and its correlation with the pathophysiology of SUI. LEVEL OF EVIDENCE: III

Nerve damage

Studies of the effect of vaginal birth on the urethral sphincter mechanism show decreases in urethral closure pressure. [82-84] These decreases have been ascribed to damage to the pelvic nerves showing delayed conduction in the pudendal nerve as well as single fibre recordings. [85, 86]

The role of vaginal birth in the denervation process has been clarified by Allen's electromyographic studies performed before and after vaginal birth. [87] Allen *et al.* found that most women have signs of neurologic injury after vaginal birth (but not after caesarean section), as shown increased motor unit potential and increasing amounts of damage correlate with more evidence of SUI.

Animal models have been used to better understand the mechanisms of postpartum SUI: a study simulating dilation of the vagina during the second stage of labour of human vaginal delivery, shown that vaginal distension leads to hypoxia and disruption of external urethral sphincter muscle fibres. The crushing of bilateral pudendal nerves results in external urethral sphincter dysfunction, caused by denervation injury to the external urethral sphincter. [88]

A rat model of simulated childbirth injury demonstrated that pudendal nerve crush and vaginal distension cause a more severe and durable damage to EUS, pudendal nerve and connective tissue than either injury alone. [89, 90]

Although urethral resistance to leakage, as measured by leak point pressure (LPP), recovers 4–6 weeks after pudendal nerve crush and vaginal distension, EUS electromyography does not recover over this time. [91] Insufficient innervation of the EUS may account in part for clinical development of recurrent SUI, [29] since recurrent SUI occurs later in life when the continence threshold is reached due to the compounding effects of aging, such as reduction of the number of muscle fibres in the EUS, loss of elasticity of supportive tissues, and denervation of smooth and striated muscles. [92]

Neurophysiological testing has revealed nerve damage in 36% of women with persistent SUI at 3 months postpartum. Compared with nulliparous control subjects, patients with SUI and pelvic organ prolapse (POP) had changes in the levator ani and external anal sphincter consistent with either motor unit loss or failure of central activation, or both [92]. LEVEL OF EVIDENCE: III

2.2.1.2. Epidural Analgesia and SUI

Meyer *et al.* [93] assessed the effects of epidural analgesia on pelvic floor function. Eighty-two primiparous women (consisting of 41 given an epidural and 41 not given an epidural) were investigated during pregnancy and at 2 and at 10 months after delivery by a questionnaire, clinical examination, and assessment of bladder neck behaviour, urethral sphincter function and intravaginal/intra-anal pressures. Ten months after spontaneous delivery, there were no significant differences in the prevalence of SUI and decreased sexual vaginal response, or in bladder neck behaviour, urethral sphincter function and pelvic floor muscle strength between women who had or had not had epidural analgesia.

LEVEL OF EVIDENCE: III

2.2.1.3. Episiotomy and SUI

In a recent study of Bø et al. [94], comparing vaginal resting pressure, pelvic floor muscle strength and endurance and prevalence of urinary incontinence at 6 weeks postpartum in women with and without episiotomy, concluded that PFM function and prevalence of postpartum UI were not affected by a lateral or mediolateral episiotomy. LEVEL OF EVIDENCE: III

2.2.2. Role of Pelvic Organ Prolapse (POP)

Failure of bladder, bladder neck, and urethral support is often part of more extensive defective pelvic organ support. Poor pelvic organ support can lead to pathological pelvic relaxation in one or more compartment(s). Marinkovic and Stanton [95] published a review of 97 articles regarding incontinence and voiding difficulties associated with POP. The authors concluded that POP appears to have significant clinical effects on urethral and voiding function; that should be quantified preoperatively to allow appropriate surgical intervention, with the aim of restoring vaginal function and correcting concurrent incontinence, whether overt or occult. Not uncommonly, POP can lead to bladder outlet obstruction, detrusor overactivity , and latent SUI that is unmasked only with reduction of the POP (potential, occult, latent, or unmasked SUI). [96] It is recognized that POP surgery can improve voiding dysfunction and unmask SUI by alleviating the urethral kinking causing outlet obstruction. [97] The findings of Karjalainen *et al.* [98] , showed that odds for occult SUI is 10.9 times higher with the cystocele with an intact retrovesical angle than with the cystocele with an open retrovesical angle. LEVEL OF EVIDENCE: III

Burrows *et al.* [99] described symptoms of bladder, bowel, and sexual function in 330 women with POP, comparing different degrees of prolapse staged by POP-Q system. Women with SUI symptoms had less advanced prolapse (median 5 cm less prolapse in apical compartment) than those without SUI. In a large community-based questionnaire survey, 44% of women who had prolapse symptoms also complained of SUI and 37% of overactive bladder. [100] LEVEL OF EVIDENCE: II

SUI can be functionally masked by POP. SUI may be uncovered by POP surgery and clinically continent women are at risk for developing symptomatic SUI after surgery.

The prevalence of latent SUI occurring after POP surgery is between 40 and 50% according to two large prospective randomized clinical trials. [101,102] LEVEL OF EVIDENCE: II

The large survey study using a validated SUI specific quality of life questionnaire completed by an unselected population of patients undergoing POP surgery followed up between 1 and 3 year after surgery, noted a 42% prevalence of SUI. [101] The degree to which these patients were bothered by their incontinence and how and when they seek therapy was less clear. The 2-year post-op questionnaire survey noted that 1/3 of their patients were moderately or severely bothered by their incontinence but only 5% sought further

surgical correction. From this study it is clear that 40-50% of patients develop SUI but it is less clear on how bothersome this is, and whether patients seek further surgical interventions. LEVEL OF EVIDENCE: II

This is an area that needs more investigation as the ultimate goal is to reduce the need for further procedures following POP surgery.

The pathophysiology of latent SUI has not been studied extensively. There are a few older studies involving small numbers of subjects suggesting that patients with advanced prolapse experience an obstructive effect of the prolapse on the urethral closure mechanism. One of these studies noted that maximal urethral closure pressures (MUCP) dropped from75 cm H_2O to 45 cm H_2O when the prolapse was reduced during urodynamic testing. [103] In another study subjects with prolapse beyond the introitus had an increase in their MUCP when they performed Valsalva, suggesting that as the prolapse was pushed out the urethra became more obstructed. [104]

In a more recent study Mueller *et al.* [105] noted that, although prolapse reduction significantly decreases MUCP, it does not alter intrinsic neuromuscular activity of the striated urethral sphincter: prolapse reduction resulted in a clinically and statistically significant decrease in maximum urethral closure pressure (31%) but it had no impact on quantitative urethral electromyography.

A more anatomic description of this phenomena was conducted using videourodynamics and a Gehrung pessary to support the POP during the exam. In this study the investigators demonstrated a hypermobile open bladder neck of SUI subjects with POP when the prolapse was reduced by the pessary. They did not study these same patients with the prolapse unreduced to describe the anatomy of the prolapse related continence mechanism. This points to the prolapse acting as an external force obstructing the urethral lumen and either through kinking or compression against the inferior pubic symphysis. [106]

Evidence of reduced peptide-containing innervation of perineal and periurethral muscles in women with SUI and POP has emerged [107], suggesting a neural abnormality in their pathogenesis. Connective tissue alterations such as decreased a-1 antitrypsin expression and altered elastin metabolism [107] , decreased collagen concentration [108], and decreased oestrogen receptors [109, 110] have been described in women with urinary incontinence and POP. LEVEL OF EVIDENCE: III

The role of urodynamic studies (UDS) before prolapse surgery remans contentious and hotly debated. Currently, it has been impossible to reach a universal consensus on the role of UDS before prolapse surgery in women with concomitant symptomatic or occult SUI. It is clear that UDS has an important role in preoperative identification of occult SUI, could add some information in women undergoing POP surgery and could facilitate counselling of patients as recently demonstrated by Martin *et al.* [111] LEVEL OF EVIDENCE: III. Weber *et al.* [112] showed that urodynamic testing in this setting is not cost-effective relative to basic office evaluation. They claimed that is possible that UDS could better identify and define some lower urinary tract dysfunction, such as a preoperative detrusor overactivity or occult SUI, but this information rarely leads to either a change in the management plan or in the type of surgical procedure. LEVEL OF EVIDENCE: III

Two randomized trials evaluated whether or not UDS may improve objective and subjective surgical outcomes in the treatment of SUI with mid-urethral sling procedures. [113, 114] However, these studies included a very selected population of women with SUI, the so called “uncomplicated” patients. LEVEL OF EVIDENCE: II.

Serati et al. [115] showed that “uncomplicated” patients represent a minority among female SUI patients evaluated before surgery. In “complicated” patients, the role of urodynamics has not been challenged and remain mandatory. LEVEL OF EVIDENCE: III

Other studies have identified different urodynamic variables (such as the median Valsalva Leak Point pressure (VLPP) and Maximum Urethra Closure Pressure (MUCP) > 40 cm H2O) as able to predict efficacy of anti-incontinence procedures and post-surgical voiding dysfunction risk [116, 117]

In 2009 Digesu *et al.* [118] showed that UDS could demonstrate that 20% of women with a history of pure SUI might not need any surgery at all. Serati *et al.* [119] showed that UDS are able to demonstrate that several patients with symptoms of pure SUI were affected by underlying detrusor overactivity and thus were ineligible for surgery.

UDS may be a useful tool in the preoperative work-up of all patients with SUI, predicting postoperative outcomes and avoiding unnecessary surgical procedures. [120] LEVEL OF EVIDENCE: III

New well-designed randomized studies are necessary to improve our understanding and to identify additional risk factors to facilitate tailoring a patient´s preoperative assessment and surgical counselling.

The surgical management of women with POP and latent SUI remains controversial and challenging. Maher *et al.* [121] determined the effects of surgery in the management of POP by searching the Cochrane Incontinence Group trials register (as of June 2004) for randomized or quasi-randomized controlled trials. The resulting metanalysis on the impact of POP surgery on continence was ‘limited and inconclusive’, but they report that 10% of women developed new incontinence symptoms postoperatively. LEVEL OF EVIDENCE: I

Levin *et al.* [122] prospectively evaluated 313 women who underwent TVT procedure for overt (228 women) or occult (85 women) SUI. Of them, about 50% also underwent POP surgery concurrently. Overall, for 241 women with at least a follow-up of 12 months, 6.6% had persistent mild SUI, an additional 7% had urodynamic evidence of asymptomatic sphincteric incontinence, whereas 8% developed de-novo UUI. LEVEL OF EVIDENCE: III

Among 130 women who underwent surgical treatment for an enterocele (75% the vaginal wall protruded through the introitus), 77% presented with SUI or detrusor instability. Sixty-seven percent of patients underwent Burch colposuspension with enterocele repair. Postoperative SUI requiring further treatment occurred in 10% after a mean period of follow up of 10 months, and cystocele developed in 1.5%. [123] LEVEL OF EVIDENCE: III

Urologists and urogynaecologists are faced with the challenge of determining which women with POP associated with SUI will benefit from concurrent surgical intervention for the UI. A comprehensive and anatomical approach to pelvic floor reconstruction is recommended, but no high-level evidence-based studies exist in the contemporary literature.

The intended goal of surgical correction of SUI and POP is durable restoration of normal anatomy and function, with symptomatic

relief and avoidance of morbidity. At present, few evidence-based conclusions can be drawn about when to surgically intervene for SUI in women who present with POP. The recent Cochrane Review published in 2018 by Baessler *et al.* [124] aiming to determine the impact of surgery for symptomatic POP with or without concomitant or delayed two-stage continence procedures to treat or prevent SUI on postoperative bladder function, included 19 RCTs (2717 women): the authors concluded that in women with POP and SUI (symptomatic or occult), a concurrent mid-urethral sling (MUS) probably reduces postoperative SUI and should be discussed in counselling. It might be feasible to postpone the MUS and perform a delayed (two-stage) continence procedure, if required. Although an abdominal continence procedure (Burch colposuspension) during abdominal POP surgery in continent women reduced de novo SUI rates in one underpowered trial, another RCT reported conflicting results. Adding a MUS during vaginal POP repair might reduce postoperative development of SUI. An anterior native tissue repair might be better than use of transobturator mesh for preventing postoperative SUI; however, prolapse recurrence is more common with native tissue repair. LEVEL OF EVIDENCE: I

Ramanah *et al.* [125] compared changes in urinary symptoms before and after POP surgery, using either laparoscopic sacrocolpopexy or transvaginal porcine dermis hammock placement with sacrospinous ligament suspension. Out of the 151 patients included, 87 patients underwent laparoscopic sacrocolpopexy, and 64 sacrospinous ligament suspension. Overall, after a median follow-up of 32 months, POP surgery improved urinary frequency, voiding difficulty, SUI, but not urinary urgency. Sacrospinous ligament suspension was more effective in treating SUI while laparoscopic sacrocolpopexy was more effective on voiding difficulty. Postoperative de novo symptoms were observed in 35.8% of patients with no difference between the two groups. The authors concluded that most preoperative urinary symptoms decreased after POP surgery with equivalent proportion of de novo symptoms after vaginal and laparoscopic approaches. LEVEL OF EVIDENCE: III

A recent study from Bideau *et al.* [126] demonstrated that preoperative SUI was the most important risk factor for postoperative SUI. However, given the higher risk of postoperative complication with concomitant MUS and the acceptable rate (29%) of the novo SUI without it, two-stage surgery seems preferable for patients with pre-operative SUI. LEVEL OF EVIDENCE: III

Recommendations for treatment of occult SUI have been recently summarized by Edenfield et al. [127]:

1) In women with prolapse and no SUI symptoms who are undergoing a vaginal prolapse repair, consider performing a MUS if the reduction cough stress test is positive preoperatively or the patient has a high risk of latent SUI. GRADE OF RECOMMENDATION C

2) If the reduction cough stress test is negative preoperatively or the patient has a low risk of latent SUI, defer a concurrent sling in women with prolapse and no SUI symptoms who are undergoing a vaginal prolapse repair. However, if the patient prioritizes decreasing the risk of latent UI, after discussion of risks and benefits, then it is reasonable to consider a concurrent sling in these women. GRADE OF RECOMMENDATION D

3) In women with prolapse and no SUI symptoms who are undergoing an abdominal mesh sacral colpopexy, a concurrent Burch retropubic urethropexy should be considered independent of preoperative reduction cough stress testing, if the surgeon's choice of anti-incontinence procedure is indeed a Burch. GRADE OF RECOMMENDATION B

4) If an anti-incontinence procedure is deferred at the time of a prolapse repair, it is still important to discuss the rate of postoperative latent UI with the patient as an interval procedure can be considered. This may indeed be some patients'preference. GRADE OF RECOMMENDATION D

2.2.3. Urethral position

Cohorts of stress incontinent women have demonstrated shorter and more cranial positioning of the urethral sphincter complex at rest [128] and smaller area and circumference of the sphincter muscles compared to continent controls [129]; the latter is consistent with MRI findings that stress incontinent women had significantly thinner striated urethral sphincter than continent women. [76] Authors reported both shorter [76, 130,15], longer [131] and no difference [80] in urethral length between stress incontinent and continent women.

Functional urethral length, defined as the length of the urethra along which urethral pressure exceeds intravesical pressure, presumably represents the location of the urethral sphincters. Several studies [15, 130, 132, 133], but not all [134] found greater functional urethral length in continent than in stress incontinent women. Shorter functional urethral length appears to be associated with greater severity of SUI. [15, 135] A metanalysis showed that functional urethral length was 3.58 mm (95% CI −5.83 to −1.33 mm) shorter in stress-incontinent women (n = 521) compared with continent women (n = 109). [1]

Another metanalysis of six studies suggests that bladder neck funneling (or dilation) is five-fold (risk ratio = 5.04, 95% CI 2.12–11.97) more prevalent at rest and 5.52 (95% CI 0.60–50.54) times more prevalent during straining among stress incontinent than continent women. [1] LEVEL OF EVIDENCE: III

2.2.3.1. Urethral support

Para-urethral connective tissues

Dense connective tissue arises primarily from the vagina and periurethral tissues and attaches to the pelvic wall laterally at the arcus tendineus fasciae pelvis and to the medial edge of the LAM (these supportive tissues are often referred to as the "pubo-urethral ligaments," although they do not insert exclusively into the pubic bone or attach directly to the urethra). Lesions of the urethral support structures were more prevalent in stress-incontinent than in continent women. [76, 77, 136]

In one study, defects in the periurethral ligament were found in 76% of stress incontinent women and in 32% of parous controls [76]. While greater pubovaginal distance and periurethral ligament disruption were significantly associated with SUI, in a multivariable model, only periurethral ligament disruption was significantly more common in incontinent than in continent women. [137] Among 31 middle-aged women, periurethral ligament symmetry reduced the odds of incontinence by 87%. (98) The urethropelvic ligaments were significantly thinner in stress-incontinent women, but the length of the pubourethral "ligaments" was similar between women with and without SUI. [138] LEVEL OF EVIDENCE: III

2.2.3.2. Bladder neck position

Compared to their continent counterparts, women with SUI demonstrated shorter distances between the bladder neck and the lower margin of the symphysis pubis at rest and during straining [139] and

shorter distances from the bladder neck to the central axis of the symphysis pubis in standing, but not in supine position. [134, 140] In women with SUI, a larger distance from the symphysis pubis to the urethra at rest in supine position was observed, and the bladder neck tended to sit in a more posterior and caudal position [141] compared to continent women. Another study showed no difference in the resting position of the bladder neck in the horizontal or vertical plane between continent women and those with SUI [142]. Falah-Hassani et al. [1] were unable to conduct a meta-analysis for bladder neck position because of the variation in measurement approaches in the different trials (e.g., using the central axis of the symphysis pubis vs. a line through the apex and measuring the direct vs. perpendicular distance from the bladder neck to symphysis pubis). LEVEL OF EVIDENCE: III

2.2.3.3. Urethral angular orientation

Compared to continent women, women with SUI had larger rotation (α) angles (defined as the angle between the axis of the proximal urethra and central axis of the symphysis pubis [143, 144], the angle between a line drawn through the bladder neck parallel to the probe and a line through the apex of the pubic bone [145] or the proximal urethral rotation angle, with a lack of clarity regarding the task [146] at rest and during straining.

However, when defined as the angle between the vertical axis and the urethral axis (a.k.a. the urethral axis angle), there was no difference in α angles at rest between women with and without SUI, and, while during Valsalva there was no difference in one study, there were larger α angles in a stress-incontinent group in another study. [136, 147] The β angle (also referred to as the posterior urethrovesical angle, posterior vesicourethral angle or retrovesical angle) was measured as the intersection between lines drawn along the urethra and the bladder base, the angle from the bladder base to the symphysis pubis, the angle from the bladder neck to the vaginal wall or undefined. Regardless of definition, women with SUI typically had larger β angles at rest than continent women, with the exception of one study [15]. The metanalysis of Falah-Hassani *et al.* [1] showed there was a large effect of incontinence on the β angle, with larger β angles observed among stress incontinent than continent women.

Urethral mobility is assessed clinically using a cotton swab inserted into the distal urethra (Q-tip test) while women are supine and at rest. Although this test has limited accuracy, women with SUI demonstrated larger angular deviations of the cotton swab from horizontal compared to those without SUI [79]. Other findings include that, compared to continent women, women with SUI demonstrated a larger retropubic space [76] and a larger bladder neck symphyseal angle at rest [144], but iliococcygeal angles and levator plate angles [136] did not differ. LEVEL OF EVIDENCE: III

2.2.4. Summary of evidence:

a) Vaginal delivery (VD) is associated with a 67% increased risk of UI compared with caesarian section (CS) 20 years after one birth. LEVEL OF EVIDENCE: III
b) UI is higher among women who had CS than among nulliparous and even higher among women who had VD. CS seems to decrease postpartum UI but its protective effect seems to diminish over time and disappears after multiple deliveries. LEVEL OF EVIDENCE: II
c) Risk of SUI after forceps delivery is 1.4 times higher compared with spontaneous delivery and 1.7 higher compared with vacuum. LEVEL OF EVIDENCE: III
d) Planned CS for twin pregnancy reduced the risk of problematic SUI. LEVEL OF EVIDENCE: II
e) Rates of UI after elective and emergency CS are mixed. LEVEL OF EVIDENCE: III
f) There is limited evidence for levator ani muscle integrity and correlation with the pathophysiology of SUI. LEVEL OF EVIDENCE: III
g) Damage to the pelvic nerves (particularly the pudendal nerve) after VD has been demonstrated in women with stress incontinence. LEVEL OF EVIDENCE: III
h) Epidural analgesia and episiotomy seem to have no effect on the postpartum UI. LEVEL OF EVIDENCE: III
i) Latent SUI develops in roughly 40% of continent women with advanced POP following surgery to correct their prolapse. LEVEL OF EVIDENCE: II
j) External compression or urethral kinking aids the continence mechanism in women with advanced POP. LEVEL OF EVIDENCE: III
k) Only about 5% of patients who develop latent SUI will undergo interval surgical management of their incontinence. LEVEL OF EVIDENCE: II

2.2.5. Recommendations for practice

a) UDS should be considered for all women for preoperative identification of occult SUI. GRADE OF RECOMMENDATION B
b) Discuss with women with POP and SUI (symptomatic or occult) that a concurrent MUS probably reduces postoperative SUI. It is possible to postpone the MUS procedure and perform two-stage surgery. GRADE OF RECOMMENDATION A

3. ROLE OF CONNECTIVE TISSUE

Collagen is the main constituent of endopelvic fascia and abnormalities in the quantity, type and quality of collagen have been observed in women with stress incontinence. Several studies have reported a decrease in the total collagen content in women with SUI [148,149,150]; moreover, a defect in endopelvic fascia is also likely to be of functional significance given that the urethra is indirectly attached to the levators by endopelvic fascia and an intact arrangement assists in urethral positioning [151]. Collagen is mainly synthesized by fibroblasts in periurethral vaginal wall tissue. Type I collagen content is significantly decreased in periurethral vaginal wall tissues and cultured vaginal fibroblasts from women with SUI. Furthermore, fibroblasts from women with SUI exhibit significant decreases in the expression levels of TIMP-1, TIMP-2 and TIMP-3, while the mRNA expression levels of MMP-1, MMP-2, and MMP-9, which reportedly increase collagen degradation in stress incontinence, are significantly increased. [152]

Stress incontinence may be acquired through conditions causing changes in connective tissue:

- SUI is more common with increasing age. In postmenopausal women, there is loss of muscle in the urethra and formation of collagen cross-links in the urethra stabilizes prevents remodelling and flexibility [153].
- Stress incontinence is more common in multiparous women. There is also evidence to suggest that trauma during childbirth may cause neuromuscular injury. However, changes in connective tissue also occur during pregnancy. Fascia becomes more elastic and vulnerable and women who have antenatal stress incontinence might have a greater degree of fascial weakness compared with those who remain continent [154]. Women who develop antenatal stress incontinence, even when it resolves

in the postnatal period, are twice as likely to develop it again in the future compared with those without antenatal stress incontinence [30]. The hormonal changes during pregnancy or abnormal remodelling of collagen may be important in the development of these conditions. The fact that incontinence may be seen during pregnancy might also be consistent with the hypothesis that the normal mechanical and hormonal effects of pregnancy unmask women with an inherently weak continence mechanism.

4. ROLE OF URETHRA AND ISD

Recent symposia sponsored by the National Institutes of Health [155] have highlighted the growing evidence that urethral failure is a primary factor in the cause of stress incontinence. The idea that primary urethral weakness could cause urinary incontinence independent of weakness in urethral support appeared in a classification proposed by Blaivas *et al.* [156]. In their classification, they named this Type III incontinence to distinguish it from Types I and II, based on bead-chain cystourethrograms, each of which showed movement, while Type III did not. This remains in the contemporary literature, although it has now been largely replaced by the term intrinsic sphincter deficiency (ISD), focusing attention on urethral elements which appear to be independent of vaginal position and mobility. These elements include pudendal innervation, striated sphincter mass and function, and urethral smooth muscle, mucosa and submucosal cushions.

When ISD was first introduced as a concept to explain surgical failures and the presence of stress incontinence in the absence of vaginal mobility, the diagnostic tendency was to consider the cause of stress incontinence as a dichotomy, due either to hypermobility (displacement, or prolapse of the vaginal wall) or ISD. The typical patient with ISD was described as having low urethral closure pressures, a “stovepipe” appearance on cystoscopy, and opening or funnelling of the urethra under resting or minimal increases in intra-abdominal pressures on radiographic images. The common causes were thought to be surgical injury, ischaemia following previous pelvic or vaginal surgery or radiation damage. The evidence that weakness in the ability of the urethral muscles to maintain closure, is very strong and it appears that the examples of “pure” ISD may have represented the most advanced or extreme forms.

4.1. Hypermobility Vs. Isd: From Dichotomy To Continuum

Currently, there appears to be a shift away from the idea that stress incontinence as being due either to hypermobility or ISD. This has arisen in part because of the of the concept of Valsalva Leak Point Pressure (VLPP) [157,158] and more recent analyses of long term results of stress incontinence surgery [159]. Most importantly, there are strong data from case control studies of well-matched continent and incontinent women showing that reduced urethral closure pressure explains 50% of the occurrence of stress incontinence and that adding urethral support parameters increases this prediction by an additional 11% showing that both factors are important.

VLPP emerged as an alternative method to study urethral closure during stress for studies of urethral bulking with collagen. Investigators recognized that improvements in continence following urethral bulking did not correlate with urethral closure pressures but did correlate with the amount of pressure required to produce leakage in the absence of intrinsic detrusor contraction. Although VLPP still lacks specific anatomic or theoretical grounding, problems related to standardization of recording methods and associated prolapse remain, low VLPP (without specified or established values) has been widely embraced as an indicator of ISD.

Just as the concept of VLPP blurred the previous distinction between simple ISD and simple hypermobility, long term outcome studies of correction of hypermobility have suggested that there may be more urethral weakness among patients with hypermobility than previously considered.

Long term outcome studies of stress incontinence surgery show a greater failure rate of many of the commonly performed stress incontinence operations than had been generally appreciated, and that slings providing direct sub-urethral support seemed to give the greatest long term protection against recurrence of incontinence [159]. Since slings had traditionally been the procedure of choice for recurrent incontinence or “Type III” (now ISD) incontinence, the possibility that ISD was more common than previously thought was more widely considered. Recently, Horbach and Ostergaard have found that age is a significant, independent predictor of ISD in the setting of urodynamic stress incontinence [160], suggesting that age-related reduction in muscle mass, slowed reflexes or repeated episodes of prolapse may all contribute to the condition.

Perucchini *et al.* [161, 162] showed that aging is associated with a decrease in the number and density of urethral striated muscle fibres at the bladder neck and along the ventral wall of the urethra [241]. The clinical correlate of this is the 15% per year decline in urethral closure pressure in nulliparous women where age effects can be determined without the confounding effect of childbirth [163].

These two developments have led to a growing clinical impression that some degree of ISD may exist in many patients who, until recently, were thought to have only hypermobility as a cause of their incontinence. Atypical expression of this approach can be found in the conclusion of Kayigil *et al.* [164] following examination of 50 patients; “The high rate of intrinsic sphincter deficiency in patients with urethral hypermobility indicates that the incidence with stress incontinence may be greater than previously believed, and may influence the apparently higher failure rates after bladder neck suspension.” In contemporary clinical practice, this impression has given rise to a growing tendency to recommend suburethral sling surgery as a form of primary surgical treatment for all women with stress incontinence, whereas formerly this approach was reserved almost exclusively for patients with recurrent stress incontinence or significant ISD [165, 166].

4.2. Direct studies of Urethral Function and Support

As recognition of the importance of urethral function has increased, so too have the number of investigations of urethral position, urethral closure and transmission pressure profiles, Valsalva leak point pressure measurements and electromyographic examinations of the pudendal nerve and the striated sphincter.

4.2.1. Studies Of Urethral Position

Stress incontinence is frequently associated with loss of urethral position. This has been the primary pathophysiological paradigm since the observations of Hodgkinson and Jeffcoate and Roberts. Similar observations are still reported today [167, 168]. Even when some displacement is seen in continent nulliparous females, incontinent women show a greater degree of mobility [169].

This pathophysiological mechanism has been supported by different authors [170, 171] using a rat model. Both and induced trauma on structured supporting the urethra (such as the pubourethral ligaments) and uretherolysis resulted in SUI in short and long term because of increased urethral mobility.

Successful suspensory operations, whether by sling or paraurethral suspension stabilize urethral position [42] and, when studied, increase pressure transmission during stress. It is not clear if the active contraction of urethral support seen in the female is restored after surgery, nor is it known if it is necessary for continence. It has been suggested that passive support alone is what restores continence after suspension. Caution is needed before assuming surgical success proves a specific causal mechanism to avoid the "post hoc, ergo proctor hoc fallacy." Application of this logic would for example, suggest that success of bariatric operations in causing weight loss "proves" that obesity is caused by a large stomach.

4.2.2. Studies of urethral pressure and resistance

Stress incontinence is thought to be characterized by a decrease in urethral transmission profiles and resting closure pressure. The correlation between low resting pressures and low leak point pressures is still controversial. With a bladder filled up to 200ml, Almeida *et al.* [172] reported a significant correlation between MUCP and LPP. Patients with a LPP of 60 cm H_2O or less also had shorter urethral functional length and lower sphincter activity. Moreover Sinha *et al.* [173] showed that women with urodynamic stress incontinence were more likely to leak at cough leak point pressure than the Valsalva manoeuvre, with the opposite happening for women with detrusor overactivity. On the contrary Martan *et al.* [174] found no significant correlation between MUCP and VLPP.

Different urodynamic parameters have also been posited to assess urethral function in with women with stress incontinence. Digesu *et al.* [175] showed that urethral resistance pressure (URP) and pressure flow parameters were reduced in women with stress incontinence. Salvatore *et al.* [176] found that reduction in opening vesical pressure was significantly correlated with ISD. Sonographic studies have recently shown a relationship between low urethral resistance and decreased urethral smooth and skeletal muscle layers [177].

Improvement in transmission pressures is associated with successful outcomes after suspensory operations for stress urinary incontinence [12, 16, 19, 20, 178,179]. The exact mechanism for this increase in transmission is not clear. Increased exposure to intra-abdominal forces [21, 180,181] and compression against the pubis by the pelvic viscera [260] has also been suggested but is anatomically implausible. The final position of the urethra may not be the key variable [182].

4.2.3. Electrophysiological studies of urethral function

Snooks and Swash [183, 184] first brought attention to the importance of urethral denervation after childbirth and its possible contribution to urinary and faecal incontinence. Stress incontinence is frequently associated with a decline in the electrophysiological function of the pudendal nerve [185], the striated urethral sphincter [186], and the pelvic floor muscles. More recent studies continue to support the finding of prolonged pudendal nerve terminal motor latency in SUI [187].

With the use of animal models simulating intrinsic urethral deficit through periurethral cauterization, urethral sphincterectomy or pudendal nerve transection, different authors reported a decrease of LPP lasting for weeks [188-190]. Injury of the pudendal nerve determined a dramatic decrease of urethral resistance causing urinary loss during an intrabdominal pressure increase.

Electromyographic studies of normal sphincter function show that in continent women, pressures begin to rise in the urethra before rising in the bladder, suggesting an active muscular component in generating this pressure [191].

Women with stress incontinence have an altered pattern of pelvic floor muscle response during successive coughing efforts [192] with a sharp decrease in MUCP after repeated coughs [193]. EMG studies have also shown that women with persistent stress incontinence after previous surgery have poorer urethral neuromuscular function than naïve stress incontinent women [194]. Experimental studies of urethral function and the role of Onuf's nucleus in the sacral spinal cord have led to recent practical innovations in the development of serotonin uptake inhibitor agents in the treatment of stress incontinence [195]. Most electrophysiological studies have concentrated on motor rather than sensory innervation, however, and the role of urethral sensation in urodynamic stress incontinence is unknown.

Needle electromyographic studies to assess urethral sphincter function have been performed by Takahashi *et al.* [186] to determine the electromyographic features of the striated urethral sphincter due to intrinsic sphincter deficiency (ISD). Myogenic dominant damage of the striated sphincter were suggested to contribute to the etiology of ISD [196]. Heesakkers *et al.* proposed circumferential sphincter surface electromyography (CSS-EMG), a less invasive and, therefore more patient friendly procedure, of the urethral sphincter and to identify CSS-EMG parameters for diagnosing ISD [197]. The authors found that the Average Rectified Value of the Motor Unit Action Potential, a measure of strength of the urethral rhabdosphincter, at 12 o'clock at 100% squeeze of the urethral sphincter, could discriminate between ISD and non ISD.

4.2.4. Genetic Factors

Recent research is now focusing on the identification of factors related to stress incontinence which might be genetically determined. Chen *et al.* [198] reported that genes involved in elastin metabolism were differentially expressed in vaginal tissue from women with stress incontinence, suggesting that elastin remodelling may be important in the molecular aetiology of stress incontinence. Wen *et al.* [199] recently reported a decreased expression of alpha2-M mRNA and protein and protease inhibitor activity in the vaginal wall tissues of women with stress incontinence. Wu *et al.* provided strong evidence that

microRNA-214 (miR-214) could promote fibroblast differentiation of adipose-derived mesenchymal stem cells (ADMS Cs) by down-regulating mitofusin-2 (Mfn2) to improve pelvic floor dysfunction in Sprague Dawley rats with birth trauma. [200] Whether these effects are mediated by altering the connective tissues supporting the urethra or those in the urethral wall itself is yet to be determined.

There is a need for a hypothesis which would integrate these various observations regarding hypermobility, ISD and pudendal nerve function, place them within the context of an abnormal pelvic floor and provide a model to guide research and studies of the natural history of the condition.

4.2.5. Role of advanced imaging in understanding pathophysiology

Many imaging modalities have been used to improve our knowledge of pelvic floor dysfunction, such as: radiographic imaging, ultrasound, computed tomography and magnetic resonance imaging (MRI).

Radiographic imaging has provided considerable insight into the pathophysiology of stress incontinence, ever since the advent of bead chain cystograms and simple static and straining lateral cystograms.

MRI and real time ultrasonography, in addition to showing the events of stress incontinence on both a global pelvic and local urethral scale, have suggested a relationship of the proximal urethra to vaginal wall movement.

4.2.6. Magnetic resonance imaging

Dynamic fastscan MRI can visualize all compartments of the female pelvis during increased intraabdominal straining [201]. MRI is comparable to standard cystography in demonstrating cystocele defects [202] and in determining the structural failures that are responsible [203]

Using the pubococcygeal line or Pelvic Inclination Correction system (PICS) [204] as a reference marker, the normal displacement of the bladder base, cervix or cervical cuff and the rectum can be identified and compared to women with prolapse. The urethra is shown in the context of global pelvic relaxation [205]. These studies show more soft tissue detail than earlier radiographic studies and continue to offer promising research opportunities. Recent studies have utilized an endovaginal coil to obtain higher resolution images of the urethra [206] but improving magnet strength and software has now largely rendered this unnecessary.

Dynamic MRI with cine-loop reconstruction produces vivid, intuitively appealing images which can show movement of all compartments of the relaxed pelvis during straining [205]. Static MRI shows details of urethral and peri-urethral anatomy and the striated sphincter can be clearly seen [207]. Pending further improvements in resolution, MRI remains a most promising tool for studying details of urethral movement [208].

Functional MRI has recently been evaluated to assess the efficacy of pelvic floor muscle training with EMG- biofeedback in women with stress incontinence. After a 12-week training period a more focused activation in the primary motor and somatosensory cortical representation sites of the lower urogenital tract was found [209].

Madill *et al.* have recently proposed another clinically promising aplication of MRI. They hypothesized that the Pelvic Floor Muscle (PFM) rehabilitation program would also exercise the striated urethral sphincter and that this would be demonstrated by hypertrophy of the sphincter on MRI [210, 211]. Their results appear to demonstrate that MRI is able to show that PFM training for SUI also trains the striated urethral sphincter and that improvement in incontinence signs and symptoms is associated with sphincter hypertrophy in older women with SUI. These findings support previous ultrasound (US) data showing an increase in urethral cross-sectional area following PFM training and extend the previous findings by more specifically assessing the area of hypertrophy and by demonstrating that older women present the same changes as younger women when assessed using MRI data. Similar data on the role of hypertrophy of the urethral sphincters after effective PFM training, and therefore in the pathophysiology of SUI, were observed also by McLean *et al.*, using a two- and three-dimensional ultrasound imaging of the pelvic structures [212].

Very recently, Macura *et al.*, stated that MRI might play an important role in assessing the contribution of hypermobility and sphincteric dysfunction to SUI in women when considering treatment options; however, the study sample was only small [213].

Ultrasonography is simpler and less expensive in comparison with MRI, and, for now, provides better visualization of moving structures.

4.2.7. Real time ultrasonography

Ultrasonography offers the advantage of capturing organ movements in real time. Several sonographic approaches have been used for the study of stress incontinence: suprapubic, translabial and transperineal.

As resolution of sonographic probes has improved, the detail previously best seen with the transrectal approach may now be seen by a transperineal approach. Earlier studies with a transrectal approach have shown that funnelling of the proximal urethra was the sonographic sign most-frequently associated with loss of urine [214].

In the study of Schaer *et a.l* in about half the patients with stress incontinence. funnelling was seen only with straining. In the other half, some degree of funnelling was already present at rest, increasing with straining and present with actual leakage. [215], Enhanced views of the urethra were possible with sonographic contrast material.

Most recently, 3-D reconstruction from translabial views of the urethra has been used to compare findings in normal volunteers and those with ISD [216].

A recent sonographic study of women with stress urinary incontinence found funnelling at rest in 109 of 330 patients and found that the degree of vaginal relaxation as well as the parameters of intrinsic urethral function, including VLPP and urethral closure pressures were worse in patients with funnelling than without. The authors of this study concluded that: “In primary genuine stress incontinence, bladder neck funnelling on ultrasound cystourethrography implies the potential coexistence of poor anatomic support and an intrinsic sphincter defect [217].” Ghoniem *et al.* [218] also found that urethral funnelling was more likely to be associated with low closure pressures, low

VLPPs, and a higher incidence of ISD in patients with stress urinary incontinence. However, recently, Tunn *et al.* [219] reported no association between the ultrasound findings of urethral funnelling with stress incontinence using an introital approach, demonstrating it only in 59% of the patients with stress urinary incontinence. Issues of whether authors are discuss funneling at rest or during stress events needs to be kept in mind as they are different things.

Improved soft tissue detail seen with ultrasound has permitted an extension of these original observations. The anterior and posterior walls of the proximal urethra appear to move differently during increases in intra-abdominal pressure. At first, they appear to move together: the urethra begins its descent as a single unit. At some point, however, the anterior urethra becomes arrested in its rotational movement and appears to move more slowly. The posterior portion of the urethra continues to descend along with the vaginal wall [214,220].

This difference in movement suggests a shearing apart of the two walls, leading to the appearance of funnelling, which can be seen as urine leaks out of the urethra.

On Valsalva, the proximal urethra rotates in a postero-inferior direction approximating to the symphysis pubis. This movement can be measured by comparing the angle of inclination between the proximal urethra and any other fixed axis. No normal values of bladder neck descent have been defined but cutoffs of 20, 25 and 30 mm have been reported to classify urethral hypermobility [221 222]. The anatomical and functional integrity of the PFM have an important role in the urethral support system and, therefore, in the continence mechanism. Women with UI, compared to continent subjects, have less effective PFM in terms of: strength, reduced endurance, reduced thickness, coordination of PFM and lower abdominal muscles, and altered elletromyographic activity [223-225]. With transperineal ultrasound it is possible to evaluate the urethral displacement towards the pubic bone caused by pelvic floor muscle contractions [226]. This mechanism is involved in maintaining urinary continence by determining a good efficacy in intraurethral pressure transmission [227].

These anatomical considerations, combined with current knowledge about pudendal nerve activity in normal, prolapse or stress incontinence, suggest an inter-relationship regarding urethral closure and vaginal movement. As intra-abdominal pressure increases, the proximal urethra experiences two kinds of forces, which may lead to opening. The first of these is a shearing force produced by the unequal separation of the anterior and posterior urethral walls from the pubis during straining. This is the effect of vaginal mobility on urethral closure. The second is an expulsive force, produced by the transmission of intra-abdominal forces to the bladder, which must be resisted by the urethra if opening is to be prevented.

The urethra resists this primarily by intrinsic closure of the pudendally innervated striated sphincter, aided by vaginal support.

3D ultrasound has introduced new insights in the image of urethral sphincters. Athanasiou *et al.* [228], using a transvaginal approach, reported a close correlation between the urethral sphincter volume and the degree of incontinence assessed on videocystourethrography (r = .-65; P <0.001). This author reported that this group of women have urethral sphincters that are shorter, thinner, and smaller in volume compared to controls.

Urethral vasculature has also been postulated to play a role in the continence mechanism and different Doppler parameters have been studied to evaluate correlation with stress urinary incontinence. Tsai *et al.* [229] reported that urethral vasculature, and in particolar the anterior branch of the middle urethral vessels, is less likely to be seen after menopause (89.1% vs. 79.2% pre- and postmenopause, P = 0.030). In postmenopausal women hormone replacement therapy did not affect the appearance of the urethral vessels. However, some authors [205] reported fewer periurethral vessels and lower flow in women suffering from stress urinary incontinence whereas others [230] could find no difference in the appearance of the urethral vasculature in subjects with or without stress urinary incontinence.

It is likely that shearing and expulsive forces are generated simultaneously as intra-abdominal pressure rises. One can easily imagine that the urethra can be brought to a continence threshold beyond which closure cannot be maintained. One can further imagine that repeated episodes of prolapse may eventually stretch, tear or attenuate sphincter mass and contribute to a chronically weakened urethra manifested by low VLPP or low urethral closure pressures, characteristic of ISD. After severe or prolonged untreated prolapse and stress incontinence, vaginal support alone may not be sufficient to correct the deficiencies of an exhausted sphincter. Although theoretical rather than evidence-based, such considerations may direct future research efforts towards a more integrated hypothesis regarding stress incontinence in women. The relative contributions of abnormal vaginal mobility and intrinsic urethral function should be considered as part of a continuum rather than a dichotomy. Current research interest has concentrated mostly on ISD as the primary cause of SUI in women, but the relationship of the many factors affecting urethral support and function need consderation in interpreting emerging findings.

Recently, Najjari *et al.* [131], using perineal ultrasound, compared the anatomical length of the urethra with the urodynamic functional urethral length to detect anatomical insufficiency of the urethra. The authors showed perineal sonographically measured urethral length was significantly longer in incontinent compared to continent patients and functional uretral length was significantly shorter in incontinent patients than in the control group.

Using ultrasound, evaluation of Levator Ani Muscles (LAM) found asymmetry of the puborectalis muscles more common in stress incontinent women in one study [206], and, while there were no differences between women with and without SUI in terms of overall levator defects (asymmetry, hypertrophy or disruption) in a subsequent study [78], a significantly greater percentage of pubococcygeal muscle defects was found in stress incontinent women (45–66%) than in their continent counterparts (10–28%). There is no high level evidence of significant morphological differences or in terms of strength between continent women and incontinent women.

5. OTHER PATHOPHYSIOLOGICAL MODELS

Reviewing all the available evidence on the pathogenesis of SUI, DeLancey tried to produce a new model to describe the interaction between the different possible mechanisms. Despite

progress made to date, our understanding is far from complete. The urethra is a dynamic structure with variation in closure from second to second, minute-to-minute, day to day and year to year. The role of the submucosal vascular plexus is still poorly understood; the complex neural control mechanisms that allow for temporary and total relaxation during voiding, that somehow know when to re-establish normal muscle function are still not entirely understood. In addition, although urethral support is not as important as previously thought, it is one of the contributing factors for stress incontinence. Understanding what it is about urethral support that lessens continence is vital. However, the finding that maximal urethral closure pressure, and not urethral support, is the factor most strongly associated with stress incontinence implies that improving urethral function may have therapeutic promise. Racial disparities exist in incontinence, and the biological basis for these differences should help our understanding [33, 231.].

5.1. Pathophysiology Of Stress Urinary Incontinence In Obese Women

Obesity has become one of the most worldwide prevalent pathologic conditions; this may be a relevant cause of several chronic diseases, such as hypertension, diabetes, dyslipidemia, many types of cancers, cardiovascular diseases [232, 233]. There is a strong relationship between obesity and urinary incontinence (UI) and weight gain is associated with a higher prevalence and severity of symptoms of UI, and in particular of Stress Urinary Incontinence (SUI)[234]. However, the pathophysiological mechanisms which explain this correlation are not completely clear and well-demonstrated.

Several studies have showed that BMI is strongly correlated with intra-abdominal pressure, and that increases in intra-abdominal pressure also increase intravesical pressure and exerts an increased stress on pelvic floor muscles, a risk factor for SUI [234, 235]. Moreover, the increase of abdominal pressure might also impair the innervation of these muscles [236]. Unfortunately, in most cases, obese patients also have many other concomitant risk factors for SUI, such as multiparity, oestrogen deficiency and history of surgical procedures for the treatment of pelvic organ prolapse. However, some studies showed that, in these women, obesity is an independent risk factor for SUI [237].

Obesity seems to be related to a higher prevalence of every type of UI, but a recent study of Brucker *et al.* demonstrated that SUI is significantly more prevalent in obese patients than Urinary Urgency Incontinence (UUI) (25% vs 15%) and that this finding is even more evident in the subgroup of younger patients (<50 years) (27% vs 11%) [238]. Waetjen *et al.*, in a study that compared the characteristics and baseline factors associated with prevalent and incident urinary incontinence in a diverse cohort of midlife women found that a BMI increase of 5 kg/m^2 increased SUI by 30% and UUI by 15% [239]

Several authors have demonstrated that increased sagittal abdominal diameter was associated with elevated abdominal pressure in obese compared to non-obese patients [240, 241]. Moreover, urodynamic evaluations may also highlight the association between increased BMI and increased abdominal pressure in female patients with SUI [236, 242]. It seems that abdominal pressure at maximum cystometric capacity significantly increases by 0.4 cm H_2O per Unit of BMI and of 0.4 cm H_2O per 2 cm increase in abdominal circumference in incontinent obese women [243]. Swenson *et al.*, in a recently published secondary analysis of a case-control study, assessed the effect of BMI on the components of the continence mechanism. The authors showed that the primary association between obesity and SUI is higher cough pressures which place increased demands on the continence system, rather than changes in urethral function or urethrovaginal support. They concluded that obese women have higher resting intravesical pressures and generate more pressure during maximal cough compared to women with BMI in the normal or overweight range [244].

Other authors, based on the systemic impact of obesity, supposed that the correlation between weight gain and SUI may not be solely due to increased abdominal and vesical pressure. Specifically, the association between obesity and neurogenic diseases has been proposed. Obesity has been shown to be a risk factor for peripheral nerve dysfunction, in terms of conduction in the median, peroneal, sural, and tibial nerves [245-247]. Additionally, obesity as a component of metabolic dysfunction or metabolic syndrome may negatively influence neural function. Callaghan *et al.* found a prevalence of polyneuropathy of 3.8% in lean controls, 11.1% in the normoglycemic obese, 29% in the prediabetic obese, and 34.6% in the diabetic obese participants ($p < 0.01$ for trend) [248]. Finally, the obese have a higher risk for lumbar intervertebral disc herniation than normal weight women [249]. Although there is an association between obesity and neurological impairment, it is not clear how much this may really influence the pathophysiology of SUI in obese women.

Lee *et al* , investigated the contractile properties of the urethral striated sphincter in obese and lean female rats in an *ex vivo* organ bath study.Ten 12-week-old Zucker Fatty (ZF) and 10 Zucker Lean (ZL) female rats were used in this experiment. Compared to ZL controls, ZF rats had significantly impaired muscle contractile activity (MCA). Also, ZF rats presented early fatiguing of MCA and had a significantly greater percentage of MCA decline from baseline in the fatiguing test. This study showed that obese female rats had significantly impaired contractile properties of the striated urethral sphincter, suggesting urethral dysfunction could be an important contributor to SUI in obesity [250].

In conclusion, there is a significative association between obesity and SUI, and that the most relevant mechanism to explain this correlation is that over-weight and obese patients have a higher resting intravesical pressures and produce more pressure during maximal cough compared to women with a normal BMI. It is plausible that neurological and metabolic factors are involved in the pathophysiology of SUI in this group of patients but more data are needed.

6. CONCLUSIONS

A recent systematic review with meta-analysis perfectly summarizes the information and knowledge on the pathophysiology of stress urinary incontinence as a multifactorial condition. The authors demonstrated that deficits in urethral and bladder neck structure and support, neuromuscular and mechanical function of the striated urethral sphincter (SUS) and levator ani muscles all appear to be associated with SUI [1].

A lower functional urethral length was significantly associated to SUI. This anatomic parameter was 3.58 mm (95% CI −5.83

to −1.33 mm) shorter in stress-incontinent women (n = 521) compared with continent women (n = 109) [77; 131].

They also considered the role of bladder neck funneling (or dilation), measured using USS, MRI or cystourethrography and demonstrated that funneling is five-fold more prevalent among stress incontinent (n = 1195 and n = 181 for rest and straining, respectively) than continent women (n = 775 and n = 193 for rest and straining, respectively) [136, 146, 251]. However, they included studies affected by biases and confounding.

Urethral resistance and competence, measured in terms of maximal urethral pressure (MUP) and maximal urethral pressure closure (MUPC), is a highly relevant factor for urinary continence. MUP was lower in stress-incontinent (n = 1034) compared to continent (n = 336) women, and MUCP was lower in stress-incontinent (n = 1122) compared with continent (n = 342) women.

The role of the Levator Ani Muscle (LAM) is controversial. Conflicting results as well as the detection bias associated with LAM strength measurement and an overall lack of assessor blinding in studies comparing LAM strength between women with and without SUI, lead us to conclude that there is limited evidence for LAM strength impairment in SUI [252]

7. SUMMARY

We are approaching a new classification of stress incontinence which will integrate hypermobility and urethral dysfunction as inter-related elements. Certain concepts have stood the test of time, and they are included below:

- Many patients with urodynamic stress incontinence show urethral mobility (Level 2), though it is not yet known what it is about that mobility which permits urethral opening during stress.
- Some patients who present with minimal urethral mobility or who have recurrent stress incontinence after successful surgery have primary or residual sphincter insufficiency.
- Sphincter insufficiency is related to a decline in striated sphincter muscle mass and function as measured by electrophysiological studies of pudendal nerve and sphincter function, and MRI and sonographic estimates of muscle mass. If repeated episodes of vaginal traction can be shown to enhance sphincter damage, then the effect of early treatment of stress incontinence and prolapse on future development of ISD should be investigated, since advanced ISD remains difficult to treat.
- Successful operations can restore urethral position but probably do not restore urethral function. A good surgical outcome probably requires a certain reserve of urethral function. It is in the area of functional understanding of urethral anatomy that the greatest progress is likely to be made.

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III. IDIOPATHIC OVERACTIVE BLADDER AND URGE INCONTINENCE

1. INTRODUCTION

The International Continence Society (ICS) defines urinary incontinence (UI) as an involuntary loss of urine experienced during the bladder storage phase [1-3]. Urgency urinary incontinence (UUI) is defined as complaint of involuntary loss of urine associated with urgency [1-3]. Urgency is defined as the complaint of a sudden compelling desire to pass urine, which is difficult to defer [1-3].

The overactive bladder (OAB) is a storage symptom syndrome which is defined by urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence (OAB-wet) or without (OAB-dry), in the absence of urinary tract infection or other detectable disease [1-3]. Therefore, urgency is the defining symptom of the OAB syndrome. A better understanding of the genesis of urgency and its relationship to other aspects of bladder function is required to unravel the pathophysiology of OAB and to develop more effective treatments [4]. Owing to the difficulty in identifying the underlying pathology for the development of OAB in most patients, it is often labelled as “idiopathic”.

The ICS acknowledged that these symptoms are usually “suggestive of urodynamically demonstrable detrusor overactivity (DO) but can be due to other forms of urethra-vesical dysfunction” [1]. DO is defined as a urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [1]. However, OAB is not interchangeable with DO. only about half of patients with DO experience urgency [5,6], whereas among patients with urgency 44–69% exhibit DO during cystometric studies [7-10].

The definition of urgency as a complaint implies that it can only be measured in patients sufficiently cognitively intact to report it [4,11]. Quantifiable and objective demonstration of urgency is difficult, and thus surrogate measures are often used as outcome measures in OAB, leading to inconsistency between clinical trials. Urgency is a pathological sensation and does not necessarily involve the same mechanisms as those underlying the physiological urge to void upon bladder filling. Therefore, comparisons between urinary urge in healthy people and urgency in patients may help our understanding of the mechanisms involved in the latter but, in fact, may be misleading [11].

The emphasis on urgency, rather than DO, as the defining element of OAB gives the condition a subjective foundation which renders derivation of basic science insights challenging. The subjective nature of urgency makes development of animal models impossible. Despite of these limitations, most studies on mechanisms related to urgency/OAB have employed the use of isolated tissues and experimental animals. Non-voiding contractions remains the most frequently used surrogate parameter in experimental animal studies [11].

The pathophysiology of OAB and DO is still incompletely known, but most probably multifactorial and results from multiple potential pathophysiological mechanisms. Identification of

the underlying causes on an individual basis may lead to the identification of OAB phenotypes, paving the way for personalized medical care [12].

This section focuses on pathophysiology of idiopathic OAB and reviews studies that have provided insight into the mechanisms underlying OAB symptoms and DO.

DO may be further characterized as neurogenic in the presence of a relevant neurological condition [13]. The dependence of lower urinary tract (LUT) functions on complex central neural networks makes these susceptible to a variety of neurological disorders. Non-neurogenic aetiologies may be related to different mechanisms relating to the role of the urothelium, suburothelium, urethra, and central nervous system (CNS) in the pathogenesis of OAB [4]. This suggests that a "bladder afferent signaling" mechanism contributes to the OAB symptom complex. Each one of these mechanisms exerts their effect at different levels of the bladder afferent pathway, and we outline these various hypotheses below. (Figure 1). Recently, Peyronnet et al reviewed the a potential classification of OAB phenotypes according to urodynamic demonstration of DO and to pathophysiological factors; this section will widely cite this elegant and useful review that is the most recent and complete paper on the topic [12] (Table 1).

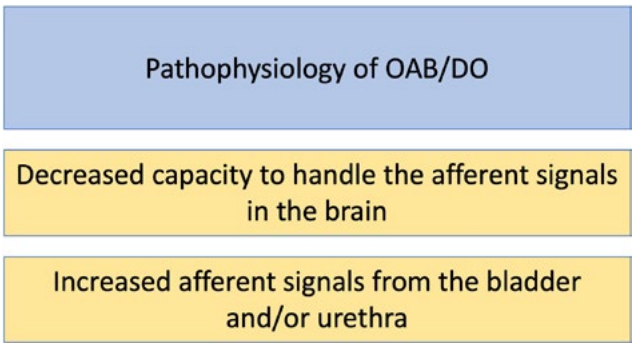

Figure 1: *Two possible origins of OAB symptoms: 1) decreased capacity to handle the afferent signals in the brain and, 2) abnormally increased afferent signals from the bladder and/or urethra.*

Table 1: Possible OAB phenotypes according to Peyronnet B, et al. Eur Urol. 2019 Jun;75(6):988-1000.

Peyronnet B, Mironska E, Chapple C, Cardozo L, Oelke M, Dmochowski R, Amarenco G, Gamé X, Kirby R, Van Der Aa F, Cornu JN. A Comprehensive Review of Overactive Bladder Pathophysiology: On the Way to Tailored Treatment. Eur Urol. 2019 Jun;75(6):988-1000. doi: 10.1016/j.eururo.2019.02.038.

Phenotyping according to pathophysiological factors	Phenotyping according to urodynamic demonstration of detrusor overactivity
Metabolic syndrome	Myogenic
Affective disorders	Urotheliogenic
Sex hormone deficiency	Urethrogenic
Urinary microbiota	Supraspinal
Functional gastrointestinal disorders	Urotheliomyogenic: detrusor underactivity
Autonomic nervous system dysfunction	
OAB = overactive bladder.	

2. PATHOPHYSIOLOGY OF INCREASED AFFERENT ACTIVITY

Different hypothetical mechanisms probably contribute in varying proportion to the complex mechanisms underlying the genesis of DO and the associated storage symptoms such as urgency composing OAB [12], have been put forward (Figure 2)

- The urothelium-based hypothesis: urgency originating from the bladder urothelium/suburothelium,
- The myogenic hypothesis: urgency originating from the detrusor,
- The urethrogenic hypothesis: urgency originating from the urethra,
- The detrusor underactivity hypothesis.
- Other factors

2.1. The Urothelium-based Hypothesis

2.1.1. Context [12]

OAB may be related to changes in urothelial receptor function and neurotransmitter release as well as in the sensitivity and coupling of the sub-urothelial interstitial cell network leading to enhancement of involuntary contractions [14,15].

In 1991, Creighton *et al.* reported that either DO or an abnormal perception of bladder filling could provoke the sensation of urgency [16]. Since then, several studies have shown abnormal detrusor sensory function in patients with OAB [17-19]. The role of increased activity of bladder afferents is well described [5,20] and supports the idea [5,21] of urgency resulting from urothelial/sub-urothelial dysfunction in some patients, which may not manifest as DO. UUI may indeed be less frequent in this subgroup of patients, but urinary frequency may be more common [18,22], and this is thought to be mediated by abnormal sensory and signaling properties of the urothelium and sub-urothelial fibroblasts [5,20] as well as possibly sympathetic dysfunction.

2.1.2. Molecular basis

There is increasing evidence that urothelial cells play an important role in modulation of bladder activity by responding to local chemical and mechanical stimuli and then sending chemical signals to bladder afferent nerves. Urothelial cells express various sensor molecules such as receptors of bradykinin, neurotrophins, purines (P2X and P2Y), norepinephrine (NE), acetylcholine ACh (nicotinic and muscarinic), epithelial sodium-channels (ENaC), and a number of transient receptor potential (TRP) channels.

These sensor molecules respond to mechanical as well as chemical stimuli and in turn release chemicals such as ATP, prostaglandins (PG), nerve growth factor (NGF), ACh, and NO. These transmitters are known to have excitatory or inhibitory actions on afferent nerves, which are located close to or in the urothelium [15].

The urothelium interacts closely with the underlying sub-urothelial layer, in particular the interstitial cell network contained within it, so that the whole structure can be regarded as a functional

unit [14]. The suburothelium is composed of nerves, blood vessels, and connective tissue in intimate contact with the urothelium. The roles of the urothelium and suburothelial myofibroblasts in afferent activation have been emphasized with intense interest. The C fibres afferents generally have endings in the suburothelial layer of the bladder wall, but in some cases, they also penetrate the urothelium [13].

ATP was the first neurotransmitter demonstrated to be released directly from the urothelium [24]. Non-vesicular ATP release is evoked by chemical stimuli or by stretch proportional to the extent of bladder distension [25-28]. ATP is released from the urothelium submitted to stretch or inflammation. ATP has been proposed as a major link to transduce bladder information into suburothelium nerve fibres, which express purinergic receptors [12]. Both P2X and P2Y purinergic receptor subtypes have been identified in the bladder urothelium. It is now thought that these purinergic receptors may respond to urothelial-derived ATP release in autocrine and paracrine signaling [25, 29-32]. By acting on structures such as nerves [33] and interstitial cells in the suburothelial space, urothelial-derived ATP may trigger the underlying afferent signaling of bladder fullness and pain and possibly even the micturition reflex [34]. The increase of ATP may result not only from an excessive release of the neurotransmitter, but also from reduced extracellular hydrolysis of the molecule [12]. Urothelial ATP may therefore contribute to DO and the emergence of storage symptoms [12].

In an additional study, including women with OAB, urinary ATP levels increased with age [35]. One should take into consideration that ATP is also released from purinergic nerves in the detrusor layer and contributes to non-adrenergic, noncholinergic smooth muscle contractions [36]. Thus, the manipulation of ATP release through pathways regulated by cyclic nucleotides offers a route for therapeutic management of OAB [37]. After successful treatment with botulinum toxin injection, a reduced P_2X3-immunoactive suburothelial nerve fibres correlated with a reduction in urgency [38]. Sugaya *et al*. reported that improvement of OAB symptoms with antimuscarinic treatment was significantly correlated with a decrease in urinary ATP level in female s with OAB [35].

The presence and localization of muscarinic receptor protein and mRNA in the human [39-44] and mouse [45] urothelium have been studied. All five muscarinic subtypes are expressed throughout the urothelial layers with a specific localization of the M2 subtype to the umbrella cells and M1 to the basal layer, with M3 receptors more generally distributed. Release of Ach from human urothelial and suburothelial sites increases with age, as well as during bladder stretch, and represents a functional, non-neuronal, alternative cholinergic system [41]. At therapeutic doses, antimuscarinics act mainly during the filling phase and exert little effect on detrusor contraction during emptying [46-48]. This lends support to the suggestion that urothelial muscarinic receptors might be involved in the generation of afferent impulses.

Urothelial cells express also both adrenoceptor subtypes, stimulation of which has been shown to trigger the release of ATP and nitric oxide (NO), respectively [49, 50]. Stimulation of urothelial adrenoceptors also triggers a urothelially-derived inhibitory factor [51]. However, β3-adrenoceptor agonists may be more potent in decreasing nerve-evoked ACh release than in producing direct relaxation of human bladder smooth muscle [52,53]. This is in line with the observed abundance of β3-adrenoceptor immunoreactivity on ACh-containing nerve fibres coursing the suburothelium and the detrusor of the human bladder, leading to the hypothesis that β3-adrenoceptor agonists act, at least in part, through inhibition of ACh release from cholinergic, most probably parasympathetic, nerve terminals through a prejunctional mechanism [54]. According to this theory, β3-adrenoceptor agonists may preferentially inhibit pathologically increased detrusor tone during bladder filling over physiological detrusor contraction during voiding and enabling them to inhibit an increased cholinergic tone in OAB [55]. Because purinergic transmission is more evident in pathological human bladders, attenuation of ATP release may be more relevant [37]. Moreover, β3-adrenoceptor agonists have more pronounced inhibitory effects on purinergic than cholinergic transmission [56].

In addition to the changes in ACh-release, several specific alterations in urothelial function and ultrastructure have been demonstrated in OAB. Expression of the mechanosensitive ENaC is increased significantly in human obstructed bladders in comparison with unobstructed controls and correlates significantly with storage symptom scores [57]. It is possible that increased expression of mechanosensitive channels such as ENaC in the urothelium enhances substance release upon bladder stretch. Levels of PG, which are locally synthesized in bladder muscle and mucosa, and levels of NGF are increased in subjects with OAB in comparison with controls; and in symptomatic patients, levels of PGE2 are positively correlated with OAB symptoms and maximum cystometric capacity [58,59].

Several channels of the TRP (transient receptor potential) family have a role in nociception and mechanosensory transduction in the lower urinary tract (LUT) [37]. A number of these channels, including vanilloids TRPV1, TRPV4, TRPM8, TRPA1, and TRPM4, have been suggested from animal studies to be able to treat OAB/DO, bladder underactivity and bladder pain disorders [60,61].

Bladder biopsies from patients with both idiopathic detrusor overactivity (IDO) [62] and neurogenic detrusor overactivity (NDO) [63] showed increased urothelial TRPV1 expression. This may be in accordance with the fact that intravesical vanilloids (resineferatoxin) have been shown to improve OAB symptoms in patients with (IDO) as well as with hypersensitivity disorders [64,65]. TRPV4 channels are present in urothelium and detrusor muscle cells and in urothelium are proposed to have important mechanosensory functions during bladder distension [37,66]. TRPM8 channels are expressed in bladder mucosa and their abundance is positively associated voiding frequency in samples from patients with idiopathic DO. This has led to the proposal that this channel subtype contributes to the pathophysiology [37,67]. TRPA1 channels have also been identified on urethral C-fibre afferents and urothelial cells as well as detrusor myocytes from human tissue. Furthermore, intravesical application of TRPA1 channel activators initiates DO-like activity. Together, it has been proposed that they have a role in modulating both efferent and afferent fibre activity in both the bladder and outflow tract [37,61].

It is clear that the sensory process is more complex than originally thought. Suburothelial myofibroblasts (interstitial cells) in the bladder wall form a functional syncytium through connexin 43 gap junction [68,69]. These myofibroblasts are in close apposition to unmyelinated nerves (afferent C-fibre nerves) [70]. Studies investigating human myofibroblasts show that these

cells can respond to ATP by generating an intracellular Ca2+ transient, which is mediated by a P2Y receptor, most likely including P2Y6 [71]. On the basis of these observations, it has been hypothesized that the close relation between nerves and myofibroblasts allows an amplification of the afferent system in its response to stimulatory mediators such as ATP.

2.2. Myogenic Hypothesis

2.2.1. Context

OAB may be related to changes to the excitability and coupling of smooth muscle cells with other myocytes or interstitial cells leading to the generation of uninhibited contractions [72,73]. Brading and Turner have suggested that myogenic changes (regardless of aetiology) may contribute to the pathophysiology of IDO [72,73]. On the basis of observation that denervation is consistently found in detrusor biopsy specimen from patients with various forms of DO, it has been proposed that partial denervation of the detrusor may alter the properties of smooth muscle, leading to increased excitability and increased coupling between cells [74]. Drake *et al.* [6] later proposed that DO may result from histological changes within the detrusor [75], leading to abnormal electrical coupling of smooth muscle cells so that physiological micromotions become synchronized into active involuntary detrusor contractions [76]. However, other data suggest that increased afferent signaling resulting from urothelial/suburothelial dysfunction may contribute to uninhibited detrusor contractions [20] or that DO could be initiated from changes in central neural control of the micturition reflex [12].

Thus, local contraction (activity) that occurs somewhere in the detrusor will spread throughout the bladder wall, resulting in coordinated contraction of the whole bladder. In addition, this local contraction in the bladder wall has been shown to generate afferent discharge [77,78]. Localized bladder activity was assessed by the micromotion detection method, demonstrating that women with increased bladder sensation on filling cystometry had a significantly higher prevalence of localized activity than the control group [79]. This observation suggests that localized distortion of the bladder wall simulates afferent activity, which would precipitate a feeling of urgency and (DO) [80,81] (Figure 3).

2.2.2. Molecular basis

Although the relationships between intercellular communication and spontaneous mechanical activity and the degree of involvement of different types of connexins (Cxs) need further study, Cx45 and Cx43 appear to be the most prominent Cxs expressed in human detrusor smooth muscle tissue and cultured cells. Observations in tissue biopsies from patients with NDO and urgency symptoms clearly demonstrated an increase in the presence of Cx43-derived gap junction channels in detrusor muscle [82].

Another population of cells in the bladder, known as interstitial cells, has been proposed for a pacemaking role in spontaneous activity of the bladder [83,84]. The number of interstitial cells is increased in a guinea-pig model of bladder outlet obstruction (BOO) [85] and that c-kit tyrosine kinase inhibitors, which inhibit interstitial cell activity, decreased the amplitude of spontaneous contractions in the guinea-pig and human bladder [86,87], interstitial cells may also be involved in the emergence of (DO) because of enhanced autonomous detrusor muscle activity.

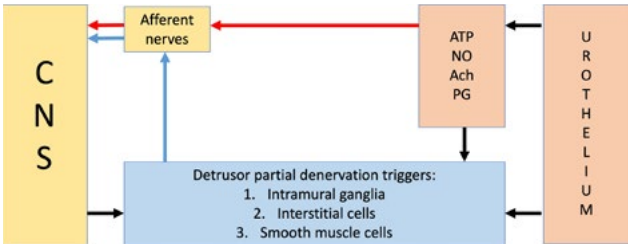

Figure 1: *Mechanisms involved in increased afferent input from the bladder: the urothelium-based and myogenic theories.*

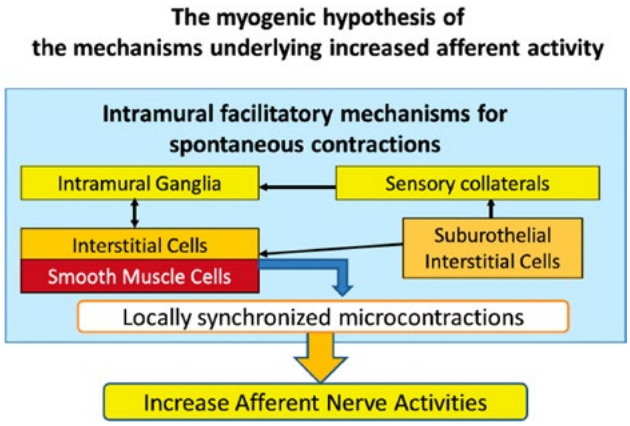

Figure 3: The myogenic hypothesis of the mechanisms involved in increased afferent input from the bladder.

2.3. Urethrogenic hypothesis [12]

In the early 20th century, Barrington described component reflexes of micturition evoked by running water through the urethra which resulted in a strong bladder contraction mediated through pudendal and pelvic afferent and efferent signals [88]. Using an animal model, Jung *et al.* hypothesized that entry of urine into the proximal urethra in patients with SUI may stimulate urethral afferents, inducing and/or increasing DO [89]. Their findings were confirmed a few years later in healthy human volunteers leading to generation of the hypothesis of an urethrovesical reflex [90].

Moving from a sitting or lying position to a standing position can cause urgency in many patients. This is considered a clinical feature of OAB originating from the urethra [91]. Urodynamics is not so useful to detect DO in these patients, as the investigation is usually performed only in the sitting position, the catheter might partially seal the bladder neck and patient positioning during filling cystometry may influence involuntary detrusor contractions. Valsalva-induced involuntary detrusor contractions may provoke DO in these patients [92].

Surgical repair of SUI improves storage LUTS in some patients with mixed incontinence [93]. However, *de novo* urgency is reported to occur in over 10% of patients undergoing any form of SUI surgery. In patients with pelvic organ prolapse, urgency may result from a prematurely activated micturition reflex caused by inability to support bladder neck/proximal urethral stretch receptors, which could explain the high rates of OAB symptom resolution after surgical correction of pelvic organ prolapse [94].

While primary deterioration of urethral tone has been advocated as a possible cause of OAB, the concept of urethral instability (i.e., urethral pressure variation during bladder filling) has been proposed as another mechanism of urethra-driven urgency, which may be due to a lack of pudendal or central neurological control [95]. Some evidence supports the role of SUI surgery in patients with urethral pressure variation [96].

Two other mechanisms of OAB symptoms due to severe SUI might be encompassed in this urethrogenic hypothesis [12]. First, constant leakage in patients with severe SUI may result in a chronically underfilled, "defunctionalized" bladder. Such patients may develop artifactual DO or impaired compliance generating urgency [97]. These abnormalities have been shown to resolve in many cases after surgical correction of SUI by restoring the physiological cycles of bladder storage and voiding [97]. The second mechanism appears to be related to pre-emptive urinary frequency voluntarily undertaken to prevent incontinence episodes in patients with severe SUI [12].

2.4. Detrusor underactivity [12]

Underactive bladder is currently a subject of considerable research [98]. While underactive bladder is considered to be the clinical correlate of urodynamicdetrusor underactivity, the voiding symptoms associated with detrusor underactivity overlap with OAB. Urgency was reported to be the most common symptom in patients with urodynamically proven detrusor underactivity (seen in over 50% of patients) [99]. In a survey-based epidemiological study including 977 patients underactive bladder symptoms were urgency, UUI, and nocturia [100]. The occurrence of urinary urgency in patients with DO can also be attributed to the well-known DO/impaired contractile function entity [101], which, in this context, is no doubt related to increased postvoid residuals and the subsequent reduced functional bladder capacity. In addition, urgency in detrusor underactivity can be attributed to urinary tractinfections (UTIs) secondary to chronic urinary retention [102] or the impact of such retention on the urinary microbiota. Current data suggest that detrusor underactivity may result from urothelial/suburothelial dysfunction (urotheliogenic hypothesis) and/or from detrusor muscle dysfunction (myogenic hypothesis) [103].

2.5. Other Factors

Several other processes may factor in development of DO/OAB. This includes ageing, bladder outlet obstruction (BOO), bladder ischaemia and mucosal injury.

Ageing and BOO may have a common pathway in contribution to DO/OAB development. Remodeling of the micturition circuits caused by ageing and BOO both involve a) ischaemia/reperfusion and oxidative stress, and b) chronic inflammation [104, 105] (Figure 4). In addition, there is an increasing evidence for the role of the urinary microbiome in relation to DO/OAB (See section I: Microbiota in incontinence and pelvic floor dysfunctions). BOO-induced bladder remodeling: hypertrophy, compensation (increased detrusor contractility during the voiding phase, often in combination with filling phase DO) followed by the phase of decompensation (detrusor underactivity) [105].

2.5.1. Process of ischaemia and reperfusion

Ischaemia/reperfusion has been proposed as a pathophysiological factor underlying DO/OAB. Recent studies suggest that macrovascular and microvascular disease may lead to OAB in both men and women via ischeemia, hypoxia and oxidative stress in the bladder [106-109]. DO associated mitochondrial stress may also have a role in epithelial damage, smooth muscle cell injury and neurodegeneration. Superoxide dismutase and aldose reductase up-regulation in OAB suggests an intrinsic defensive reaction against free radicals that apparently fails to prevent oxidative damage and neurodegeneration [108]. Up-regulation of HIF, TGFB, VEGF and NGF in the ischaemic bladder is accompanied by the loss of mitochondrial structural integrity, fibrosis, and the degeneration of microvasculature and nerve fibres [110,111]. These observations may suggest the role of ischaemia in OAB with impaired contraction, as reported in elderly patients without obstruction. Ischaemia may be a key factor in age associated LUTS.

2.5.2. Inflammation

By definition, the presence of bladder inflammation precludes a clinical diagnosis of OAB. However, there are increases in the amount of pro-inflammatory mediators within the bladder and urine of OAB patients [112-114].

Different studies have inflammation in bladder biopsy specimens from OAB patients [110, 115]. Increases in cytokines, chemokines, and growth factors have been reported in the urine of OAB patients [116]. Consistent association of increasing serum C-reactive protein (CRP) levels and OAB has been demonstrated in the literature [117-119]. Moreover, Liu *et al.* demonstrated increased levels of serum adipokines (adipose tissue secreted cytokines), including IL- 6, IL-8, and TNF, refractory to antimuscarinic therapy compared to the control subjects [119]. In this study, no significant difference was found in adipokine levels between OAB-dry and OAB-wet, while serum CRP and NGF levels were significantly higher in OAB-wet, compared to controls. The prevalence of OAB increased with increasing CRP levels in both men and women, supporting the role of inflammation in the development of OAB. These findings suggest that some OAB patients might have pathophysiology linked to urinary or systemic inflammatory conditions.

Serum monocyte chemotactic protein-1 (MCP-1) levels have been shown as significantly higher only in OAB-dry compared to controls [119]. This suggests that more systemic inflammatory disorders exist among OAB-dry patients, as MCP-1 provokes mast cell activation and has chemotactic activity for monocytes that mature into macrophages at the site of inflammation.

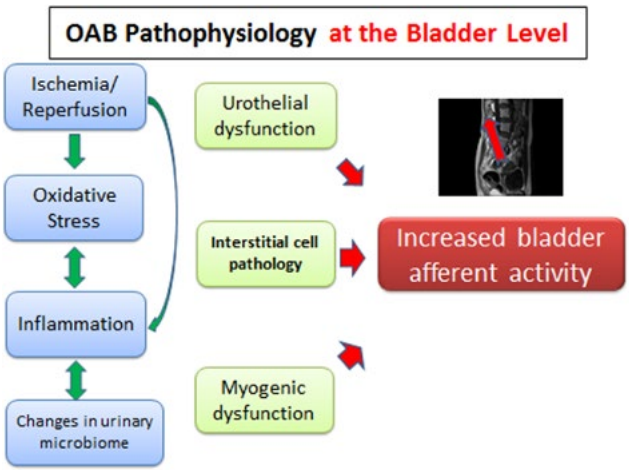

Figure 4: Potential factors involved in OAB pathophysiology at bladder level.

Age-associated biochemical changes may accentuate the inflammation associated with OAB. A study on urinary chemokines in OAB patients showed an age-associated elevation of NGF, suggesting a homeostatic response to counter the senescence of bladder nerves and arrest the progression of OAB into detrusor hyperactivity with impaired contractile finction [120]. All together, these findings support the hypothesis for the role of chronic inflammation at the local and systemic levels in the development of OAB.

3. NEUROPATHOLOGY: ABNORMAL HANDLING OF AFFERENT SIGNALS IN THE BRAIN

Among the theories contributing to the complex mechanisms underlying the genesis of DO/OAB we report the supraspinal hypothesis with urgency originating from the brain and brainstem [12].

3.1. Supraspinal hypothesis

Control of the LUT by the brain has received increasing attention over the past 15-20 years, and investigation with imaging techniques has revealed several brain centres associated with control of urine storage and voiding [121]. Theories have evolved regarding interconnection of these centres and further control of micturition by “circuits” associated with: a) the decision “to void or not to void” following contextualization of bladder sensory information with preconscious and conscious control over bladder filling and voiding (circuit 3, frontal brain); b) pattern/environmental recognition and relation of urinary status to emotional state (circuit 2, subcortical/limbic system); and c) the registration of bladder sensory information and preparation of motor responses (circuit 1, relation to desire to void) [122].

Since the late 1990s the decreased capacity to functionally integrate afferent information or reduced supraspinal inhibitory control of the micturition reflex has been suggested as a possible pathophysiological mechanism of OAB with the emergence of functional brain imaging [12, 123]. Increasing evidence supports the idea of two distinct subtypes of “brain OAB”: one with and one without DO [124]. Activity in the insula (lower bladder volumes) and anterior cingulate gyrus/supplementary motor area (higher volumes) may be neural characteristics of urgency without DO, while the neural signature of DO seems to be deactivation in the prefrontal cortex [124]. The difference in supraspinal activity between OAB patients with or without DO was confirmed by Tadic *et al.* [125], demonstrating that older age and a greater burden of white matter damage in patients with DO are associated with more severe functional urinary impairment. Several reports support the hypothesis that this “white matter disease” could be the anatomical substrate for the brain aetiology of OAB associated with DO, maybe through frontal hypoperfusion [122].

Blood oxygen level-dependent (BOLD) fMRI is a functional neuroimaging modality that has emerged as a useful tool in the study of the central pathways of micturition and bladder dysfunction [126]. As recently reported by Smith [127], the anterior cingulate gyrus, insula, and frontal cortices have been implicated as areas of increased activation in women with OAB [123, 128]. Furthermore, studies using bladder filling to provoke urgency suggest a neural correlate of the experience of urgency [124]. The cerebellum and parietal lobe have demonstrated increased activation during inhibition of voiding and contraction of the pelvic floor muscles [129]. Increased connectivity between the cerebellum and parietal lobe and the right insula and anterior cingulate gyrus has been demonstrated in women with UUI compared with controls [125].

Neurogenic Detrusor Overactivity (NDO) is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked in the setting of a clinically relevant neurologic disease [2,13]. The pathophysiology of NDO is described elsewhere. (See section V: Neurological patients: neurogenic basis of overactive bladder).

4. OAB PHENOTYPING ACCORDING TO PATHOPHYSIOLOGICAL COFACTORS

According to Peyronnet et al [12], different pathophysiological factors may configure different OAB types. The relation between OAB phenotypes according to urodynamic demonstration of DO and according to pathophysiological factors are shown in Figure 5.

4.1. Metabolic syndrome [12]

A link between metabolic syndrome and OAB has been demonstrated in many studies, especially between obesity and OAB [130,131]. While this association was initially thought to be driven through benign prostatic hyperplasia/chronic prostatic inflammation [131], increasing evidence has shown that OAB occurs equally in both men and women with metabolic syndrome [130,131]. OAB may have its own pathophysiology in patients with metabolic syndrome, relying on increased mechanical load stimulating sensory afferents of the trigone and bladder neck, but also on oxidative stress, systemic inflammation, and insulin resistance that promote chronic pelvic ischaemia and urothelial dysfunction [130,131].

4.2. Affective disorders [12]

Recent data demonstrate the influence of emotional stress and affective disorders on the natural history of OAB [132]. Hence, there may be a bidirectional association between affective disorders and OAB. Corticotrophin- releasing factor (CRF) has been investigated as a possible common pathophysiological contributor to OAB and anxiety/depression [133]. The concomitant decrease in serum CRF levels and improvement of depression induced OAB observed using a CRF receptor type 1 antagonist in a recent animal model study confirms this possible mechanism, while highlighting a possible therapeutic pathway for social stress induced OAB [134]. Serotonin depletion has been postulated as another shared pathophysiological candidate for both anxiety/depression and OAB, as its role in affective disorders is well established and several experimental studies have demonstrated that lowering of serotonin levels in the CNS was accompanied by urinary frequency and DO [135-137].

4.3. Sex hormone deficiency [12]

Sex hormone deficiency has been described as having a role in the pathogenesis of LUTS, with up to 70% of women relat-

ing the onset of UI to their final menstruation [138]. Oestrogen deprivation may lead to urgency with increased detrusor contractility through Rho-kinase pathway activation, increased acetylcholine release, changes in urothelial afferent signaling, or increased connexin-43 expression [138,139].

4.4. Urinary microbiota

The urinary microbiota may play a role in the pathogenesis of OAB. (See section I: Microbiota in incontinence and pelvic floor dysfunctions).

4.5. Functional gastrointestinal disorders [12]

The gastrointestinal condition that has most frequently been -related to OAB is irritable bowel syndrome (IBS) [140–142], with a prevalence as high as 33.3% in patients with OAB [143]. Both disorders are characterized by increased frequency of visceral emptying due to increased sensation (urgency for OAB; pain and discomfort for IBS) [144]. Central sensitization has been hypnotized as a primary dysfunction affecting the concurrence of both gastrointestinal and urological functional disorders alongside affective disorders (e.g., anxiety and depression) as part of a brain-gut-bladder axis [145]. This possible brain-gut-bladder axis–OAB phenotype might be induced by stress due to either psychological factors (e.g., a previous traumatic event) or physical factors (e.g.,internal/external physical threat) [12].

4.6. Autonomic nervous system dysfunction [12]

In several neurological conditions, sympathetic, parasympathetic, and somatic nerves dysfunction hasbeen associated with N-LUTS (See section V: Neurological patients: neurogenic basis of overactive bladder). Blanc *et al.* were the first authors to hypothesize that subclinical autonomic nervous system dysfunction may be a causative factor of “idiopathic” OAB [146]. Hubeaux *et al.* suggested that bladder filling induces a global sympathetic response in women with OAB [147]. The same group reported that sympathetic dysfunction might be predominant over parasympathetic dysfunction in OAB patients and that OAB patients with autonomic dysfunction maybe less likely to exhibit DO on urodynamics [148].

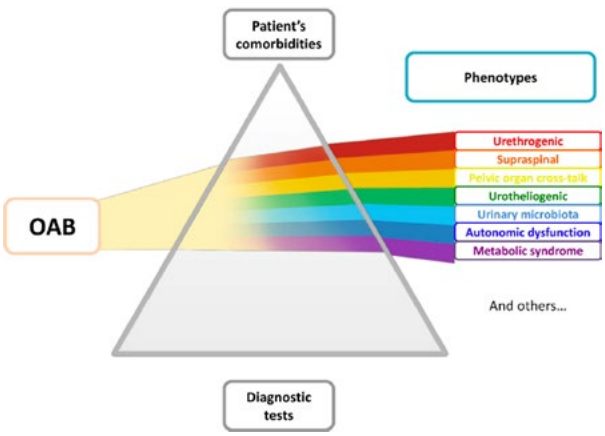

Figure 5: The diagnosis “prism” approach of OAB phenotypes. The new diagnostic approach should seek for the underlying pathophysiological phenotypes, which could probably be achieved through a thorough clinical examination (though the clinical hallmarks of some phenotypes are still to be identified), eventually associated with urodynamics and other testing in selected cases.

ASK FOR PERMISSION Peyronnet B, et al. Eur Urol. 2019 Jun;75(6):988-1000.

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IV. NEUROLOGICAL PATIENTS: NEUROGENIC BASIS OF OVERACTIVE BLADDER

1. INTRODUCTION

This chapter deals with basic information related to neurologic urinary and faecal incontinence; Literature searches were undertaken with keywords; “neurologic”, neurogenic”, “bladder”, “bowel”, “lower urinary tract”, “anorectal”, “incontinence “, “continence”, “urinary”, “faecal”, “paralysis”, “dysfunction”, “retention”, “constipation”. Searches for specific neurologic diseases were undertaken, looking into selected neurological diseases of particular relevance to neurourology, comprising those more prevalent or more challenging in terms of continence diagnosis and treatment.

Continence relates to reservoir functions of the bladder and rectum, and closure of their respective outlets by contraction of smooth muscle (bladder neck and internal bowel sphincter) and striated muscle (urethral and anal sphincters). Expulsion requires relaxation ofthe sphincters , and contraction of the musculature of the reservoirs, to permit evacuation of urine or faeces.

The lower urinary tract (LUT) and the lower bowel tract (LBT) are interrelated structures. Embryologically, bladder and rectum originate from the same basic structure, the cloaca [1]. Anatomically both viscera lie in close proximityand close to the muscular structures of the pelvic floor. Both are innervated by autonomic and somatic nerves (Table 1), and have similar principles underlying central control [2, 3].

The lower bowel tract (LBT) differs from the urinary bladder in having an enteric nervous system [4]. Interactions between the two organ systems are increasingly recognized, and their activity is coordinated. Voiding can occur without defecation [5], and the initiation of micturition often precedes that of defecation, even if both organs are considered equally full [6]. The filling status of the bladder influences sensation in the rectum and vice versa [7], and the potential for mutual influence in pathology is emerging [8]. Nonetheless, little information is available on co-ordination of both functions in patients with neurological pathology.

Table 1: Overview of function of the abdominal sympathetic, the pelvic parasympathetic and somatic nerves in the LUT and LBT.

	Sympathetic T10-L1	Parasympathetic S2-4	Somatic S3-5
Bladder	-	+	
Bladder neck	+	-	
External urethral sphincter	exp	exp	+
Bowel		+	
Internal anal sphincter	+	-	
External anal sphincter	exp	exp	+
Pelvic floor			+

Exp= only suggested in animal experiments, no definite clinical evidence.
Suggestion to take exp = experimental out because it is for the common reader misleading and it is depending to the chosen animal model.

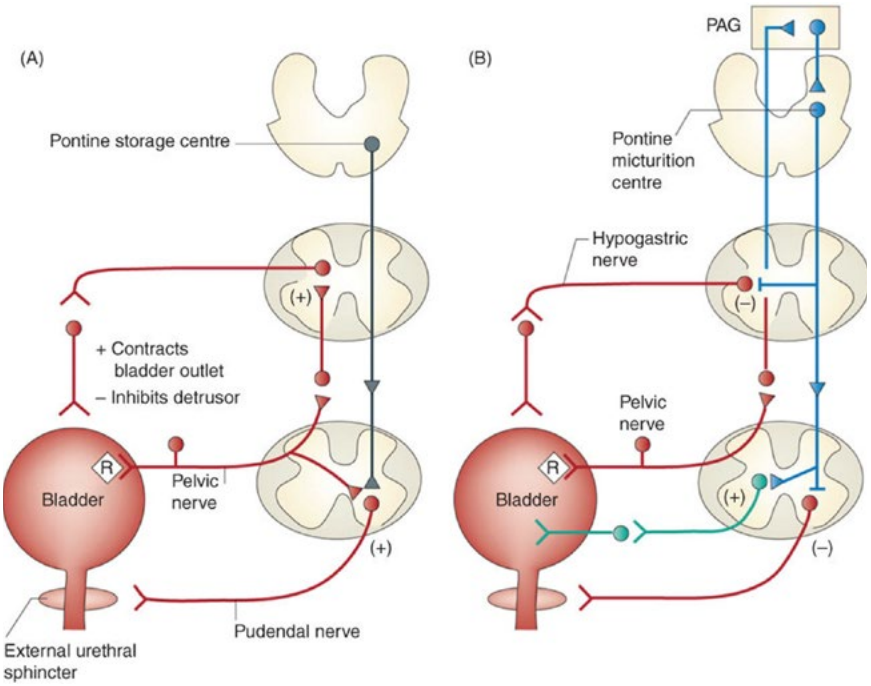

Figure 1: Neural circuits that control continence and micturition. (A) Urine storage reflexes. During the storage of urine, distention of the bladder produces low-level vesical afferent firing. This in turn stimulates the sympathetic outflow in the hypogastric nerve to the bladder outlet (the bladder base and the urethra) and the pudendal outflow to the external urethral sphincter. These responses occur by spinal reflex pathways and represent guarding reflexes, which promote continence. Sympathetic firing also inhibits contraction of the detrusor muscle and modulates neurotransmission in bladder ganglia. A region in the rostral pons (the pontine storage centre) might increase striated urethral sphincter activity. (B) Voiding reflexes. During the elimination of urine, intense bladderafferent firing in the pelvic nerve activates spinobulbospinal reflex pathways (shown in blue) that pass through the pontine micturition centre. This stimulates the parasympathetic outflow to the bladder and to the urethral smooth muscle (shown in green) and inhibits the sympathetic and pudendal outflow to the urethral outlet (shown in red). Ascending afferent input from the spinal cord might pass through relay neurons in the periaqueductal gray (PAG) before reaching the pontine micturition centre. Note that these diagrams do not address the generation of conscious bladder sensations, nor the mechanisms that underlie the switch from storage to voluntary voiding, both of which presumably involve cerebral circuits above the PAG. R represents receptors on afferent nerve terminals.

(original from: de Groat WC1, Griffiths D2, Yoshimura N3. Neural control of the lower urinary tract. Compr Physiol. 2015 Jan;5(1):327-96. doi: 10.1002/cphy.c130056 .)

Any disturbance of the nervous system can result in signs and symptoms of lower urinary tract dysfunction (LUTD). [9] The extent and location of the neurological dysfunction will determine the type of LUTD, which can be symptomatic or asymptomatic. Neuro-urological symptoms can cause a variety of long-term complications; the most significant being deterioration of renal function. [10]

Neurogenic LUTD (nLUTD) applies to a spectrum of clinical conditions and refers to the presence of LUTD symptoms 'when there is a relevant neurological condition'.[11] Urodynamics (UDS) can measure LUTD caused by a lesion in the brain and or spinal cord or peripheral nerves; associated with a congenital condition (e.g.myelomeningocele), an acquired, stable condition (e.g., stroke, spinal cord injury), or an acquired, progressive condition (e.g., multiple sclerosis [MS], Parkinson's disease, dementia).[12] Because not all patients with neurogenic conditions develop LUTD or have abnormal UDS findings, a specific understanding of the dysfunction in each individual is a prerequisite for the correct choice of therapy.

2. NEUROPATHOLOGY

2.1. Pathophysiology

With a neurologic lesion the type of dysfunction that follows in LUT (and LBT) will depend on the site, the extent and the evolution of the deficit. Traditionally neuro-urological pathology has been divided into the upper motor neuron lesions (UMNL), comprising suprapontine (cerebral) and suprasacral (brainstem, and spinal cord); and lower motor neuron lesions (LMNL), comprising sacral and subsacral (cauda equina and peripheral nerve). Brainstem lesions are rarely compatible with more than short-term survival, so they are only infrequently encountered in neurourological practice.

Powell proposed a new step in classification of the neurogenic bladder: SALE (Stratify by Anatomic Location and Etiology). [13] The classification is based on seven categories, each having a neurologic defect in a distinct anatomic location. In addition, the presence or absence of bowel dysfunction and autonomic dysreflexia is reported. In the future, as more definite prognostic information can be gleaned from biomarkers [14], urinary nerve growth factor (NGF) and urinary brain-derived neurotrophic factor (BDNF) levels were hoped to be added to the classification. The SALE system should efficiently describe a patient suffering from neurogenic bladder (NGB) and simultaneously inform the most appropriate treatment, follow-up regimen, and long-term prognosis. [15]

2.2. Neurogenic Detrusor Overactivity

Damage to the central inhibitory pathways, or sensitization of afferent nerves, may lead to the unmasking of primitive voiding reflexes, which may trigger involuntary detrusor contractions [89,90]. In addition, increased release of nerve growth factor (NGF) in DO has been reported, which may alter the neural regulation of detrusor muscle [16-18]. Plasticity in peripheral innervation and within the central nervous system (CNS) may both play a pathophysiological role in DO [19]. Peripherally, neurological diseases might cause a sensitisation of C-fibres that are silent under normal circumstances, thereby leading to the emergence of a C-fibre-mediated reflex.

While many neurological diseases predispose patients to NDO, the only populations that have been systematically studied are adults with multiple sclerosis, adults with SCI and children and young adults with myelodysplasia [20].

3. STROKE, CEREBRAL INFARCTION

3.1. Suprapontine lesions

It is generally accepted that suprapontine lesions such as stroke and Parkinson's disease produce DO. The patient with a suprapontine lesion loses voluntary inhibition of micturition, which corresponds to uninhibited overactive bladder according to a classification by Fall *et al* [21, 22]. Higher brain centres provide an additional level of urinary control, which is responsible for conscious sensation, volition and emotional response. Key higher centres include the prefrontal cortex, insular cortex and anterior cingulate gyrus, and functional brain imaging has shown changes in higher CNS activity in OAB [20, 23, 24]. Although such observations have been made infrequently, they do point to some key areas for consideration. For example, the participation of several brain areas in urinary control may explain why brain disease and cerebral atrophy are risk factors for lower urinary tract dysfunction. [20, 25]

Variation in observations between individuals implicates a diversity of processes in the mechanisms that underly OAB, although these are manifest clinically in OAB symptoms. The increased activity observed in certain regions of the brain in patients with OAB may actually be compensatory, to counteract urgency, rather than being responsible for the symptom [20]. This confounds interpretation of function, and there are many questions that still need to be answered.

Brain transection studies in animals with an intact neuraxis show that suprapontine areas generally exert a tonic inhibitory influence on the pontine micturition center (PMC). [25-27] [Figure 1] In humans, the cerebral cortex (medial frontal lobes) and the basal ganglia are thought to suppress the micturition reflex. Thus, damage to the brain induces DO by reducing suprapontine inhibition.

In the CNS,a glutamatergic pathway plays a role in both excitatory and inhibitory regulation of micturition. Results from animal models indicate that bladder overactivity induced by cerebral infarction occurs in two phases, both of which depend on activation of NMDA glutamatergic receptors. The cerebral infarction model demonstrates that bladder overactivity is mediated by NMDA glutamatergic and D2 dopaminergic excitatory mechanisms, suggesting that cerebral infarction may alter a balance between the facilitatory and inhibitory mechanism that results in up-regulation of an excitatory pathway and down-regulation of a tonic inhibitory pathway. [27]

4. PARKINSON'S DISEASE

Parkinson's disease (PD) has been long characterized by the degeneration of dopamine-producing cells in the substantia nigra of the midbrain and Lewy body formation, leading to motor dysfunction such as bradykinesia or akinesia. Degeneration of the nigrostriatal pathway is accompanied by decreases in corresponding biochemical markers, including dopamine, tyrosine hydroxylase, dopamine metabolites, and dopamine transporter. These central nervous system changes also have influence on

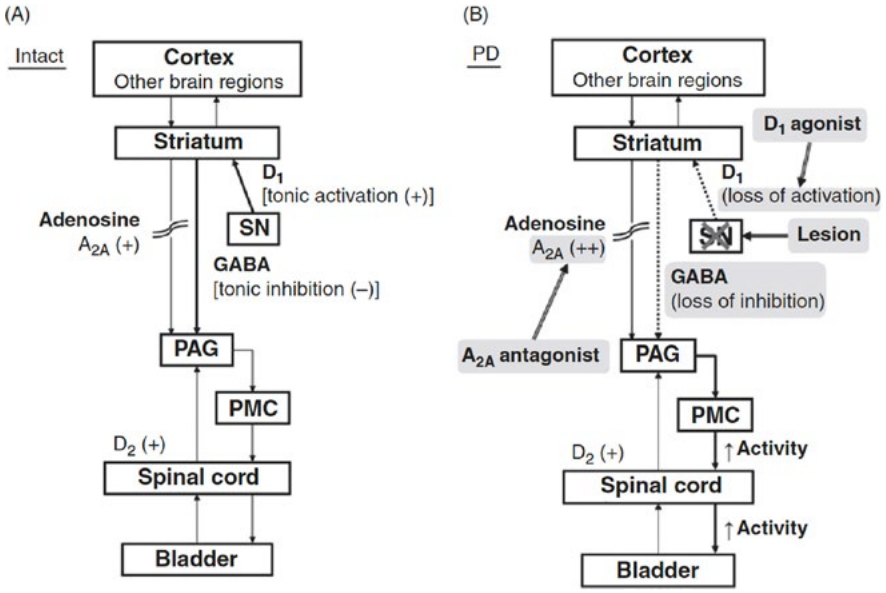

Figure 2: Hypothetical diagram showing dopaminergic and adenosinergic mechanisms inducing bladder dysfunction in Parkinson's disease (PD). The micturition reflex is controlled by the spinobulbospinal pathway passing through the PAG in the midbrain and the PMC in the pons. This neural circuit is under the control of higher centers including the striatum and the cortex region. A. Under normal conditions (Intact), tonic firing (+) of dopaminergic neurons in the SN activates dopamine D, receptors expressed on GABAergic inhibitory neurons in the striatum to induce tonic GABAergic (-) inhibition of the micturition reflex at the level of the PAG. At the same time, D, receptor stimulation suppresses the activity of adenosinergic neurons, which exert an excitatory effect on micturition via adenosine A2A receptors (Adenosine A2a (+)]. B. In PD, dopaminergic neurons in the SN are lost (lesion), leading to the loss of dopamine D1 receptor activation [D1 (loss of activation)], which results in reduced activation of inhibitory GABAergic neurons in the striatum (GABA (loss of inhibition)]. At the same time, reduced D1 receptor stimulation enhances the adenosinergic mechanism to stimulate adenosine A2A receptors [Adenosine A2A (++)], leading to facilitation of the spinobulbospinal pathway controlling the micturition reflex (activity). Administration of dopamine D, receptor agonists (D, agonist) can restore the GABAergic nerve activity and suppress Aza receptor-mediated activation to reduce bladder overactivity in PD. Also, administration of adenosine A2A receptor antagonists (A2A antagonist) can suppress A2A receptor-mediated activation of the micturition reflex to reduce bladder overactivity in PD. Dopamine D2 receptors [D2 (+)] expressed in the spinal cord enhance the micturition reflex. Abbreviations: dopamine Di receptor (D1); dopamine D2 receptor (D2); gamma-aminobutyric acid (GABA); periaqueductal gray (PAG); pontine micturition center (PMC); substantia nigra pars compacta (SN).

(original from: de Groat WC1, Griffiths D2, Yoshimura N3. Neural control of the lower urinary tract. Compr Physiol. 2015 Jan;5(1):327-96. doi: 10.1002/cphy.c130056 .)

autonomic function; the most common problems are gastrointestinal (constipation), perspiratory (hypohidrosis) and urinary system.

However, the symptomatology of Parkinson's disease is heterogeneous, with clinically significant non-motor features. Similarly, its pathology involves extensive regions of the nervous system, various neurotransmitters, and protein aggregates other than just Lewy bodies. The cause of Parkinson's disease remains unknown, but risk of developing Parkinson's disease is no longer viewed as primarily due to environmental factors. Instead, Parkinson's disease seems to result from a complicated interplay of genetic and environmental factors affecting numerous fundamental cellular processes.[28]

PD patients often exhibit overactive bladder symptoms such as urinary urgency, frequency, and incontinence which are induced by DO, estimated to be as high as 50% to 70%. [27]

The most widely accepted theory of pathophysiology of DO in PD is that basal ganglia inhibits the micturion reflex in the normal situation via D1 receptors, and that cell depletion in the substantia nigra in PD results in loss of D1-mediated inhibition and consequently DO. (Figure 2, [27])

LUT dysfunction in PD is estimated to occur in 50-70% [27]. Among these, Hattori et al. [29] (LOE3) reported 60% of PD patients with urinary symptoms, which could be divided in three categories: storage LUTS in 28%, voiding in 11%, and mixed in 21%. Prevalence correlated with PD severity, but not with duration of illness. Gray et al. [30] (LOE3) reported that LUT functional disturbances in PD were not disease-specific and only correlated with age.

In controlled studies [31-34] (LOE2) the prevalence of LUT symptoms (LUTS) was 27-64%, significantly higher than healthy controls. The majority of patients had onset of bladder dysfunction after the appearance of motorsymptoms. Bladder dysfunction substantially affects the quality of life in patients with PD. Bladder dysfunction in PD correlates with neurological disability, and stage of disease, both suggesting a relationship between dopaminergic degeneration and LUTS. LUTS was more common in a group of older PD patients, as in healthy populations. Among LUTS, nocturia (nighttime urinary frequen-

cy) is the most prevalent symptom (>60%) [33, 34] (LOE2). Patients also complain of urinary urgency (33-54%), daytime frequency (16-36%), and urinary incontinence in 26% of males and 28% of females. These figures are almost the same in untreated, early PD patients [35]. Although less common than storage symptoms, PD patients also report voiding symptoms. Sakakibara *et al.* [36] (LOE2) reported significantly higher rates of delay in initiating urination (44% of men), prolongation/poor stream (70% of men), and straining (28% of women) compared with the control group. However, despite the voiding symptoms, PD patients have low post-void residuals. Impaired detrusor contractility is reported in urodynamic studies in PD and is related to the degree of motor impairment [37]; impaired detrusor contractility was observed in 66% of women and 40% of men. [38, 39] (LOE2)

4.1. Pathology and disease-specific urinary tract problems

Deep brain stimulation in the subthalamic nucleus results in amelioration of the motor disorder as well as increased bladder capacity and decreased post-void residuals [40] (LOE2).

Related to the recent COVID-19 pandemic urinary issues and fatigue were notice in a Community-Based Case-Control Study, the most prominent nonmotor issues.**[41]**

4.2. Conclusions

In Parkinson's disease, LUT symptoms are associated with degeneration of dopaminergic neurotransmission (LOE2). The most common LUT disturbances are detrusor overactivity during storage, and impaired detrusor contractility during voiding (LOE2). The effect of levodopa on LUTS in PD patients remains to be fully elucidated (LOE3).

5. MULTIPLE SYSTEM ATROPHY (MSA)

Multiple system atrophy (MSA) is a rare and fatal neurodegenerative disorder characterized by a variable combination of parkinsonism, cerebellar impairment, and autonomic dysfunction.[42] Some MSA patients survive as little as 2 years, whereas a few survive much longer, up to 20 years. [43, 44]. The term MSA was introduced by Graham and Oppenheimer in 1969 to describe a disorder of unknown cause affecting extrapyramidal, cerebellar, and autonomic pathways [45]. The exact mechanisms leading to neurodegeneration still remain elusive – a accumulation of aggregated α-synuclein in oligodendrocytes forming glial cytoplasmic inclusions (GCIs), which qualifies MSA as a synucleinopathy together with Parkinson's disease (PD) and dementia with Lewy bodies (DLB). MSA-specific α-synuclein species have yet to be formally identified from oligodendrocytes of MSA patients. [42]

Autonomic failure (AF) is almost invariably present and can be an initial manifestation (AF-MSA) [46]. Autonomic failure occurs in other neurodegenerative diseases, for example in a subset of patients with IPD (AF-PD), as well as in pure autonomic failure (PAF), both of which are considered Lewy body diseases.

5.1. Pathology and disease-specific LUT problems

In male erectile dysfunction is often the first presentation [47-49] possibly preceding the occurrence of urinary dysfunction in MSA. Both OAB and large post-void residuals occur in MSA. The second consensus statement on the diagnosis of MSA recognizes that the disease frequently begins with bladder dysfunction (although erectile dysfunction usually precedes that complaint).

Reports of focal lesions have shown that postural hypotension occurs in lesions below the medulla, whereas urinary dysfunction occurs in lesions at many sites in the neuroaxis. These might be investigated by a brain 18-FDG-PET [50]. MSA lesions involve the pons, the hypothalamus, and the basal ganglia, all of which might affect LUT function. Urinary dysfunction also precedes the motor disorder, approximately 60% of patients with MSA develop urinary symptoms either prior to or at the time of presentation with the motor disorder [51]. Many of these patients may seek urological advice early in the course of their disease.

Patients may present with urinary incontinence, urinary retention, or a combination of incontinence and incomplete bladder emptying and other common causes of poor bladder control are excluded [52, 53]. For example, the prevalence of troublesome urinary symptoms in 256 patients with MSA compared with 158 aged matched control subjects [54] showed that MSA patients had significantly higher increased daytime frequency (45% of women, 43% of men), night time frequency (65%, 69%), urinary urgency (64% of men), and urgency incontinence (75%, 66%) than the controls. They also had more hesitancy of micturition (62%, 73%), prolonged poor stream (71%, 81%), or intermittent stream (61%, 47%), or the need to strain to void (48%, 55%). The quality of life (QOL) index in the MSA group was significantly worse in MSA patients for bladder dysfunction (70%, 76%) than that in controls. Many show larger post-void residual urine volumes > 100 ml. Therefore, as reported in the initial publications. both overactive bladder and large post-void residuals are common in MSA [55, 56]

Of various symptoms of autonomic failure (erectile dysfunction, urinary dysfunction, postural hypotension, respiratory stridor) in patients with MSA, urinary dysfunction has attracted less attention than postural hypotension, although urinary dysfunction may result in recurrent urinary tract infection and cause morbidity.

If severity of urinary symptoms is severe enough for surgical intervention, males with MSA may undergo surgery for prostatic outflow obstruction before the correct diagnosis has been made. The results of such surgery are often transient or unfavourable because of the progressive nature of the disease. In addition, UI results in impaired self-esteem, stress on the caregiver, and considerable financial cost..

Gallien *et al.* found urinary symptoms (96%) to be more common than orthostatic symptoms (postural faintness (43%), blurred vision (38%) and syncope (19%)).[57] The most frequent urinary symptom was voiding difficulty (79%) followed by nocturnal urinary frequency in 74%. Other symptoms included urgency (63%), urgency incontinence (63%), diurnal urinary frequency (45%), nocturnal enuresis (19%), and urinary retention (8%) as reported by others. [58, 59]

The urologist confronted with a patient with these features should be cautious about embarking on an operative approach. The neurologist encountering a patient with marked urinary symptoms might consider future investigation by brain MRI and sphincter EMG. Since motor disorders in MSA mostly mimic those in IPD, the urogenital distinction between these two dis-

eases is worth considering, although a number of earlier studies on 'Parkinson's disease and the bladder' might inadvertently have included patients with MSA. The prevalence of urinary dysfunction and urgency incontinence in MSA is higher than that reported in IPD. Urinary dysfunction is almost never the initial presentation in IPD.

6. SPINAL CORD LESIONS (NOT INCLUDING NEWBORN AND CHILDREN)

A spinal cord lesion above the lumbosacral level eliminates voluntary and supraspinal control of micturition, leading to DO mediated by spinal reflex pathways [60]. Disruption below the level of the pons leads to unsustained and uncoordinated detrusor contractions often associated with uncoordinated sphincter overactivity (detrusor-sphincter dyssynergia, DSD). [61] Impairment or loss of bladder sensation is a typical feature.

On the bladder level: increased TRPV1, P2X3 and pan-neuronal marker (PGP9.5) staining in suburothelial nerves and increased TRPV1 staining in the basal layer of the urothelium have been observed in patients with neurogenic bladder due to SCI and multiple sclerosis [62].

These results indicate that an abnormality of the C-fibre afferent innervation contributes to NDO [63].

Upregulation of TRPA1 protein and mRNA levels, in bladder and in dorsal root ganglia (DRG; L6-S1) has been reported in rats with SCI. Moreover, HC-030031 (a TRPA1 antagonist) treatment decreased the number and the amplitude of DO contractions, suggesting that the TRPA1 activation and upregulation seem to exert an important role in DO following SCI [64].

Following SCI, changes in the electrophysiological properties of bladder afferent neurons have also been observed consisting of multiple action potentials (tonic firing) in response to long depolarizing current pulses [65, 66]. In addition, A-type K^+ channels are suppressed in parallel with an increased expression of TTX-sensitive Na^+ currents, thereby increasing excitability of C-fibre bladder afferent neurons [67]. These electrophysiological changes contribute to the emergence of the C-fibre-mediated spinal micturition reflex following SCI.

Sacral reflex testing has been studied extensively and is used to prove objectively the integrity of the S2-S4 reflex arc. The sacral reflex evoked on dorsal penile or clitoral nerve stimulation (the bulbocavernosus or penilo-/clitoro-cavernosus reflex) was shown to be a complex response, often forming two components.

The first component with a typical latency of about 33 ms, is the response that has been most often called the bulbocavernosus reflex. It is stable, does not habituate, and has other attributes of an oligosynaptic reflex response. [68] The second component has latency similar to the sacral reflexes evoked by stimulation peri-anally or from the proximal urethra, and is not always demonstrable as a discreet response. In those subjects in whom the first reflex component is difficult to elicit, stimulation strength should be increased, but preferably double electrical stimuli should be used. A complete reflex arc lesion should not be inferred by absence of a response if only single pulse is used for stimulation.During voiding sacral reflexes are un-elicitable but in presence of spinal cord lesions such as myelodysplasia this normal suppression is lostSacral reflex responses recorded with needle or wire electrodes can be analyzed separately for each side from the EAS or bulbocavernosus muscle.

6.1. Spinal cord lesions

Spinal cord injury (SCI) can be a devastating consequence of a variety of insults to the spinal column including road traffic accidents, gunshot wounds, surgical injuries, disc lesions or sports injury. It can be accompanied by vertebral fractures. Unlike other neurological diseases, once established the neurologic status generally remains stable.

6.2. Epidemiology and prevalence

SCI epidemiology has evolved over the last three decades. The incidence in women has increased over time. The male/ female ratio is now is 3.5:1. Taking into account that traumatic SCI occur mostly at a young age below 30 years [69] and nontraumatic spinal cord disease affects people at an olderage, i.e., above 55 years, the average age of persons at the time of injury is steadily increasing, but has increased in average from 29 years during the 1970s to 43 by 2015. This comprises incomplete quadriplegics (47.2%), complete paraplegics (20.2%), complete quadriplegics (13.3%) and incomplete paraplegics (19.6%). [70]

There has been a steady improvement in life expectancy and quality of life after SCI. At present, the life expectancy of paraplegic patients is similar to the general population. This has been accomplished by development of multidisciplinary teams, introduction of clean intermittent self-catheterization (CSIC) and an improved and protocol driven follow-up plan.

The SCI is classified using the American Spinal Injury Association (ASIA) impairment scale of motor and sensory function [71].

6.2.1. ASIA Impairment scale

A = Complete: No motor or sensory function is preserved in the sacral segments S4–S5.

B = Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4–S5.

C = Incomplete: Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

D = Incomplete: Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 of more.

E = Normal: Motor and sensory function are normal.

It separates into 5 clinical syndromes [4] as follows:

- **Central cord syndrome** is most commonly due to hyperextension injury and results in haemorrhagic necrosis of the central gray matter and some of the medial white matter. Arm function is less at risk than legs because more caudal fibres of the corticospinal and spinothalamic tract are localized in the spine more laterally so are better protected. Bladder dysfunction is also less common.

- **Brown–Séquard syndrome** is a unilateral cord condition. It presents as ipsilateral motor weakness and contralateral sensory impairment of pain and temperature. Bladder dysfunction in the pure condition is uncommon.
- **Anterior cord syndrome** is characterized by injury to the anterior aspects of the cord. The posterior columns and dorsal horns are preserved. There is a motor deficit and loss of pain and temperature sensation below the level of the injury.
- **Conus medullaris and cauda equina syndrome** result from damage to the conus and spinal nerve roots, leading to flaccid paraplegia and sensory loss. Sacral reflexes can be partially or totally lost.

American Spinal Injury Association/International Spinal Cord Society published the first guideline and International Standards to document remaining Autonomic Function after Spinal Cord Injury (ISAFSCI). [72] This guideline should be used as an adjunct to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), including the ASIA Impairment Scale (AIS), which documents the neurological examination of individuals with SCI. The Autonomic Standards Assessment Form is recommended to be completed during the evaluation of individuals with SCI, but is not a part of the ISNCSCI. This scale involves an assessment of general autonomic function, lower urinary tract, bowel, sexual function and urodynamic evaluation. The impact of SCI on the pelvic organ function constitutes a major part of this classification [73].

6.3. Bladder dysfunction after SCI

SCI can be divided into two phases; spinal shock and a chronic phase, and can be categorized according to the level of injury.

6.3.1. Spinal shock

Spinal shock is the period just after the injury. It lasts on average three months. It is characterised by loss of muscle tone and segmental spinal reflexes caudal to the SCI. There is detrusor areflexia and the bladder is acontractile but the bladder neck and proximal urethra remains closed. This areflexia cannot be reversed with bethanechol, which is relevant in the way to describe the pathology – but although a diagnostic tool. [74]. The only reflex activity that rapidly returns are the anal or bulbocavernosus reflexes. Spinal shock is initially managed with an indwelling urinary catheter. Recently it has been demonstrated that bladder overdistension during the acute phase deteriorates lower urinary tract storage function in patients with SCI during the later phase. [75] The recovery of bladder function usually follows that of skeletal muscle reflexes. The removal of an indwelling urinary catheter and initiation of self-catheterization should be instituted as soon as practical

6.3.2. Neurogenic Bladder Dysfunction in the chronic phase

6.3.2.1. Suprasacral lesions

The spinal shock phase is followed by the appearance of a segmental spinal bladder reflex. This relates to emergence of unmyelinated C-fibre afferent function [76]. As a result, some stimuli can influence bladder and sphincter activity that were seemingly irrelevant prior to injury [77, 78]. The sacral micturition centre is disconnected from the control of higher centres and produces what is functionally an isolated spinal cord segment. This results in neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD). DSD is defined as intermittent or complete failure of relaxation of the urinary sphincter during a bladder contraction and voiding. It has been reported to occur in 96% of individuals with suprasacral lesions. In addition to DSD, internal sphincter dyssynergia also

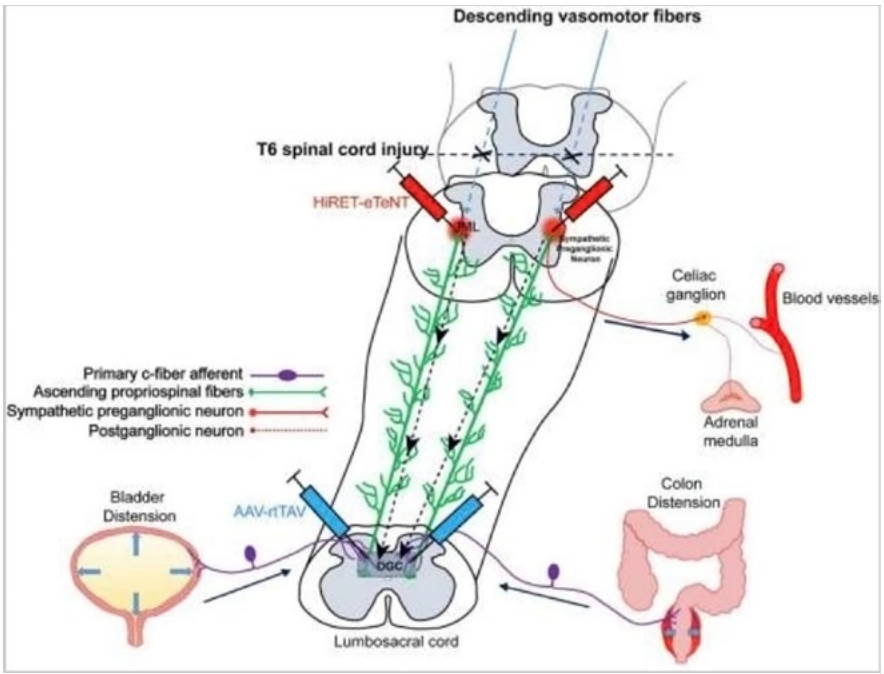

Figure 3: Eldahan KC1, Rabchevsky AG2. Autonomic dysreflexia after spinal cord injury: Systemic pathophysiology and methods of management. Auton Neurosci. 2018 Jan;209:59-70. doi: 10.1016/j.autneu.2017.05.002. Epub 2017 May 8. (original from: de Groat WC1, Griffiths D2, Yoshimura N3. Neural control of the lower urinary tract. Compr Physiol. 2015 Jan;5(1):327-96. doi: 10.1002/cphy.c130056 .)

has been reported, often occurring at the same time as DSD. Patients present with both storage and voiding dysfunction [79].

DSD can manifest with both complete and incomplete lesions. However, complete injuries are significantly more often associated with DSD. This leads to high voiding pressure, dis-coordinated voiding, residual urine and incontinence. If left untreated, this can lead to recurrent urinary infections, hydronephrosis and renal failure. Ambulatory patients with incomplete spinal cord may have significantly less urinary tract dysfunction, but the urodynamic parameters may still be abnormal.

6.3.2.1.1. Detrusor-(external) sphincter dyssynergia

Schurch *et al.* [80] assessed types of DSD in 105 chronic SCI males and evaluated change in the pattern over time. Those with an incomplete sensory and motor SCI presented with DSD type 1 whereas those with complete sensory and motor SCI lesion had DSD type 2 to type 3. At medium to long-term follow-up, a significant change was found in the DSD type.

6.3.2.1.2. Autonomic dysreflexia

Autonomic dysreflexia (AD) is a clinical emergency in patients who have a SCI, usually at level of T6 or above. It is caused by a massive sympathetic discharge triggered by either a noxious or non-noxious stimulus originating below the level of the SCI (Figure 3, [81]. Bywater *et al.* revealed an unfavourable urodynamic parameters in 63% of the investigated patients within the first 40 days after SCI. [82]

The mechanism might be changes occurring within the spinal and peripheral autonomic circuits. There is a loss of inhibitory and excitatory supraspinal input to the sympathetic preganglionic neurons secondary to the destruction of the descending vasomotor pathways. [83] AD is characterized by severe hypertension and reflex bradycardia, though tachycardia also may occur.

An increase in systolic blood pressure greater than 20 to 30mmHg is considered a dysreflexic episode. The other symptoms could be severe headache, feeling of anxiety, profuse sweating, flushing and piloerection above the injury level with dry and pale skin below. It might also cause blurred vision, nasal congestion, cardiac arrhythmias and atrial fibrillation. It can vary in intensity, from mild discomfort to life-threatening. Untreated episodes may cause intracranial haemorrhage, retinal detachment, seizures, and death.

The severity of AD symptoms increases with completeness of injury and higher level of lesion (27% of patients with incomplete quadriplegia vs 91% of patients with complete tetraplegia) [84]. The commonest trigger for AD is bladder or bowel distention. Immediate recognition and reversal of trigger factors is essential [85.

6.3.2.2. Infrasacral lesions

In patients with injury to the sacral pathways there is decentralization of parasympathetic pathways to the detrusor with the loss of somatic innervation to the external sphincter. This results in loss of conscious awareness of bladder filling. In some people there is partial preservation of pain sensation transmitted via hypogastric nerves. Patients present with hesitancy, slow and interrupted stream, feeling of incomplete emptying, and are often in retention. The bladder has little or no contractile ability. Nevertheless, because of loss of compliance of the bladder wall, the bladder may still be subject to high intravesical pressure during filling, especially in individuals with conus medullaris lesions or with partial injuries. In the chronic state there is an increase in adrenergic innervation to the detrusor, resulting in change of functional role from beta- mediated adrenoreceptor relaxation to alpha-mediated contraction [86, 87]. The sympathetic nervous system supplies the main innervation to the urethra. However, there may be a contribution of the somatic innervation to external sphincter [88, 89]. The perineal floor electromyography shows denervation of the perineal floor and an underactive urethral sphincter in infrasacral cord lesions.

6.3.3. Natural History of Neurogenic bladder after SCI

SCI usually causes impairments of urinary function such as UI and/or difficulty in urination. Podnar *et al.* [90] studied 55 patients with chronic cauda equina or conus medullaris injury: 76% of the patients reported LUT dysfunction, 70% had urinary incontinence (56% of men and 71% of women); and a post void residual (>100 ml) was found in 40% of men and 17% of women. Perianal sensation was abnormal in 96%, electromyography (EMG) of the external anal sphincter (EAS) muscle in 88%, and sacral reflex in 84% of patients; using multiple linear regression analysis, perianal sensory loss and female gender had a significant positive effect on urinary incontinence score.

6.3.4. Disease-specific LUT mechanisms

Pontari *et al.* [91] analyzed 7 bladder specimens from 6 cervical SCI patients and 1 L1 congenital myelomeningocele (MMC) and compared them with bladder specimens obtained from 8 organ transplant donors to determine whether the muscarinic receptor subtype mediating contraction alters, and found that whereas normal detrusor contractions are mediated by the M3 receptor subtype, in patients with neurogenic bladder dysfunction, contractions can be mediated by the M2 muscarinic receptor subtype.

Drake *et al.* found a marked reduction in the range of transmitters expressed in bladder nerves in SCI [92]. Haferkamp et al. [93] evaluated the role of neuropeptide Y in 31 patients with NDO and 7 patients with stress urinary incontinence (SUI) and concluded that the reduction of neuropeptide Y-containing nerves, inhibiting the contractile response of the detrusor, may play a role in the development and persistence of NDO in SCI patients, concentrations were significantly increased in SCI, and the lowest concentrations of urinary 8-iso PGF2alpha were observed in the areflexic group. [94] According to the study of viscerosensory pathway of the lower urinary tract (LUT) by Schmid *et al.* [95], after electrical stimulation (ES) of the posterior urethral mucosa (single square pulses of 0.2ms, 2 to 3- fold sensory threshold, 60mA in complete SCI patients), evoked skin sympathetic responses (SSRs) of the hand could be recorded in 14 of 15 sensory incomplete SCI patients with disturbed urethral sensation but not in 13 sensory complete SCI patients with loss of any urethral sensation. Electrically evoked urethral sensations resembled the subjective desire to void at full bladder reported by controls and patients.

Schmid *et al.* [96] did a comparative study of motor evoked potentials (MEP) and evoked pressure curves (EPC) from the urethral compressive musculature (UCM) in 9 healthy persons and 33 patients with neurogenic UI (15 SCL, 14 cauda equina lesion, and 4 multiple sclerosis). In healthy subjects the central latency was 19.0 msec, the peripheral latency was 4.25 msec, and the ratio between central and peripheral latencies was 4.4. In patients with incomplete SCI, the central latency was significantly delayed (22.7 msec), whereas the peripheral responses

were normal, and the ratio (5.5) was increased. Those with a complete SCI showed no UCM reaction after transcranial stimulation, whereas peripheral responses were normal. The increased ratio of 6.0 indicated a spinal cord lesion. Ten patients with incomplete cauda equina lesions and UI had normal central latencies but prolonged peripheral latencies of 6.7 msec; the ratio of 3.4 indicated a lesion of the sacral caudal roots.

According to Dai and Xiao [97], the thresholds of stimulation on ventral roots were 0.02 ms duration, 0.2-0.4 mA, (mean 0.3 mA+/-0.07 mA), compared with 0.2-0.4 ms duration, 1.5-3 mA (mean 2.3 mA+/- 0.5 mA) for dorsal root (P<0.01) to cause evoked potentials and EMG. Continuous stimulation for about 3-5 seconds on S2 or S3 ventral root (0.02 ms, 20 Hz,and 0.4 mA) could result in bladder detrusor contraction, but the strongest bladder contraction was usually caused by stimulation on the S3 ventral root in 7 of the 10 patients.

Beside the electrophysiological changes the detrusor undergoes a significant morphological change after complete SCI, which had been investigated in the pig model. They demonstrated the shift towards intercellular tissue and loss of contractile tissue. [98]

6.3.5. Assessment/investigations (different to diagnostics)

6.3.5.1. Urodynamic studies

Ersoz and Akyuz [99] investigated bladder-filling sensation in 73 consecutive traumatic SCI patients to examine the quality of the preserved sensation and to determine the potential for sensation-dependent bladder emptying. Bladder-filling sensation was present to some degree in all incomplete SCI patients, in 82.4% of the patients with complete lesions below T10, and 38.9% of the patients with complete lesions above T11. There were significant differences between three groups with respect to bladder sensation category. About 86% of the patients with incomplete lesions, 53% of the patients with complete lesions below T10 and 22% of those with lesions above T11 had bladder-filling sensation before Pves reached 25 cmH2O and simultaneous bladder capacity of more than 150 ml was present in 61.2%, 41.2% and 22.2% of the patients in the groups, respectively. Bladder-filling sensation investigations were reliable in terms of bladder filling sensation category in 36 SCI patients who had a second cystometric examination.

To measure bladder mucosal sensory function quantitatively, Ukimura *et al.* [100] used neuroselective Current Perception Threshold (CPT) tests in 8 healthy volunteers and 38 patients with NBD. Standardized neuroselective CPT measures were obtained from the left index finger and the mucosa of the posterior bladder wall. The CPT values in the bladder could be determined using the neuroselective measures in all patients but three who had no sensory response (absence of sensation) caused by complete SCI. In the 8 patients with NDO due to incomplete suprasacral SCI, the bladder CPT value (4.0+/-1.9) at 5Hz was significantly lower than that in the controls (26.2+/-17.7). In the NBD determined to be underactive (n=11, including post pelvic surgery, post infrasacral level SCI and diabetes patients), the higher CPT values of bladder mucosal sensory functions were found at 5Hz (p<0.05), 250Hz (p=0.07), and 2000Hz compared to the controls. No fibre specificity has so far been found depending on frequency of current used or current type.

6.3.6. Vesicoureteral Reflux (VUR)

VUR seems common among SCI patients with upper motor neuron (UMN) neurogenic bladder. According to the study of Linsenmeyer *et al.,* there was an association of posterior position of ureteral orifices and reflux but no differences were found with regard to bladder capacity, bladder wall compliance, or voiding pressures between the reflux group and non-reflux group. [101]

6.3.7. Bacteriuria

Levendoglu *et al.* prospectively studied 27 SCI patients who applied CIC during the initial rehabilitation with 40 controls. [102] E. coli was predominantly isolated from the urine and the urethral cultures of both female and male patients; there was concordance between urethra and urine cultures concerning the growth of E. coli; and Pseudomonas was colonized more in male patients. Waites et al. found that among 77.1% of men with bacteriuria, uropathogens were shown in the perineum in 57.4% and in the urethra in 85.2%; differences in the occurrence of uropathogens in men with and without bacteriuria were statistically significant, and organisms were present in higher numbers in men with bacteriuria. [483] Over the time the changes in the bacterial spectrum and resistance for in- as well as for outpatients is seen where strategies to control urinary tract infections need to be further developed[103]

6.3.8. Urinary Microbiome

In the LUT, influence on the microbiome as a result of SCI and other neurogenic cases influencing the LUT has been examined. [104, 105] Urinary microbiome variations were also observed using 16S rRNA sequencing analysis for male and female patients with normal bladder function compared to NBD patients. [106] Urine samples from healthy control bladders had significant enrichment in Lactobacillus and Corynebacterium genera, whereas other bacterial general such as Klebsiella, Enterococcus, and Escherichia were predominant in NBD urine. Bacteriuria is associated with a range of LUT symptoms, and the role of a putative bladder microbiome in the sensitization of spinal neurons needs to be further explored. [107] Although recent research is focused on the gut-brain-axis, the bladder-brain-axis remains an area of interest related to the significant changes in uroepithelial morphology as early as two hours post-injury and catheterization. [108, 109] The understanding of the urinary microbiome will hopefully not only help to understand but develop treatment options to control the growth of more virulent bacteria and potential protective treatment against UTIs [110].

7. SPECIFIC NEUROLOGICAL DISEASES: DEMENTIA

The dementias can be categorized according to clinical presentation, neuropathology and/or aetiology into four major dementia groupings, (I) the Alzheimer's group (Alzheimer's disease, AD); (II) the vascular group (including large and small vessel disease, particularly white matter disease); (III) the Parkinson's group (including Parkinson's disease dementia complex (PDD, being regarded as identical to DLB), and dementia with Lewy bodies (DLB), (IV) the frontotemporal group (including Pick's disease and Semantic dementia) [111] (II-III were grouped into the non-AD dementia syndromes [112]). Normal pressure hydrocephalus (NPH) is a less common pathology, but nonetheless important.

7.1. Alzheimer's disease [113]

Alzheimer's disease (AD) [113] is the most common type of dementia in clinical and autopsy surveys. AD mostly affects older adults. AD affects more than 40 million people globally, this is expected to reach 75.6 million by 2030. It is the biggest killer in women at 15.3% and the second biggest killer in men at 8%. [114] The symptoms include worsening of memory, impairment of language and other cognitive functions (analytical thinking, abstract reasoning). Ultimately, there is loss of self-hygiene, eating, dressing and mobility, incontinence and motor dysfunction. The onset of incontinence usually correlates with disease progression (LOE 3) [115] and almost inevitably occurs in the advanced stage of disease, while UI is less common in the early stage of AD. This is in contrast with early occurrence of urinary urgency and incontinence in vascular dementia and dementia with Lewy bodies. The prevalence of incontinence in AD is between 23 % and 48 % (LOE 3) [116, 117]. However, most previous studies do not mention the type of dementia. The prevalence of incontinence in advanced, institutionalized individuals with dementia reaches more than 90% (of) (LOE 3) [118].

Pathology and disease-specific urinary tract problems in AD at the outset was identified by its unique pathology, the amyloid plaques and neurofibrillary tangles containing phosphorylated tau that Alzheimer referred to as "a clotting of fibrils…. in addition to an extraordinary number of peculiar patches disseminated throughout the entire cortex". Omega-3 fatty acids might be a potential therapeutic tool to reduce the burden of accumulated protein. They appearto be a competitive inhibitor of ARA and reduce the production of inflammatory lipid mediators'and hence reduce the inflammatory condition. [119] Amyloid and tau can now be measured in vivo by positron emission tomography and/or examination of the cerebrospinal fluid (CSF). New research demonstrated the first evidence for the capacity of extracellular DNA from certain bacterial species to substantially promote tau misfolding and aggregation identified in the CSF, amyloid plaques, or brains of patients with AD (*B. burgdorferi, P. gingivalis, C. albicans*, and *E. coli.)*. Orally localized bacteria (Microbiome) may gain access to the brain via multiple pathways. Notably, the DNA of *T. alzheimeri* (belonging to *Brucellaceae;* together with that of *E. coli*) evinced the highest promoting activity relative to other bacteria. This can possibly lead to tau protein misfolding and aggregation, suggesting their potential role in the initiation and progression of pathological abnormalities responsible for AD. [120]

The clinical hallmark of AD is memory impairment. Memory failure, detected by the patient or a close relative, is usually the presenting symptom. Motor and sensory symptoms are absent until late in the course of the disease. However, other cognitive domains, such as language, praxis and recognition skills, are affected even early in the presentation. AD has a gradual and progressive course, and duration is typically 10 years from diagnosis to death. The advent of central cholinesterase inhibitors and glutamate receptor antagonists has had a positive effect on the memory symptoms of AD [121-123].

In early stages of AD, the prevalence of urgency incontinence is lower than in dementia with Lewy bodies [124, 125]. During stage III (advanced) AD, urinary and faecal incontinence occur due to loss of sphincter control [125]. In a study by Del Ser *et al.* (LOE 3) urinary incontinence was associated with severe cognitive decline in pure AD but usually preceded severe mental failure in patients with dementia due to diffuse Lewy body disease [125]. Nobili *et al.* (LOE 3) performed quantitative EEG in AD patients, finding that incontinence was predicted by alpha power in the right hand side [126]. In another study by Nobili *et al.* (LOE 3) the value of regional cerebral blood flow from a posterior temporal-inferior parietal area in each hemisphere predicted development of incontinence [127].

A brain computer tomography study done by Sugiyama *et al.* (LOE 3) in AD patients showed that the degree of brain atrophy was more severe in those with detrusor overactivity (DO) than those withoutDO was found in 40-61 % of patients. [128] (LOE 3). The incidence of DO in AD patients is low as compared with vascular dementia and dementia with Lewy bodies [129]. Haddad *et al.* (LOE 3) described two patients with vesicoureteral reflux, one of them showing buccosalivary, gastroesophageal, vesicoureteral, urethroprostatic and urethrovesical reflux as a consequence of the neurologic dysfunction [130]. In a study of 144 patients with AD reportingUI , the most common type of UI was urgency urinary incontinence. Clinical Dementia Rating and Barthel's Activities of Daily Living predicted the severity of detrusor overactivity in urodynamics [131].

7.1.1. Guidance for further research

We are still lacking studies evaluating LUT disorders in AD. Recently Averbeck *et al.* published a systematic review regarding medical management (both pharmacological and behavioural) of incontinence. [132] The role of surgery for LUT problems in these patients andthe issue of perioperative careremain unaddressed. [133]

7.1.2. Conclusions

Detrusor overactivity seems to be the most common underlying cause of lower urinary tract dysfunction patients with Alzheimer's disease (AD) (LOE 3), while the incidence is low as compared with vascular dementia and dementia with Lewy bodies.

UI in AD is also commonly as a result of disability associated incomtinence resulting from cognitive and physical impairment (LOE 3)

EEG studies, occurrence of developmental reflexes and regional blood flow studies can predict the development of incontinence in AD patients (LOE 3)

7.2. Non-AD dementia syndromes [134]

7.2.1. Vascular dementia

7.2.1.1. Epidemiology and prevalence

Vascular dementia is the second most common form of dementia after Alzheimer's disease (AD) among the elderly. The Rotterdam Study found that 72% of dementia cases were AD, 16% were VaD, and 12% other dementias, [135] while the Cardiovascular Health Study (CHS) found that 12% of the all cases met criteria for VaD, and of that group 27% met criteria for "pure" VaD, and 63% exhibited different degrees of cerebrovascular disease associated with other disease processes, mainly AD. [136] Pooled prevalence from eight European countries was 1.6% for vascular dementia in subjects older than 65, compared to a prevalence of 4.4% for AD (LOE 3) [137]. A meta-analysis of the European studies on the incidence of dementia showed vascular dementia constituted 17.6% of all incident dementia (LOE 3) [138].

Population-based MRI (MRI measures, [139]) studies suggest that moderate white matter disease (WMD, a major cause of

vascular dementia) affects around 10% (7.6–24%) of the general population of persons over 55 years of age [140], comparable to type 2 diabetes. WMD is associated with three different geriatric syndromes; 1) vascular dementia (usually mild in the Mini-Mental State Examination and other general cognitive function), 2) vascular parkinsonism, and 3) so-called vascular incontinence, i.e. urinary frequency/ urgency with or without incontinence [141]. Among these three syndromes, urinary and gait disorders are more prominent than dementia, and usually precede dementia. Coexistence of Alzheimer's disease (a degenerative disease) and WMD (a vascular disease) is not uncommon.

Vascular dementia may be the result of a single infarct, particularly involving the thalamus and left angular gyrus, or multiple cortical or subcortical infarcts. There is an elevated risk for subsequent dementia in patients who have had a stroke in comparison to controls without any evidence of a stroke (LOE 2) [142]. Diabetes and hypertension are stronger risk factors for vascular dementia than for Alzheimer's disease (LOE 3) [143]. The apolipoprotein e4 genotype is a risk factor for vascular dementia as well as AD (LOE 3) [144].

7.2.1.2. Pathology and disease-specific urinary tract problems

In patients with WMD, diffuse abnormalities are seen in the small deep perforating vessels of the hemispheric white matter, basal ganglia and brain stem. Pathological changes range from lipohyalinosis to fibrinoid necrosis and disintegration of small vessels. Disruption of the blood brain barrier is likely to precipitate or worsen progression of WMD [145] (LOE 3). Positron emission tomography imaging with 18F-fluoromisonidazole showed higher susceptibility to ischaemia of white matter than gray matter in stroke [146]. Cortical WMD in MRI looks diffuse. However, within the brain, detailed pathology studies confirmed that the frontal lobe is most severely affected [147]. This is in line with documented frontal lobe atrophy on MRI volumetry, where glucose metabolism was also most severely reduced [148] (LOE 3). Corresponding to this, brain perfusion is most reduced in the frontal lobe of subjects with WMD [149] (LOE 3), a finding that remains to be fully explained. In patients with WMD reporting incontinence ("vascular incontinence"), performance on the frontal assessment battery suggests that performance on an inhibitory control task is decreased in patients with detrusor overactivity [150] (LOE 3). The frontal cortex is an important higher centre for micturition: damage to the prefrontal cortex, medial superior/middle frontal gyri, anterior cingulate cortex, supplemental motor area and insula result in marked lower urinary tract dysfunction in humans [151] (LOE 3), corroborated by functional neuroimaging [152, 153] (LOE 3). It seems that the density of the frontal **white matter** hyperintensity predicts lower **urinary tract** dysfunction. [154]

Altered spinobulbospinal micturition reflex control may contribute to DO emergence in lesions of the brain [155] (LOE 3). Functional neuroimaging studies show that the prefrontal cortex was deactivated in elderly subjects with urinary frequency/ urgency (LOE 3). [156], [154] Jirovec *et al.* (LOE 3) found that cognitive ability and mobility differ significantly between continent and incontinent patients [157]. When the variables were examined together, mobility, followed by cognitive impairment emerged as the best predictor of the patient's urine control.

The prevalence of DO in WMD is reported as 70-91%. In Sakakibara's study, urodynamic studies in 33 subjects found DO more commonly in grade 1-4 white-matter lesions (82%) than grade 0 white-matter lesions (9%). [153] Yoshimura *et al.* (LOE 3) found a 47% prevalence of DO which correlated with the presence of dementia [158], confirmed by Ogama *et al.* with a predominance to the age and the athrophy of the front lobe. [154]

7.2.1.3. Recommendations for further research

Since dementia is not a homogeneous disease, a population study specifically reviewing disorders of lower urinary tract function is needed. A study evaluating different treatment modalities in patients with dementia (especially anticholinergic treatment for overactive bladder and surgical treatment for stress incontinence) is lacking.

7.2.1.4. Conclusions

Incontinence occurs in 30-100 % of patients with dementia (LOE 3).

The degree of incontinence is strongly associated with the patient's general status and mobility(LOE 3).

There is no one major cause for incontinence in these patients; however overactive bladder is responsible for a significant proportion of incontinence (LOE 3).

7.2.2. Dementia with Lewy bodies

7.2.2.1. Epidemiology and prevalence

Dementia with Lewy bodies (DLB) is thought to be the third most common type of dementia, accounting for 10 – 15% of cases at autopsy. In population-based studies of subjects aged 65 and older, the prevalence of DLB was found to be 0.7%. [159] The epidemiology of DLB is sparse; age and gender distribution, and potential risk factors have yet to be defined.

Pathology and disease-specific urinary tract problems in DLB primarily affects the basal ganglia (as in Parkinson's disease) and the cerebral cortex. Lewy bodies and Lewy neuritis are pathologic aggregations of alpha-synuclein (SNCA), a ubiquitously-expressed synaptic protein that has been implicated in vesicle production [160]. Lewy bodies also contain chaperone proteins and elements of the ubiquitin-proteasome system. Immunohistochemical staining for alphasynuclein is the most sensitive and specific method for detecting Lewy bodies and can be used in a semiquantitative grading of severity of Lewy-related pathology [161]. Alpha-synuclein can now be measured in vivo by positron emission tomography and/or in the cerebrospinal fluid.

Many patients with DLB also have Alzheimer's disease pathology, which alters the clinical presentation. DLB patients who also have numerous neurofibrillary tangles display more core clinical features of AD [162]. Conversely, Lewy bodies also occur in more than half of patients with sporadic and early-onset AD [163]. The essential feature for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Fluctuations (waxing and waning of cognition, functional abilities and arousal, from almost normal to markedly confused or hypersomnolent) are a core feature of dementia with Lewy bodies. In DLB, autonomic dysfunctions occur and are included as a supportive feature for clinical diagnosis [164].

Horimoto *et al.* (LOE 3) found a 97% incidence of UI amongst patients with DLB. From the urological point of view, patients with DLB tend to develop urgency and urgency incontinence

more often than do patients with Parkinson's disease (PD) or AD. Similar bladder capacity, detrusor pressure at maximum voiding, maximum urine flow, mean voided volume and post-void residual volume were found in each disease; DO was more prevalent in DLB than in PD and in AD [165]. Urinary symptoms were recorded in 35 % of patients with DLB, compared to 70 % in MSA and 25 % in PD patients. No detrusor-sphincter-dyssynergia (DSD) was observed. DLB patients with DO had significantly higher Hoehn and Yahr scores than those without. Since the prevalence of frequency, urgency, urgency incontinence and DO is markedly lower in AD than in DLB, LUTS may contribute to the differential diagnosis of these two entities.

7.2.3. Frontotemporal dementia (FTD)

7.2.3.1. Epidemiology and prevalence

FTD commonly presents in oounger patients and the average age of onset is 56. [166] The estimated prevalence is 0.16-31.04 per 1000 persons and incidence (0.0-0.3 per 1000 person-years). FTD accounted for an average of 2.7% (range 0-9.1%) of all dementia cases. [167] A high familial occurrence of FTD is reported [168]. In such cases, a combination with parkinsonism, and rarely amyotrophic lateral sclerosis, also occurs. The distribution of FTD is almost equal between men and women (52.5:47.5). The mean duration of illness from onset to death is 4-6 years, with a range of 2-20 years.

7.2.3.2. Pathology and disease-specific urinary tract problems

Frontotemporal dementia (FTD), also known as Pick's disease, encompasses a diverse group of clinical and pathological disorders. There are several distinct clinical presentations, most commonly behavioural changes, but a language disorder, usually in the form of a progressive non-fluent aphasia, can be the main presenting sign. The most common clinical presentation of FTD is characterized by profound changes in personality and social conduct, including a decline in manners and social skills that are incongruent with the patient's premorbid behaviour. Affected patients lack emotional warmth, empathy and sympathy and are indifferent to others.

MRI of patients with FTD often shows atrophy in the frontal and temporal lobes (LOE 2), which may be asymmetrical [63]. At autopsy, markedly gross atrophy of the frontal and temporal lobes is seen in FTD. On histological examination the salient features include neuronal loss, micro-vacuolization and astrocytes gliosis centred on cortical layer II.

Molecular pathology of FTD has identified four subtypes: [169]
- classical FDT (Pick's disease; Pick body with accumulation of 3-repeat tau);
- mutations in the MAPT (microtubule-associated protein tau) gene;
- accumulation of TDP-43 (TAR DNA binding protein-43) with mutations in the PGRN (progranulin) gene; and,
- accumulation of FUS (fused in sarcoma) protein

FTD is subdivided in Behavioral Variant FTD (bvFTD) and Frontotemporal Dementia-Motor NeuronDisease (FTD-MND) associated with a shorter survival (2.4 years from symptom onset) compared with bvFTD alone (6.6 years). [170]

There are no published data on LUTS in patients with FTD, but due to the cognitive state these patients have incontinence, either because they forget to take down clothes when they go into the toilet, or they have difficulty finding the toilet, or they may urinate in inappropriate places. They may also be affected by constipation, diarrhoea or faecal incontinence.

8. NEUROLOGICAL URINARY INCONTINENCE

8.1. Introduction

NLUTD may be caused by a variety of neurological diseases and/or events affecting the various parts of the nervous systems controlling the LUT. The resultant dysfunction depends grossly on the location, extent, and nature of the causative neurological lesion or lesions. Overall prevalence estimates for NLUTD in the general population are scarce, but data are available on the prevalence of the underlying conditions and, in some cases, the relative risk for the development of NLUTD. It is important to realize that most of these data show a very wide range of prevalence figures, due to low level of evidence in most published data and smaller sample sizes.

Nevertheless, worldwide estimates of the prevalence of spinal cord injury (SCI) are at over 2.5 million, multiple sclerosis (MS) considerably greater than 1.5 million and Parkinson's disease (PD) approximately 6 million [171-174]. Spinal cord injuries are common, with an estimated between 10.4 and 83 per million people per year which represents an absolute annual number of 80,000–630,000 new cases worldwide sustaining a traumatic spinal injury every year in the Western world [175]. Non-traumatic injury (vascular, infection, tumour) is more common, and cancer alone is estimated to cause more SCI than trauma [176]. The incidence of nontraumatic SCI varies between 6 and 76 per million population per year. [177-179] Nontraumatic SCI is attributed in 41% of the cases to degenerative spine diseases with consecutive spinal canal stenosis, 26% to tumours compressing the spinal cord, 20% to infectious diseases, and 16% to ischaemia and in most cases is an incomplete injury. [180]

Traumatic injury mostly affects young men, and advances in rehabilitation medicine mean that the longevity of paraplegics is similar to the general population while that of tetraplegics is 10 years shorter [181]. The prevalence of MS varies from North America and Europe (more than 100 cases per 100,000 population) to low levels in Eastern Asia and Sub-Saharan Africa (2 cases per 100,000 population). [182]

Mobility, pain and bladder dysfunction in neurological patients has been relatively well studied, while bowel and pelvic floor dysfunction has been neglected by comparison. With rapid advances in rehabilitation medicine resulting in increased survival of patients, these individuals are experiencing bladder and bowel symptoms for ever-longer periods.

The conclusions and recommendations on epidemiology of the previous ICI report therefore remain unchanged.

8.2. Conclusions

- Dysfunction of the LUT occurs in patients with a variety of neurological diseases but precise epidemiological data are seldom available
- Common manifestations of NLUTD include urinary incontinence, voiding difficulties, and urinary retention.
- Because neurological disease is often present in older populations, it is frequently difficult to discriminate if LUTS are due

to aging alone, or due to the presence of neurological disease. This difficulty is reflected in widely varying prevalence estimates.

8.3. Recommendations

Patients with neurological disease known to be associated with NLUTD should be evaluated for the presence of lower urinary tract symptoms.

- In certain neurologic disease states, NLUTD may be relatively asymptomatic, yet represent a risk of upper urinary tract impairment.
- In the appropriate clinical setting, a neurological evaluation may be recommended in a patient with unexplained LUTS and no known neurological disturbance. This is particularly true in the case of a young patient with idiopathic severe LUTS after proper office evaluation for common aetiologies.
- Prevalence estimates of NLUTD would be improved by multicentreco-operative studies from large tertiary centres utilizing established outcomes and evaluation tools.

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V. PELVIC ORGAN PROLAPSE

1. INTRODUCTION

The most accounted model describing the pathophysiology of pelvic floor disease (PFD) is the chronic disease life span approach, which emphasizes the chronological impact of different types of exposure variables as well as their interrelationship [1, 2].

According to DeLancey, three specific phases can be identified [2]. Phase I accounts for predisposing factors such as genetic predisposition and growth. Phase II corresponds to provoking factors, in which birth-induced damage to the pelvic floor has a major role. Phase III accounts for intervening factors such as aging, obesity and lifestyle practices.

A new study supports a multifactorial aetiology for pelvic organ prolapse considering altered smooth muscle, vasculature, and connective tissue content as crucial for pelvic support structures [3]. Histological phenotypes exist in pelvic support ligaments that can be distinguished using the pelvic organ prolapse histologic quantification system and principle component analysis. Vaginal delivery is associated with aberrant adipose accumulation in uterosacral ligaments. The prolapse ligaments in the premenopausal group had significantly more loss of smooth muscle fibres within the fascicles, increased inflammatory infiltrates of neutrophils within the tissue and perineural inflammatory cells and reduced neointimal hyperplasia. Prolapse ligaments in the postmenopausal group exhibited elevated adipose content compared with that of the control group. Amount of fibrillar collagen, total nonvascular smooth muscle, and muscle fibre vesicles of prolapse ligaments did not differ in either the premenopausal or postmenopausal group compared with that of the control group. Unbiased principal component analysis of the histological scores separated the prolapse ligaments into 3 phenotypes: (1) increased adipose accumulation, (2) increased inflammation, and (3) abnormal vasculature, with variable overlap with controls. *Post hoc* analysis of these subgroups demonstrated a positive correlation between increasing number of vaginal deliveries and BMI with increasing adipose content in the adipocyte accumulation and inflammatory phenotype and increasing neointimal hyperplasia in the vascular phenotype [3].

2. ANATOMY

A basic understanding of pelvic floor anatomy is essential for adequate anatomical and functional evaluation of the pelvic floor. For purposes of clinical evaluation, the female pelvis is classically divided into 3 compartments: the anterior compartment containing the bladder and urethra; the middle compartment containing the uterus, cervix, and vagina; and the posterior compartment containing the rectum and anal canal. These compartments are closely interrelated, and patients often present with multicompartment dysfunction [4-6].

The compartments of the pelvic floor are supported by a complex network of fascia, ligaments, and pelvic floor muscles that form 3 layers of support:
- the endopelvic fascia (superior),
- the pelvic diaphragm (middle),
- the perineal membrane or urogenital diaphragm (inferior).

The fascia and ligaments provide passive support, whereas the musculature of the pelvic diaphragm provides the underlying tone and can be recruited for active support.

2.1. Endopelvic Fascia

The endopelvic fascia is a sheet of connective tissue that extends across the pelvic floor from the bony pelvis on one side to the other and forms the superior-most layer of support of the pelvic floor. It covers the levator ani muscles and pelvic viscera. Various components of the endopelvic fascia are named according to their location:

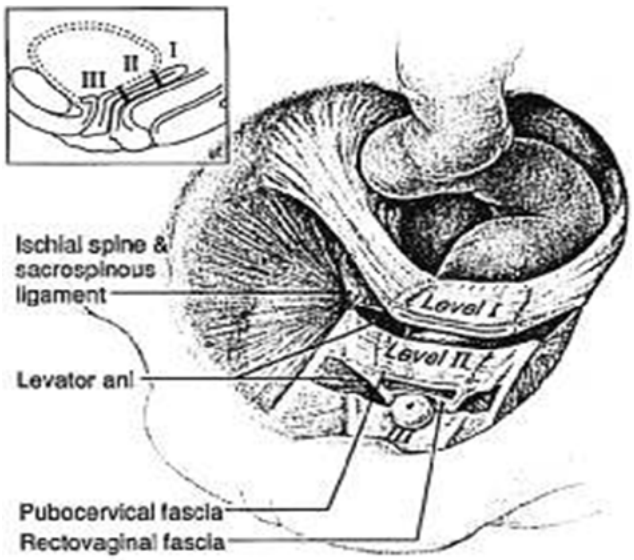


Figure 1. Level I (suspension) and level II (attachment). In level I the paracolpium suspends the vagina from the lateral pelvic walls. Fibers of level I extend both vertically and also posteriorly towards sacrum. In level II vagina is attached to arcus tendineus fasciae pelvis and superior fascia of levator ani. From DeLancey et al, Clin Obstet Gynecol,1993 [7].

- the pubocervical fascia between the bladder and vagina or cervix
- the parametrium extending from the cervix to the lateral sidewalls
- the paracolpium extending from the vagina to the pelvic sidewalls
- the rectovaginal fascia between the vagina and rectum.

The cardinal and uterosacral ligaments arise from condensations of the endopelvic fascia superiorly. Laterally, the endopelvic fascia coalesces to form the arcus tendineus along the bony pelvis, which serves as an attachment site for the muscles that form the pelvic diaphragm.

The endopelvic fascia provides 3 levels of support in relation to vagina: level I (vaginal apex), level II (mid vagina), level III (distal vagina), and defects in each level may present with unique physical signs and symptoms (Figure 1) [7].

Deficiencies within different portions of the fascia may determine the degree of prolapse in each compartment. For example, defects in the uterosacral ligaments or the paracolpium/parametrium may result in cervical or vaginal prolapse; tears in the pubocervical fascia or urethral ligaments may result in cystocele and urethral hypermobility; and defects in the perineal body or rectovaginal fascia may present with anterior rectocele or enterocele [8].

2.2. Pelvic Diaphragm

The pelvic diaphragm provides the middle layer of support of the pelvic floor and consists of the ischiococcygeus muscles and the levator ani muscles.

The levator ani is a vaselike or hourglass-shaped group of striated muscles composed of the iliococcygeus, pubococcygeus,

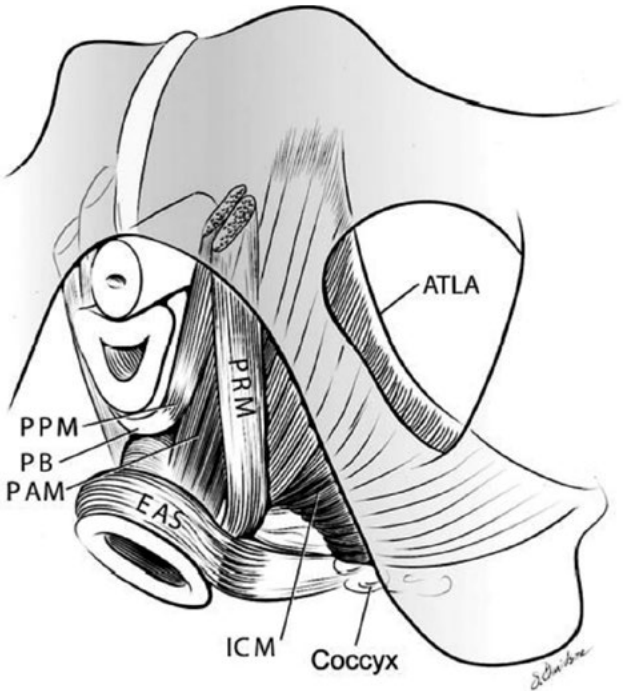


Figure 2: Schematic view of the levator ani muscles from below after the vulvar structures and perineal membrane have been removed showing the arcus tendineus levator ani (ATLA); external anal sphincter (EAS); puboanal muscle (PAM); perineal body (PB); uniting the 2 ends of the puboperineal muscle (PPM); iliococcygeal muscle (ICM); puborectal muscle (PRM). Note that the urethra and vagina have been transected just above the hymenal ring. Copyright © DeLancey 2003. [11]

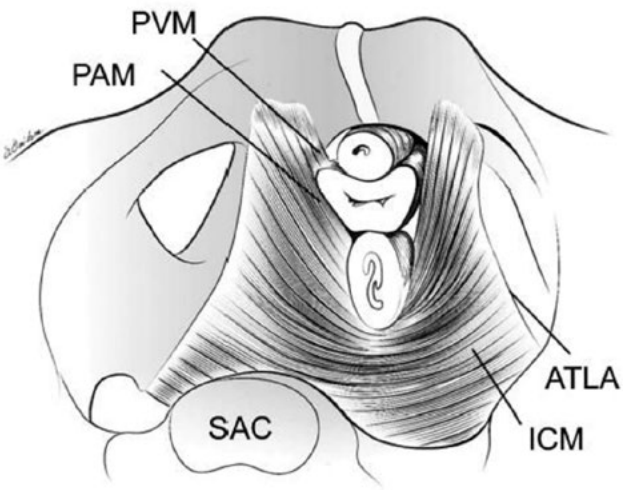


Figure 3: The levator ani muscle seen from above looking over the sacral promontory (SAC) showing the pubovaginal muscle (PVM). The urethra, vagina and rectum have been transected just above the pelvic floor. PAM = puboanal muscle; ATLA = arcus tendineus levator ani and ICM= iliococcygeal muscle (The internal obturator muscles have been removed to clarify levator muscle origins). Copyright © DeLancey 2003. [11]

and puborectalis muscles. These muscles normally maintain a convex appearance superiorly. The relatively thin iliococcygeus muscle attaches anteriorly to the pubic bone, laterally to the arcus tendineus, and inferiorly to the external anal sphincter. The thicker pubococcygeus muscle is more medially located relative to the iliococccygeus; it arises from the superior pubic rami and wraps around the bladder, urethra, vagina, and rectum. Posteriorly, the iliococccygeus and pubococcygeus form a thick condensation of tissue called the levator plate, which inserts upon the sacrum and coccyx. The iliococccygeus and pubococcygeus muscles are difficult to differentiate on imaging owing to the overlap in fibres and morphology. The most caudal component of the levator ani muscle group is the puborectalis, which attaches anteriorly to the pubic symphysis and forms a U-shaped sling around the anorectum. The level of the puborectalis impression upon the posterior rectum demarcates the anorectal junction, and the margins of the puborectalis form the urogenital or pelvic floor hiatus. Superiorly, the puborectalis muscle fibres overlap with the pubococcygeus. The ischiococcygeus or the coccygeus muscle is a relatively minor part of the pelvic diaphragm, extending from the coccyx in the midline to the ischial spine bilaterally [8-10] (Figure 2, Figure 3).

The pelvic diaphragm provides continuous tone to the pelvic floor, but can be contracted or relaxed actively.

2.3. Perineal Membrane/Urogenital Diaphragm

The perineal membrane (also referred to as the urogenital diaphragm) forms the caudal-most layer of the pelvic floor and comprises primarily the deep transverse perineal muscle and connective tissue that extend from ischial rami laterally to the perineal body in the midline. The perineal membrane attaches anteriorly to the pubic symphysis, giving the perineal membrane a triangular shape (Figure 4).

Anatomical support of pelvic viscera is mainly provided by the levator ani muscle complex and connective tissue attachments of the pelvic organs: vaginal support arises from the connective tissue attachments between the vagina and the pelvic sidewall, the vaginal wall, and the levator ani muscles [12, 13].

Two mechanical principles explain how the uterus and vagina are normally held in place. First, the uterus and vagina are attached to the walls of the pelvis by the endopelvic fascia that suspends the organs from the pelvic sidewalls. Second, the levator ani muscles costrict the lumen of these organs closed, forming an occlusive layer on which the pelvic organs may rest [14].

The levator ani complex consists of the pubococcygeus, the puborectalis, and the iliococcygeus muscles [11]. These muscles are tonically contracted at rest and act to close the genital hiatus, providing a stable platform for the pelvic viscera. Decline of normal levator ani tone by denervation or direct muscle trauma, results in an open urogenital hiatus, weakening of the horizontal orientation of the levator plate, and a bowl-like configuration [15, 16].

The supportive connective tissues are a continuous, highly interdependent sheet in which all members interact to achieve support of the vagina and, therefore, of the pelvic organs. DeLancey has introduced the concept of dividing the connective tissue support of the pelvis into three levels, with level I, II and III representing apical, midvaginal and distal support respectively. The upper portion of the paracolpium (Level I) consists of

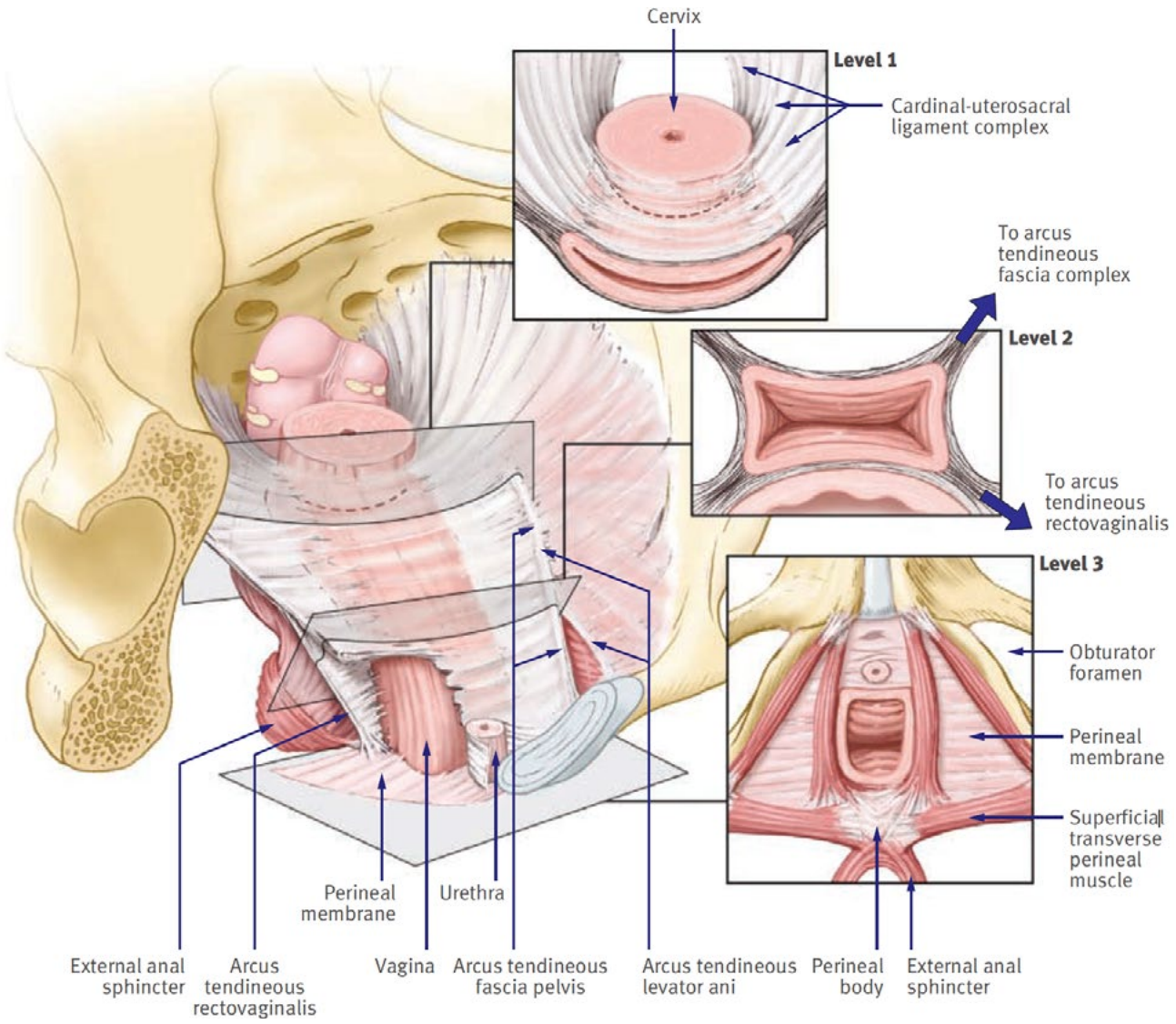


Figure 4: DeLancey´s three level of pelvic support. Reprinted from Barber [18], with permission from the Cleveland Clinic Foundation [19].

a relatively long sheet of tissue that suspends the vagina by attaching it to the pelvic wall, and it is responsible for suspending the apex of the vagina after hysterectomy. In the middle third of the vagina, the paracolpium attaches the vagina laterally, to the arcus tendineus and fascia of the levator ani muscles (Level II). This attachment stretches the vagina transversely between the bladder and the rectum. The structural layer that supports the bladder (pubocervical fascia) is composed of the anterior vaginal wall and its attachment through the endopelvic fascia to the pelvic wall. Similarly, the posterior vaginal wall and endopelvic fascia (rectovaginal fascia) form the restraining layer that prevents the rectum from protruding forward. The vagina´s lower third (Level III) fuses with the perineal membrane, levator ani muscles and perineal body, without any intervening paracolpium (Figure 4) [14, 17]. Damage to the upper suspensory fibres of the paracolpium causes a different type of prolapse from damage to the mid-level supports of the vagina. Defects in the support provided by the mid-level vaginal supports (pubocervical and rectovaginal fascia) result in cystocele and rectocele, while loss of the upper suspensory fibres of the paracolpium and parametrium is responsible for the development of vaginal and uterine prolapse. These defects usually occur in varying combinations and this is responsible for the diversity of clinical problems encountered within the overall spectrum of pelvic organ prolapse [14].

For conceptual purposes the supportive connective tissue has been related with structural elements of pelvic floor: the uterosacral ligaments (level I); the paravaginal attachments (endopelvic fascia) that connect the lateral vaginal walls to the arcus tendineous fascia pelvis (ATFP) and the fascia of the levator ani muscles (level II); the perineal membrane and the perineal body (level III) [17].

Table 1: lists the structural elements of pelvic organ supports, their possible damage and subsequent site of pelvic organ prolapse. The integrity of muscular, connective and nerve structures is essential to guarantee a normal pelvic organ support. If one of these factors fails, the other might be able to compensate to a certain degree.

Structural elements of pelvic organ support, their possible damage and subsequent site of pelvic organ prolapse. The levels of support and anatomical defects are derived from the anatomical studies of DeLancey [14, 17].

	Structure	Failure/Defects	Anatomical results
Level 1	Uterosacral ligaments	• Disruption • Overdistension • Elongation	• Uterine prolapse • Vault prolapse
Level 2	• Anterior endopelvic fascia (pubocervical fascia) • Posterior endopelvic fascia (rectovaginal fascia)	• Central impairment of fascia • Lateral detachment of fascia from ATFP • Impairment of fascia	• Midline cystocele • Paravaginal defect-cystocele • Rectocele
Level 3	Perineum	• Disruption from endopelvic fascia • Disruption of bulbocavernosus muscles	• Excessive perineal descent • Rectocele

3. AETIOLOGY

In an American gynaecologic clinic population (18-83 years), approximatively 3-6% of women had pelvic organ prolapse descending beyond the vaginal opening on routine pelvic examination [20]; an estimated 11% of women will undergo surgery for pelvic organ descent and urinary incontinence sometime in their life [21].

The aetiology of pelvic organ prolapse (POP) is thought to be multifactorial with contributions from both environmental and genetic risk factors. Environmental factors that contribute to POP include vaginal delivery, chronic increases in intra-abdominal pressure, obesity, advanced age and oestrogen deficiency [22, 23]. Evidence for a genetic contribution to pelvic organ prolapse has been found in family-based studies, candidate gene association studies, expression studies and linkage studies [24].

Vaginal delivery has been considered the main causal factor in the development of pelvic organ prolapse for some years [21, 25-29]. However, if it is true that all women undergo pelvic floor stretching during vaginal delivery, not all of them develop a further prolapse; moreover, pelvic floor dysfunction has also been described in women who gave birth by caesarean section only [23, 26] and in nulliparous women [30]. Therefore, the vaginal delivery does not totally explain the origin and progression of pelvic floor descent in all women. This supports the hypothesis

Table 2: lists anatomical and functional determinants of normal pelvic organ support. It also summarizes the possible nature of failure and its potential causes as well as the established and theoretical risk factors.

Determinants of normal pelvic organ support. Possible sites of failure and possible causes, established and theoretical risk factors. LE= LEVEL OF EVIDENCE

Normal support	Failure	Possible cause/risk factors
Normal connective tissue including normal tone (smooth muscle cells)	• Reduced tone • Pathological type and cross linking (LE 2) • Disruption (LE 2)	• Genetic (LE 2) • Pregnancy (connective tissue remodelling) (LE 3) • Vaginal birth (mechanical) (LE2) • Chronic pelvic floor stress 8straining, constipation, asthma) • Obesity
Normal attachment of connective tissue and pelvic floor musculature	• Disruption, detachment (LE2)	• Vaginal birth (LE 1) • Hysterectomy, pelvic operations (LE3) • Chronic pelvic floor stress (LE3) • Pelvic trauma (accidents, falls) (LE3)
Normal tone of the pelvic floor muscle	• Hypotonic pelvic floor muscle (LE4)	• Pregnancy, childbirth (ischemic, mechanical, hormonal) (LE2) • Reduced connective tissue tone • Chronic pelvic floor stress
Normal, nearly horizontal, axis of the vagina	• Vertical course of the vagina (LE3)	• Hysterectomy, pelvic operations including Burch colposuspension (LE3) • Chronic pelvic floor stress • Vaginal birth (LE2)
Normal innervations and pre-programming of abdominal capsule and pelvic floor muscle	• Denervation/re-innervation (LE1) • Loss of pre-programming (LE4)	• Vaginal birth (LE1) • Pelvic trauma/pain • Delayed or lack of pelvic floor contraction during increased abdominal pressure (LE3)

that other causes, besides obstetrics, are involved in the aetiology of the pelvic organ prolapse: connective tissue deficiencies, genetic predisposition, sexual hormones, pregnancy, ageing, menopause, obesity, neuropathies, ethnicity and family history.

Miedel *et al.* [31] showed that age and parity are the dominating risk factors for symptomatic pelvic organ prolapse, but significant independent associations with markers suggestive of congenital susceptibility (family history and conditions signaling weak connective tissue) and non-obstetric strain on the pelvic floor (overweight/obesity, heavy lifting and constipation) imply that individual predisposition and lifestyle/environment also may play an important role. (LEVEL OF EVIDENCE: II)

In the last decade, attention has increasingly focused on understanding of the molecular basis of POP and the recognition of the potential molecular markers and their modulators in pelvic floor supportive tissues in order to identify the women predisposed to develop POP.

3.1. Inheritance, Genetic and Ethnic Predisposition
Several studies have focused the attention on the inheritable predisposition for pelvic organ prolapse.

A recent metanalysis showed that positive family history of POP is on average associated with 2.3- to 2.7-fold increased risk for POP as well as a 1.4-fold increased risk for POP recurrence [32]. Positive family history has been recently identified as independent risk factor (OR 8.016) for prolapse [33].

The findings of high concordance in the POP stage between nulliparous women and their parous sisters strongly support the hypothesis of a familial basis for POP. Buchsbaum *et al.* [34] investigated the role of familial factors in the development of pelvic organ prolapse by comparing the prevalence of this condition in nulliparous postmenopausal women and their parous sisters. By compartment, there was a 74.3% to 91.1% concordance in prolapse stage within sister pairs. In discordant sister pairs, the parous sister was found to have the more advanced prolapse 88% of the time. Based on these results, the authors conclude that a high concordance of pelvic organ prolapse in nulliparous and parous sister pairs suggests a familial predisposition toward developing this condition. However, vaginal delivery appeared to confer a risk for more advanced pelvic organ prolapse. LEVEL OF EVIDENCE: II-2.

In the large case-control study carried out by Chiaffarino *et al.* [35], a higher risk of prolapse was reported in women whose mother (OR: 3.2; 95% CI: 1.1-7.6) or sister (OR: 2.4; 95% CI: 1.0-5.6) were affected by the same condition; also their data support that first-degree family history of prolapse is a risk factor for POP.

The systematic review by Lince *et al.* [36] found a substantially greater likelihood of SUI in family members with women with POP compares with women without POP, indicating that genetic predisposition play an important role in the development of POP. In a study of nulliparous women, Dietz *et al.* [37] showed also the heritability of bladder-neck mobility.

Jack *et al.* [38] demonstrated that the risk of POP among siblings of young women (average age: 37 years) with stage III and IV POP was five times higher than in the general population. Genetic analysis of the inheritance pattern within these families showed that POP segregated in a dominant fashion with incomplete penetrance. Some studies have drawn attention to the incidence of pelvic organ prolapse amongst identical twins. In the large Swedish twin registry of 3,376 monozygotic and 5,067 dizygotic female twin pairs, a greater twin similarity among the monozygotic twins was found, indicating the influence of a genetic component to the aetiology of pelvic organ prolapse. Genetic and non-shared environmental factors seemed to contribute equally to the development of pelvic floor disorders in these women, about 40% for each factor [39]. A study of twins by Altman *et al.* [39] on SUI and POP analyzed 3,376 monozygotic and 5,067 dizygotic female twins and found a greater similarity in outcomes in monozygotic twins.Buchsbaum *et al.* [40] even reported that vaginal delivery was not associated with clinically relevant differences in relaxation of the pelvic support system within four sets of postmenopausal identical twins with different parity status.

Genetic variants that run in families with an increased incidence of pelvic organ prolapse have been documented.

A recent genome-wide association study of POP using data from Iceland and the UK biobank found eight sequence variants at seven loci associating with POP; seven common (minor allele frequency >5%) and one with minor allele frequency of 4.87%. Some of the variants associating with POP also associated with traits of similar pathophysiology. Of these, rs3820282, which may alter the oestrogen-based regulation of WNT4, also associates with leiomyoma of the uterus, gestational duration and endometriosis. Rs3791675 at EFEMP1, a gene involved in connective tissue homeostasis, also associates with herniae and carpal tunnel syndrome. These results highlight the role of connective tissue metabolism and oestrogen exposure in the etiology of POP [41].

Allen-Brady *et al.* [42], using a genome-wide association study, demonstrated that 6 single-nucleotide polymorphisms (SNPs) are significantly associated with POP in high-risk familial case group participants. LEVEL OF EVIDENCE: II. Their results showed that two of the six SNPs are located within the genes ZFAT and COL18A1, both with Mendelian inheritance. The ZFAT has been found to play a transcriptional regulator role for immune regulation and apoptosis and, hence, may affect development of the muscle and connective tissue of the pelvic floor. The COL18A1 gene (precursor of the collagen XVIII) may play a role in the structural organization of basement membranes. The other four SNPs identified are intergenic, but one of them is close to the ANTXR2 gene, which binds intravenously to collagen and laminin, suggesting that it may be involved in extracellular matrix adhesion. The authors identified at least three strong candidate genes for POP that warrant follow-up. Another genome-wide linkage analysis to identify pelvic organ prolapse predisposition genes using a resource of high-risk POP pedigrees, provided evidence that loci on the chromosomes 10q and 17q may contribute to POP aetiology [43].

Further data suggest a role of genetic influence in early onset of POP. In a family in which three generations of female relatives suffered from prolapse at a very young age, a polymorphism in the promoter of LAMC1 gene has been found that seems to increase the susceptibility to early onset pelvic organ prolapse, as an autosomal dominant transmission [44]. A recent study on Chinese population strongly supports the involvement of LAMC1 in POP development [45].

A metanalysis of genetic association studies provided moderate epidemiological credibility for association of variation of COL1A1 gene with prolapse [46]. The authors suggested that clinical testing for these polymorphisms cannot be recommended based on current evidence. A recent study lack of association between DNA polymorphisms rs1800012 of COL1A1 and rs1800255 of COL3A1 with advanced POP [47].

One study examined gene expression of structural proteins that are related to actin and myosin in five women with, and five women without, pelvic organ prolapse in the pubococcygeal muscle. Several genetic differences between subjects and controls with gene under- and overexpression were found [48]. In mice, HOXA11 has been identified as an essential gene for the development of the uterosacral ligaments [49]. In HOXA11-null mice, the uterosacral ligaments were absent. Women with POP might have weakened connective tissue due to changes in a signaling pathway involving HOXA11 [49].

Increasing evidence supports a genetic aetiology of POP, also with respect to abnormal extracellular matrix remodeling [50]. A genetic predisposition to POP specific to elastin metabolism was noted in the rodent model, in which genetic mutation of the LOXL1 or the fibulin-5 gene in mice are involved in the altered elastic fibre assembly and then in the pathogenesis of the pelvic prolapse [51]. Altered gene expression of elastin has also been described in women with POP [52].

The study carried out by Wang *et al.* [53] supported the view that the polymorphism of the matrix metalloproteinase-10 (MMP-10) gene may be associated with an increased risk of POP.

Genetic screening may be a future tool for identifying the woman at risk for POP and for refining the counseling of women deemed to be at elevated risk; with the aim of preventing the condition and providing a targeted treatment. Primary prevention could be the adaptation of the delivery mode in at-risk groups. These patients could also benefit from changing management, such as whether surgery should be considered early or late in the woman´s lifespan.

Race is another demographic factor that seems to be associated with the development of POP. Some studies reported that Hispanic and European women appear to be at higher risk for POP than those of African, Asian or other descent [20, 23, 28, 54, 55]. This is also supported by evidence suggesting that women of Asian descent have reduced inherent pelvic organ mobility. In a cadaveric study, Zacharin [56] reported that Chinese women have stronger and thicker pubourethral ligaments, endopelvic fascia and endopelvic attachment to the obturator fascia compared to Caucasian women. More recently, Dietz *et al.* [55] confirmed these results using pelvic floor ultrasound, showing that Asian women have significantly less pelvic organ mobility than Caucasian women both antepartum and postpartum. In a cohort analysis of 27,342 women, Hendrix *et al.* [28], confirmed previously reported differences between white and African-American women. Hispanic women had the highest rate of uterine prolapse (OR: 1.24, 95% CI: 1.01-1.54) and an increased risk for cystocele (OR: 1.20, 95% CI: 1.05-1.36) but not rectocele (OR: 0.95, 95% CI: 0.82-1.11). The reasons for these ethnic differences are unclear; however, some evidence indicates that African-American women have smaller pelvic outlets than those of European descent [57].

Other connective tissue deficiencies such as herniae may share common pathophysiological mechanisms with POP. In a group of 60 women with advanced prolapse, the total prevalence of hiatal and inguinal herniae was significantly higher than in a control group of 60 women with mild or no prolapse (31.6% vs. 5%, $p<0.001$) [58].

A Stockholm population-based, cross-sectional study of 5,489 women found an OR of 1.8 for a positive association with symptomatic prolapse in women with a history of conditions suggestive of deficient connective tissue (varicose veins/herniae/haemorrhoids) [31].

McLennan *et al.* [59] demonstrated that the risk of prolapse was 1.4 (95% CI 1.2-1.8) times higher in women with a family history of prolapse and/or hernia, after adjusting for vaginal deliveries, hysterectomy and incontinence. The authors confirm that heredity is a risk factor for prolapse and suggest that history taking should include both male and female family members.

Taken together, this evidence suggests that exists a familial or genetic basis for POP in some women, and that heritable or genetic factor plays a role in its development.

3.2. Role of connective tissue

Young women with POP are more likely to have connective or neurological tissue diseases and congenital abnormalities [60]. Women with Marfan or Ehlers-Danlos syndrome have high rates of POP. Intrinsic joint hypermobility is another well recognized connective tissue disease that is associated with pelvic descent [61-64]. This finding supports the hypothesized aetiological role of connective tissue disorders as a factor in the pathogenesis of this conditions [65].

The vaginal wall is comprised of four layers: a superficial layer of non-keratinized stratified squamous epithelium; a subepithelial dense connective tissue layer composed primarily of collagen and elastin; a layer of smooth muscle referred to as the muscularis; and a layer of adventitia, composed of loose connective tissue. The subepithelium and muscularis together are thought to confer the greatest tensile strength to the vaginal wall. In the normally supported vagina, the supportive connective tissues pull the vagina up and back away from the vaginal introitus over the levator ani muscles. A normally supported vagina, in turn, provides support to the bladder, urethra, uterus and rectum. Disruptions of, or damage to, these connective tissue structures and injury to the vaginal wall are thought to be two important mechanisms causing prolapse.

The connective tissue of the vagina and supportive tissues contains a fibrillar component (collagen and elastin) and a non-fibrillar component (non-collagenous glycoproteins, hyaluronan, and proteoglycans). In addition, and with the exception of the arcus tendineous, these tissues contain a significant amount of smooth muscle. The fibrillar component is thought to contribute the most to the biomechanical behaviour of these tissues. The quantity and quality of collagen and elastin are maintained through a precise balance between synthesis, post-translational modification, and degradation.

Therefore, the integrity of the vagina and its supportive connective tissues are essential for keeping the pelvic organs in their normal anatomic position. Evaluation of these tissues from a biochemical perspective enables us to better discern the com-

plex interplay between structural composition and supportive capacity.

Collagen types I, III and V are the main structural components of vaginal epithelium and endopelvic fascia and they are thought to be the principal determinants of tissue strength. Type I collagen confers strength to tissues while type III contributes to elasticity. Type III collagen is the primary collagen subtype in the vagina and its supportive structures. The ratio of collagen I to III is an indicator of tensile strength: the higher the amount of collagen type III, the lower is the mechanical strength. To our knowledge the role of type V collagen, which is found in small quantities in the vagina, is still unknown.

The turnover of connective tissues throughout the body is maintained by a family of highly conserved, zinc-dependent endopeptidases referred to as matrix metalloproteinases (MMPs). The MMPs are involved in both normal physiological and pathological proteolytic processes, which are an integral part of tissue remodeling in both women with and without prolapse. An excessive tendency toward connective tissue degradation may underlie the predisposition of some women to prolapse.

Interstitial collagens (types I, II and III) are cleaved by MMP-1, 8 and 13. The cleaved collagen fragments are susceptible to rapid gelatinase (MMP-2 and 9) degradation into amino acids. These gelatinases (MMP-2 and 9) also degrade elastin.

Reports of decreased total collagen in pelvic tissue from women with POP suggest that collagen degradation may contribute to POP. Collagen degradation depends on the activity of MMPs produced by connective tissue cells. MMP proteolytic activity is specifically regulated by their inhibitors, TIMPs, which bind stoichiometrically to MMPs to inhibit their activity. The balance between MMPs and TIMPs defines the collagenolysis.

In women with prolapse, MMP-2 mRNA expression is increased with a concurrent decrease in the inhibitor TIMP-2 [66]. Recent data also indicate increased MMP-1 expression and decreased collagen I in the uterosacral ligaments of women with POP [67]. In contrast, collagen I and III mRNA expression was increased in vaginal tissue from women with POP [68]. Discrepancies in the literature can be due to the different methodological issues (different tissues targeted or a different method of protein quantification) used. Mismatches between mRNA and protein data are often found when examining proteins in the extracellular matrix. Thus, gene expression should always be confirmed with protein expression. These issues contribute to significant variations in the reported data and underscore the importance of careful research method. These discrepancies also suggest the possibility that different pathways in the extracellular matrix may be activated depending on injury type and severity, mechanical load and environmental factors [50].

Despite discrepancies in the precise MMP/TIMP or collagen type, the mentioned data and numerous other publications indicate that women with POP show an abnormal pelvic extracellular matrix metabolism with increased collagen remodeling.

Recent data suggested that oxidative stress (a well-recognized mechanism involved in fibre metabolic disorders) may be involved in the pathophysiology of POP by contributing to collagen metabolic disorders in a severity-dependent manner in human uterosacral ligaments fibroblasts, possibly through the regulation of metalloproteinase (MMPs), tissue inhibitor of metalloproteinase (TIMPs) and transforming growth factor (TGF)-ß1 indirectly [69]

Takano *et al.* [70] demonstrated that the general amount of collagen in the parametria is reduced in pre- and postmenopausal women with pelvic organ prolapse compared with women without prolapse. Moalli *et al.* [71] showed that collagen III is increased in vaginal subepithelium and muscularis in patients with prolapse relative to patients without prolapse, independent of age and parity. LEVEL OF EVIDENCE II-2. Increase in collagen III has been reported also in the uterosacral and cardinal ligaments of women with prolapse [72, 73]. The Moalli's group [74] demonstrated that collagen III is the primary subtype in the arcus tendineus fascia pelvis; a decrease in the ratio of collagen I/(III+V) is associated with menopause in the absence of hormone therapy and a restoration of this ratio to premenopausal levels with hormone therapy. From these data the authors suggested that sex steroid hormones may improve the biomechanical properties of the supportive tissues of the vagina. Recent findings report that decreased β-catenin in the anterior vaginal wall tissues may play an important role in the onset of POP by affecting collagen anabolism [75]. As all studies involving the procurement of human tissue are by necessity cross-sectional, it is impossible to determine whether the increase in collagen III reflects the causes or effects of prolapse. In either case, the increased flexibility and distensibility plus the decreased tensile strength associated with an increase in collagen III very likely contribute to the progression of POP.

Elastin is primarily laid down during fetal development and rarely synthesized in adult tissues. In contrast to the other tissues in which elastin fibres do not experience a turnover in a lifespan, there is cyclical remodeling of elastin fibres in the reproductive tract. A massive degradation of elastin occurs at the time of parturition, followed by postpartum resynthesis, allowing recovery of reproductive tissues to their pre-pregnancy state [76]. Mice deficient in LOX (lysyl oxidase) fail to replenish mature elastin fibres in the reproductive tract following parturition and develop spontaneous prolapse [77][52] found a marked decrease in elastin mRNA and tropoelastin protein in the cardinal ligaments of women with pelvic organ prolapse relative to women without prolapse. Chen *et al.* [78] demonstrated a significant decrease in the endogenous inhibitors of elastases with increase in elastolytic activity in vaginal tissue from women with stress urinary incontinence and pelvic organ prolapse compared with control subjects. Therefore, these data suggest that the proper degradation, synthesis, and regeneration of elastic fibres are essential for maintaining pelvic organ support.

If damaged or destroyed, metabolically repaired elastin frequently results in malformed and dysfunctional repair products. Proteolytic enzymes capable of degrading elastin include the serine proteases, such as neutrophil elastase, the cysteine proteases, and MMP-2, 9 and 12. Marked decreases in elastin gene transcripts and elastin synthesis in pelvic fibroblasts were noted in women with POP [52], suggesting that altered elastin metabolism may contribute to prolapse. In rodent models with genetic disruption to LOXL1 or fibulin-5 gene, prolapse develops due to failure to synthesize and assemble functional elastic fibres [77]. Elastin content was decreased in the uterosacral ligaments of women with POP, as were LOX, and LOXL1 and LOXL2 gene expression [79].

A recent study by Moon *et al.* [80], evaluated the alteration of elastin metabolism in women with pelvic organ prolapse in a

prospective case-control study: their results showed that expression of neutrophil elastase and matrix metalloproteinase-2 mRNA was higher in women with than in those without POP. Compared to before menopause, neutrophil elastase and matrix metalloproteinase-2 showed a significant decrease in postmenopausal women without POP, although they remained increased in postmenopausal women with POP. Alpha-1-antitrypsin was significantly lower in postmenopausal women with pelvic organ prolapse than in postmenopausal women without. The activities of neutrophil elastase, matrix metalloproteinase-2 and matrix metalloproteinase-9 were increased in women with POP, and these trends were similar to neutrophil elastase and matrix metalloproteinase-2 expression even after adjusting for age, parity and menopausal status. This study demonstrates that after menopause increased elastolytic protease has a significant role in the development of POP.

In a recent clinical trial of de Landsheere *et al*. [81], the authors shown that biomechanical testing highlights the hyperelastic behavior of the vaginal wall: at low strains, vaginal tissue appeared stiffer when elastin density was low, with a significant inverse relationship between low strains and the elastin/collagen ratio in the lamina propria. They suggested that elastin density deserve consideration as a relevant factor of vaginal stiffness in women with POP.

The strongly heritable connective tissue diseases, in which pelvic organ prolapse predominates as a result of an elastinopathy, highlight the importance of elastic fibres for maintaining vaginal support. Marfan's syndrome, characterized by mutations in the fibrillin-1 gene, and cutis laxa with mutations in the elastin and fibulin-5 genes, are notable for an increased incidence of POP in affected women [82-85].

Childbirth is an important risk factor for POP, not only for the mechanical trauma that the pelvic floor is submitted to: also inflammatory pathways are activated during the complex process of tissue healing after birth trauma. During healing proteinases, growth factors such as TGF-β, cytokines and chemokines are secreted into the extracellular matrix by surrounding cells. TGF-β is one of a family of 25 kDa polypeptide growth factors that is currently viewed as the most important fibrosis promoting cytokine. It is responsible for extracellular matrix synthesis in fibroblasts, the differentiation of fibroblasts to myofibroblasts and the inhibition of matrix degradation by inhibiting MMP expression and up-regulating TIMP expression. Thus, it is important in extracellular matrix metabolism and affects tissues or organs in various ways. There is sparse but growing evidence of TGF-β modulation in pelvic connective tissue. Large quantities of TGF-β1 are stored in readily available form in the extracellular matrix. Release and activation of stored latent TGF-β1 by proteases can generate rapid, highly localized signals. Therefore, the modulation of TGF-β1 activity by extracellular proteases provides faster signal transduction than alterations in gene expression. This is important for tissue remodelling during pregnancy and repair after birth trauma [50] .

3.3. Pregnancy and Delivery

3.3.1. Effect of pregnancy on pelvic floor function

Pregnancy has significant effect on lower urinary tract function. By the sixties, it was demonstrated that in uncomplicated pregnancy, micturition frequency is influenced by the physiological state of the bladder. Frequency has been described as diurnal changes, which maybe up to seven times or more of normal, and slight nocturnal changes of one or more times during the night. The incidence is the same in both primigravidae and multigravidae women. The first trimester is the most common time of onset. The uterine weight is the most important factor affecting frequency throughout the pregnancy. Uterine weight not only exerts pressure on the bladder but also irritates the bladder. Normal bladder capacity in the first trimester is 410 ml [86]. In late pregnancy, descent of the presenting part of fetus has an additional effect on bladder irritation. Bladder capacity in the third trimester reduces to 272 ml in conjunction with increased irritability of detrusor muscles [86]. Alternative causes include nervous and hormonal influences. Indeed, the onset of frequency in late pregnancy is a common symptom of engagement of the fetal head [86]. Approximately 80% of pregnant women, both primigravidae and multigravidae, experience increased micturition frequency at some time during pregnancy [86]. Increased frequency usually begins in early pregnancy but can occur in the later stage; it disappears in mid pregnancy, which maybe due to the increase in bladder capacity to 460 ml in the second trimester, and returns in the later weeks [86]. Once increased frequency has occurred, it is nearly always progressive and becomes increasingly worse until term [86]. Increased frequency during pregnancy results in polyuria and is associated with increased fluid intake. However, which is the cause and which the effect remains an unsolved issue. Average daily excretion, output, and fluid intake are highest in the second trimester and lowest in the third. Uterine position also plays a significant role. The impacted retrovert gravid uterus causes fluid retention because it interferes with the obliteration of the posterior urethrovesical angle [86].

Pregnancy is associated with bladder-neck descent, increased bladder-neck mobility, increased POP, decreased urethral resistance and loss of pelvic floor contractility (111). These changes are compatible with changes in mechanical properties of fascial tissue and can be considered a physiological adaptation to mechanical and hormonal alterations in pregnancy [87, 88].

Several of the changes occurring prior to delivery are in all likelihood normal physiological changes and may be secondary to hormone-induced collagen alterations. Hormonal alterations are essential to prepare the body and to adjust the musculature and connective tissue for vaginal birth.

Changes in relaxin and progesterone levels during pregnancy may have a significant role in the development of SUI [89]. The high progesterone levels during pregnancy influence the pelvic floor structures: progesterone has smooth muscle-relaxing and estrogen-antagonizing effects, reducing the tonus in ureters, bladder and urethra [90].

Progesterone increases during pregnancy from 24 ng/ml at the 8th week to 150 ng/ml at the 36th week [91]. Increased progesterone may relax smooth muscles in the urinary system [92], result in reduced ureter, bladder, and urethral tone [93]. Values urethral pressure profile parameters below the median value and defective transmission of pressure over the urethra were observed in almost all pregnant women who experienced SUI during pregnancy. These observations suggest that an inherent weakness of the urethral sphincter mechanism plays a key role in the pathogenesis of SUI during pregnancy. However, correlation between alterations in hormone levels during pregnancy and changes in urethral pressure profile measurements has not been demonstrated [91].

Relaxin increases markedly during pregnancy and it modifies the connective tissue: its collagenolytic effect, that allows appropriate stretching during vaginal birth, has been demonstrated in guinea pigs [94]. As a likely result of connective tissue remodeling in preparation for birth, Landon *et al.* [95] found that the connective tissue of the rectus sheath fascia and the obturator fascia could be stretched to greater length during pregnancy, but it is also much weaker. In some women, these changes may be irreversible and further stretching beyond physiological limits may result in permanent dysfunction.

Relaxin, which plays an important role in maintaining urinary continence during pregnancy [96], could stimulate tissue growth in the lower urinary tract and increase urethral pressure. There is a marked increase in relaxin concentration to peak at a gestational age of 10–14 weeks and then decrease to a stable level of approximately half the peak value at the 17th–24th week of pregnancy, resulting in decreased growth of the urethral epithelium [97, 98]. This may lead to a decrease in urethral pressure [99]. As pregnant women with SUI have lower urethral pressure than continent pregnant women [100], lower relaxin concentrations in late pregnancy, therefore, correlate with a higher prevalence of SUI at the second and third trimesters [96]. Collagen changes included modifications of tensile properties. Changes in tensile properties contribute to reduced functional support of PFM, and reduced total collagen content may result in joint laxity and stretching of pelvic ligaments [99]. The effect of the pregnancy on pelvic soft tissues was investigated through animals' studies [101, 102]: these researches has shown that along the reproductive statuses, the pelvic floor soft tissue undergoes profound histological changes. Particularly, during pregnancy the vaginal wall tissue and cervix became very compliant. This is associated with significant decrease in total collagen and a significant increase of elastin and smooth muscle cell content.

When the pregnant woman coughs, sneezes, laughs, or moves, intra-abdominal pressure increases, and this pressure is transmitted to the bladder. When pressure inside the bladder is greater than urethral closure pressure, incorporated with weakness of the urethral sphincter, SUI is the result.

Pregnancy is one of the main risk factors for the development of SUI in young women [103-106]. In fact, a significantly higher prevalence of SUI in pregnant women than in non-pregnant women has been demonstrated [26, 107, 108]. Pregnant women with SUI have significantly decreased PFM strength than continent pregnant [109]. It is known that PFM weakness causes bladder-neck and urethral mobility, leading to urethral sphincter incompetence [103, 110] .

Reduced PFM strength and SUI development in pregnant women are supposed to be due by weight. The growing uterus and fetus weigh solely on PFM, which contributes to chronic stress on PFM throughout pregnancy and results in PFM weakness. That lead to increased pressure on the PFM and bladder, which may result in greater urethral mobility [111, 112]. Furthermore, excess maternal weight gain may impair blood flow and innervations to the bladder and urethra [113]. Sphincter strength and its supportive function of PFM are consequently jeopardized [26, 103, 114] . Furthermore, multigravidity causes a decrease in PFM strength at a rate of 22–35% beginning at a gestational age of 20 weeks and lasting until 6 weeks postpartum [110].

During the last 20 years, several researches have focused on the effect of pregnancy on the pelvic floor and on the development of prolapse. Rahn *et al.* [115] identified pregnancy-induced changes in biomechanical properties of the vaginal wall and compare these with fibulin-5 knockout mice (Fbln5−/−) with and without prolapse. Compared with non-pregnant mice, vaginas of pregnant and Fbln5−/− (with prolapse) mice exhibited decreased maximal stress, increased distensibility and strain, plus decreased stiffness. Tissues from Fbln5−/− mice without prolapse were similar to nonpregnant wild-type animals. The authors conclude that pregnancy confers remarkable changes in the vaginal wall that include increased distensibility, decreased stiffness and maximal stress.

O'Boyle *et al.* [116] showed in a series of 135 nulliparous pregnant women that POP-Q stage increase during pregnancy and does not change significantly following delivery. These findings suggest that significant changes may be objectively demonstrated prior to delivery. In fact, in nulliparous women pregnancy is associated with increased POP-Q stage compared with non-pregnant control subjects [117].

These findings were confirmed by the data of Sze *et al.* [118] reporting that 46% of 94 nulliparous women had pelvic organ prolapse at their 36-week antepartum visit and of them, 26% had a stage II prolapse.

A recent prospective cohort study assessing 300 nulliparous pregnant women [119], showed that vaginal POP-Q points made a cranial shift from mid to late pregnancy, a caudal shift following delivery, and again a cranial shift after 6 weeks postpartum. Postpartum change was present following both vaginal and caesarean deliveries, but was more pronounced following vaginal delivery. The perineal body and genital hiatus became longer from mid to late pregnancy, and shortened after 6 weeks postpartum. At 12 months postpartum all POP-Q points, except cervix, had recovered to baseline in the vaginal delivery group. The authors considered good the short-term ability to recover after the first pregnancy and delivery.

Gachon *et al.* [120] in their review concluded too that pelvic organ mobility, ligamentous laxity, levator hiatus and urethral mobility change in a similar way during pregnancy (increase of mobility or distension) and postpartum (recovery). Clinical assessments performed in the reviewed studies showed an increase of pelvic organ mobility and perineal distension during pregnancy followed by a recovery phase during postpartum.

A recent review of Soave *et al.* [121] evaluated the efficacy of PFMT for prevention and treatment of UI during pregnancy and after childbirth and its effect on urinary system and supportive structures assessed by objective measurement techniques. They concluded that at the present time there is insufficient evidence to state that PFMT is effective in preventing and treating UI during pregnancy and in the postpartum. However, based on the evidence provided by studies with large sample size, well-defined training protocols, high adherence rates and close follow-up, a PFMT program following general strength-training principles can be recommended both during pregnancy and in the postnatal period.

3.3.2. Obstetric and maternal factors

In 1997 the Oxford Family Planning Study showed that increasing vaginal parity was the strongest risk factor for pelvic organ prolapse in women <60 years [27]. Compared with nulliparous individuals, the relative risk of developing prolapse was 8.4 for a woman who had delivered two children and 10.9 (95% CI: 4.7–

33.8) for someone with four or more children [27]. The Women's Health Initiative reported that single childbirth was associated with raised odds of uterine prolapse (OR 2.1;95% CI: 1.7–2.7), cystocele (OR 2.2; 95% CI: 1.8–2.7), and rectocele (OR 1.9; 95% CI: 1.7–2.2) [28]. Every additional delivery up to five births increased the risk of worsening prolapse by 10–20% [28]. The Progetto Menopausa Italia study confirmed that risk of pelvic organ prolapse increases with the number of vaginal births [122].

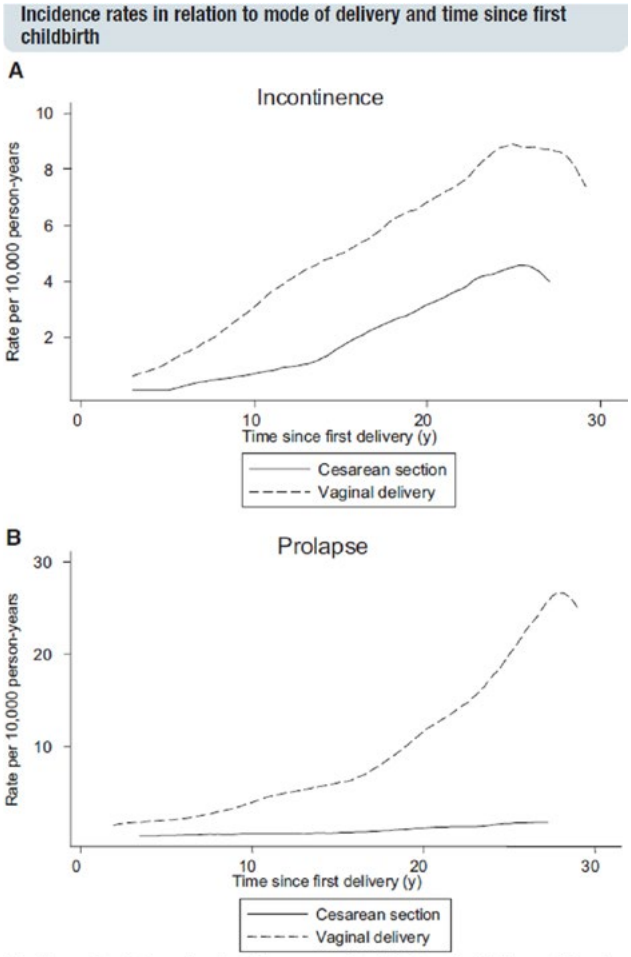
To ascertain the effect of a second delivery on pelvic floor anatomy, Horak *et al.* [123] showed that a second pregnancy and delivery do not seem to have a major effect on bladder support and/or levator function. However, findings of a cross-sectional study of 3050 women randomly selected from a large southern California Health Maintenance Organization, showed that women who had undergone one or more vaginal deliveries had a significantly greater risk of developing symptomatic pelvic organ prolapse than did those who had only caesarean sections (OR 3.21; 95% CI: 1.96–5.26) [124]. The attributable risk of vaginal delivery for development of symptomatic prolapse, or the proportion that could have been prevented with a policy of routine elective caesarean section, in this population was 46%. LEVEL OF EVIDENCE: II-2 [124].

The association between caesarean section and POP was investigated by Larsson *et al.* [125]: the Swedish Hospital Discharge Registry was used to identify women with an inpatient diagnosis of pelvic organ prolapse, and the data were linked to the Swedish Medical Birth Registry. A total of 1.4 million women were investigated. A strong and statistically significant association between caesarean section and pelvic organ prolapse was found (Adjusted OR 0.18 [95% CI: 0.16-0.20] and overall hazard ratio=0.20 [95% CI: 0.18-0.22]). The authors concluded that caesarean section is associated with a lower risk of pelvic organ prolapse than vaginal delivery.

In another study from the Swedish Medical Birth Registry [126], POP surgery was observed in 2.2% of vaginal deliveries and 0.2% of caesarean sections (follow-up time 25.9 years). Among women only having had vaginal deliveries, rates of POP surgery increased with number of childbirths. In the caesarean delivery cohort, rates of POP surgery slightly decreased with increasing parity number. Compared with a caesarean delivery, the risk of POP surgery was increased nine-fold both after non-instrumental vaginal delivery and after vacuum extraction, whereas among women with forceps delivery a twenty-fold increase in risk was observed. The incidence rate of POP in women with caesarean deliveries showed very little variation over time, but started to diverge more notably from the vaginal delivery cohort 10 years after the first birth (Figure 5B).

Another registry-based national cohort study [127], confirmed that the prevalence of symptomatic POP was doubled after vaginal delivery compared with caesarean section, two decades after one birth.

A clear link between vaginal delivery and symptoms and signs of pelvic organ prolapse in urogynecological patients was demonstrated by Trutnovsky *et al.* [128]: nulliparae showed the lowest prevalence of POP, followed by women exclusively delivered by caesarean section. Highest prevalences were consistently found in women delivered at least once by forceps, although the differences between this group and women delivered by normal vaginal delivery and/or vacuum extraction were significant in three out of eight POP-Q measures only. Compared with women in the caesarean section group, the adjusted odds ratios for reporting symptoms of prolapse were 2.4 (95% CI 1.30-4.59) and 3.2 (95% CI 1.65-6.12) in the normal vaginal delivery/vacuum extraction group and forceps group, respectively.



A, Incidence rates of stress urinary incontinence surgery in relation to mode of delivery and time since first childbirth; B, Incidence rates of pelvic organ prolapse surgery in relation to mode of delivery and time since first childbirth.

Figure 5: [126] From: Leijonhufvud et al. Incontinence and prolapse surgery after childbirth. Am J Obstet Gynecol 2011 [126]

A register-based national cohort study [129] of primiparae who delivered between 1985 and 1988 and had no further deliveries confirmed these results: 20 years after the birth the late prevalence of UI, symptomatic POP and faecal incontinence were almost identical between vacuum extraction (VE) and spontaneous vaginal delivery (SVD).

Lisonkova *et al.* [130] designed a retrospective analysis to examine age-specific trends in vaginal and caesarean delivery, obstetric trauma, and surgery for pelvic organ prolapse among all women in Washington State. From 1987 through 2009, caesarean delivery rates among women aged 15-44 years increased from 12.7-18.1 per 1000 women, vaginal delivery rates remained stable, and instrumental vaginal delivery rates declined from 6.3-3.9 per 1000 women. Obstetric trauma decreased from 6.7 in 1987 to 2.5 per 1000 women aged 15-44 years in 2009. Surgery for pelvic organ prolapse decreased

from 2.1 in 1987 to 1.4 per1000 women aged 20-84 years in 2009. Obstetric trauma rates in 1987 through 1999 among women 15-44 years old were strongly correlated with the rates of surgery for pelvic organ prolapse among women 25-54 years of age 10 years later in 1997 through 2009 (correlation coefficient 0.87, P<.001). Similarly, rates of midpelvic forceps delivery in 1987 through to 1999 were correlated with the rates of surgery for pelvic organ prolapse 10 years later (correlation coefficient 0.72, P<.01). Regression analyses showed a strong effect of age on surgery for prolapse, temporal decline in surgery, and an effect of birth cohort, as younger cohorts (women born in ≥1965 vs 1940) had lower rates of surgery for pelvic organ prolapse. The authors concluded that temporal decline in instrumental vaginal delivery and obstetric trauma may have contributed to the reduction in surgery for pelvic organ prolapse.

Blomquist *et al.* [131] recruited women from a community hospital for a cohort study 5 to 10 years after their first delivery and followed up annually for up to 9 years. Among 1528 women (778 in the caesarean birth group, 565 in the spontaneous vaginal birth group and 185 in the operative vaginal birth group), after a median follow-up of 5.1 years, there were 138 cases of SUI, 117 cases of OAB, 168 cases of AI, and 153 cases of POP. For spontaneous vaginal delivery (reference), the 15-year cumulative incidence of POP was 30.0% (95% CI, 25.1%-34.9%). Compared with spontaneous vaginal delivery, caesarean delivery was associated with significantly lower hazard of POP (aHR, 0.28 [95% CI, 0.19-0.42]), operative vaginal delivery was associated with significantly higher hazard of POP (aHR, 1.88 [95% CI, 1.28-2.78]). Stratifying by delivery mode, the hazard ratios for POP, relative to a genital hiatus size less than or equal to 2.5 cm, were 3.0 (95% CI, 1.7-5.3) for a genital hiatus size of 3 cm and 9.0 (95% CI, 5.5-14.8) for a genital hiatus size greater than or equal to 3.5 cm. The authors concluded that, compared with spontaneous vaginal delivery, caesarean delivery was associated with significantly lower hazard pelvic organ prolapse, while operative vaginal delivery was associated with significantly higher hazard pelvic organ prolapse. A larger genital hiatus was associated with increased risk of pelvic organ prolapse independent of delivery mode.

The occurrence rate of pelvic organ prolapse stage ≥2 in the first 3-6 months postpartum has been described in literature between 18.1-56% [132-134].

In a cross-sectional study of 382 primigravid women, pelvic organ support was explored 6 months postpartum: POP-Q stage ≥II was present in 7.7%, 18.1% and 29% of women who delivered by caesarean section, spontaneous and instrumental vaginal delivery, respectively. Spontaneous vaginal delivery increased the risk by more than three times (OR 3.19) while instrumental vaginal delivery increased it more than five-fold (OR 5.52) in comparison with caesarean section. Instrument-assisted delivery did not increase the risk of prolapse in women who delivered vaginally. The authors concluded that caesarean section is associated with a lower prevalence of pelvic organ prolapse after delivery and instrument assisted delivery is not associated with an increased risk of postpartum prolapse among women who delivered vaginally [132].

Other obstetric factors that have been associated with an increased risk of pelvic organ prolapse, albeit less consistently, are delivery of a macrosomic infant, prolonged second stage of labour, age and BMI [135-137].

To date, the studies are controversial considering younger age (25 versus 28 years of age) [136] as well as older age (more than 30 years) [138] at first delivery as a risk factor to develop pelvic organ prolapse. Another large study did not reveal any association at all [23].

Somewhat more controversial is whether pregnancy itself, distinct from mode of delivery, alters the risk of pelvic organ prolapse. In a small case-control study, pregnancy was associated with worsening prolapse compared with non-pregnant controls matched for age and ethnic origin [117]. A substantial proportion of pregnant nulliparous women show progression from stage 0 or I support in the first trimester to stage I or II in the third trimester [116]. This loss of vaginal support does not seem to return to baseline in the postpartum period. Significant risk factors from Chen *et al.* (n=108) were POP during pregnancy (OR 8.2, 95% CI 3.07-21.9) and higher first-trimester body mass index (BMI) (OR 1.31, 95% CI 1.01-1.70) [139].

Significant risk factors from Reimers *et al.* (n=284) were a more caudal position of the anterior vaginal wall (point Ba measured with the POP-Q) at gestation week 21 (OR 2.45, 95% CI 1.29-4.67), a longer distance from the meatus urethra to the anus (Gh + Pb measured with the POP-Q) (OR 1.58, 95% CI 1.05-2.38), a more distensible levator ani muscle at gestation week 21 (OR 1.13, 95% CI 1.03-1.23), and an episiotomy (OR 19.84, 95% CI 6.18-63.73) [140].

Handa *et al.* [141] investigated whether episiotomy, perineal laceration and operative delivery are associated with pelvic floor disorders after vaginal childbirth. Episiotomy was not associated with pelvic floor disorders. Forceps delivery increased the odds of prolapse (OR 1.95, 95%CI 1.03 - 3.70). In contrast, women with a history of more than one spontaneous perineal laceration were significantly more likely to have prolapse to or beyond the hymen (OR 2.34, 95% CI 1.13 - 4.86). Few others studies investigate the relationship between POP surgery and episiotomy. Abdel-Fattah *et al.* [142], in a large register linkage study, reported a POP surgery rate of 44% irrespective of previous episiotomy. The difference between groups was not significantly different (OR 1.05, 95% CI 0.94–1.18). Similarly, Uma *et al.* [143] did not show any difference between patients who underwent episiotomy and controls in terms of POP surgery rates (21.1% vs 19.2%; CI 0.99–2.10; p = n/a). Recently Frigerio *et al.* [144], confirmed that episiotomy does not seem to negatively influence genital prolapse development and might even be protective with respect to prolapse severity and prevalence without affecting surgery rates. Based on these studies, episiotomy does not seem to affect POP surgery rates. Lovejoy *et al.* [145] recently demonstrated that breastfeeding after vaginal childbirth was not associated with the development of stress urinary incontinence, pelvic organ prolapse, or anal incontinence 1-2 decades after the first vaginal delivery.

3.3.3. Pathophysiologic mechanism of childbirth injury to the pelvic floor

Undoubtedly, vaginal delivery constitutes a traumatic event for the pelvic floor: it affects the pelvic nerves, the pubococcigeus-puborectalis muscle complex, the pelvic fascial structures and the anal sphincter. However, all women sustain the trauma of their pelvic floor during vaginal birth, but only some of them experience injury.

The first vaginal delivery is when most women are likely to sustain pelvic floor damage, such as, neurogenic injury, change in

bladder-neck position and mobility, levator ani trauma, increase in levator hiatus, and anal sphincter disruption. In most women, the pelvic floor muscle function recovers during the year following delivery. In a minority, symptoms persist and may finally lead to PFD in later life [146].

Several attempts have been made to define the fascial trauma after vaginal delivery. In the anterior compartment, the childbirth may result in disruption of the 'endopelvic fascia', in particular of the paraurethral and paravaginal structures. Analogous to increased bladder descent after childbirth, there is a highly significant increase in caudal displacement of the rectal ampulla after childbirth [147]. The rectovaginal septum and the Denonviller's fascia are the connective structures involved in the posterior compartment damage that appears as a rectocele. It has been shown that vaginal childbirth also results in an increased prevalence of true rectocoele, i.e. presumptive defects of the rectovaginal septum [148]. Such defects are strongly associated with symptoms of pelvic organ prolapse and obstructed defecation [149].

Specific features of injury during vaginal birth influence whether a woman develops prolapse later in life. Several factors, that can be grouped together as descriptors of difficult vaginal delivery, are associated with increased occurrence of prolapse: forceps delivery, a prolonged second stage of labour, and large infant birth weight. Unfortunately, because of the overlapping nature of these different factors, it is difficult to determine which of them is causal and which of them is associated (e.g., forceps delivery is used when there has been a prolonged second stage of labour, and both of these factors increase in large-sized infants).

A mechanical model study has shown that even an apparently uneventful vaginal delivery inflicts injuries to the pelvic floor muscles, particularly during the extension of the fetal head, having been obtained more than 10% of damaged fibres; the puborectalis component of the levator ani muscle (LAM) is the most prone to be damaged [150].

The role of childbirth in causing damage to the LAM, which is associated with both vaginal delivery and with pelvic organ prolapse, is probably the mediating mechanism in these injuries. In the last decades the imaging techniques such as magnetic resonance imaging and 3D and 4D ultrasound have focused on the morphology of the levator ani complex and its integrity after delivery.

The occurrence of levator trauma after vaginal delivery (Figure 12) is reported to be between 15-39.5% when investigated with ultrasound [151-158] and between 17.7%-19.1% when assessed with MRI [159-161]. This difference in occurrence rate is probably due to the different postpartum assessment of levator ani muscle (which varies in these studies between 24-72 hours to 12 months postpartum). In fact, it has been demonstrated by Staer-Jensen *et al.* [162] that the LAM has the ability to recover after pregnancy and delivery and most of the recovery occurs during the first 6 months postpartum (LEVEL OF EVIDENCE: II). These results are consistent with other research evaluating levator morphology using either MRI or ultrasonography: 26 primiparous women demonstrated major levator ani defects at 6 weeks, but at 12 months postpartum, 10 of these 26 women no longer had a major defect. Others similarly have found that avulsion injuries of the levator ani after childbirth resolve in 10-20% of women [160, 163, 164]. On the other hand, Valsky *et al.* [165] showed that a sonographic finding of LAM defect identified in the period immediately postpartum persists months or year after delivery; therefore this test may be performed following the delivery, or may be delayed without impact the result. Also the Delancey´s group demonstrated that the magnitude of LAM tear did not substantially change by 8 months postpartum, but LAM edema and bone injuries showed total or near total resolution [166].

The following risk factors for levator trauma after vaginal delivery have been described in the literature: obstetric anal sphincter injuries (OR: 4.4-8.1); prolonged active second stage of labour per hour (OR: 2.2); forceps delivery (OR: 14.7); fetal head circumference (OR: 3.3); episiotomy (OR: 3.1); increased maternal age [151, 153, 158, 161, 164, 167-169].

Memon *et al.* [170] showed that ten years after delivery, the prevalence of levator avulsion is almost tripled after forceps compared with vacuum-assisted vaginal delivery (LEVEL OF EVIDENCE II).

An observational study done in women 2–4 weeks before and 2–6 months after vaginal childbirth provided a direct proof for the hypothesis that childbirth is responsible for certain morphologic abnormalities of LAM observed in parous women and suggests that older age at first delivery is a risk factor for such trauma (LEVEL OF EVIDENCE II-3) [155].

Third-fourth-degree perineal tears were found to be independent clinical indicators of an increased risk of levator trauma. Such clinical markers may become useful in the identification of women at high risk of levator trauma and future pelvic floor disorders [171].

Kamisan Atan *et al.* [172] investigated in a prospective randomized study if the antepartum use of a birth trainer (Epi-No®) may prevent such injuries by altering the biomechanical properties of the pelvic floor. 504 women were assessed with 4D translabial ultrasound in the late third trimester, and again 3-6 months postpartum, after randomization to control or intervention (use the Epi-No® device from 37 weeks of gestation until delivery) groups. The results of this trial showed no significant difference in the incidence of levator avulsion, irreversible hiatal overdistension, clinical anal sphincter trauma and perineal tears. A marginally higher rate of significant defects of the external anal sphincter on ultrasound was observed in the intervention group. The authors concluded that the antenatal use of Epi-No® device is unlikely to be clinically beneficial in the prevention of intrapartum levator ani damage, or anal sphincter and perineal trauma.

The systematic review of pelvic floor interventions during pregnancy published on 2018 by Schreiner *et al.*, [173] confirmed that pelvic floor muscle training and perineal massage improved childbirth-related parameters and pelvic floor symptoms, whereas Epi-No® showed no benefit.

To estimate the risk of prolapse associated with levator avulsion injury among a urogynaecological clinic population, Dietz *et al.* [174] considered 781 women retrospectively, with a mean age 53 years (range 15-89 years), and a median parity of 2 (range 0-12). Significant prolapse (stage II or higher) was diagnosed in 415 (53%) women, and 181 (23%) women were found to have levator avulsion defects. Prolapse was seen in 150/181 (83%) women with avulsion and in 265/600 (44%) women without

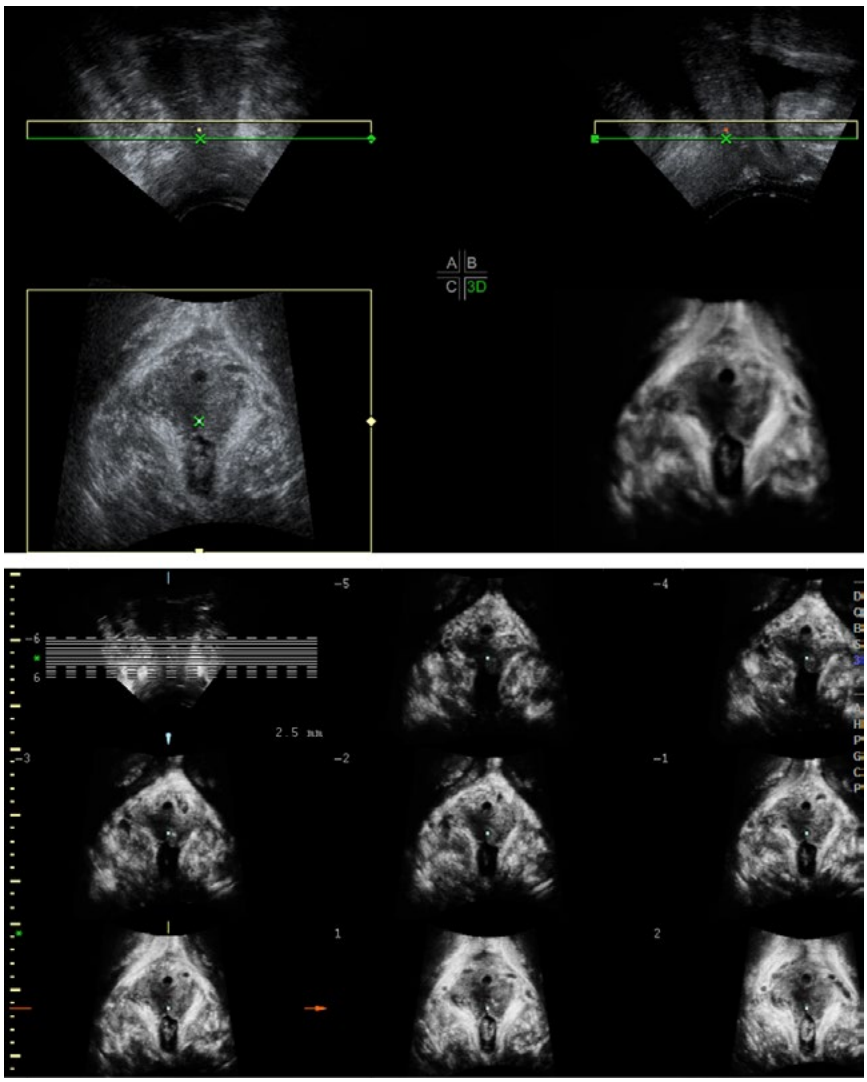


Figure 6: Levator ani defect early postpartum in a patient had spontaneous vaginal delivery (acquisition screen GE Voluson-e ® System). A) In the multiplanar mode, the axial plane (lower left) and the rendered image (lower right) show an unilateral levator discontinuity (**) on the right side of pubococcigeal-puborectalis muscle. B) Eight slices obtained with TUI in coronal-C plane in the same patients: the discontinuity (arrow) is demonstrated in at least three consecutive slices at and above the plane of minimal hiatal dimension (frames *,-1,-2,-3). From Albrich et al, BJOG 2011 [156] with permission

avulsion, giving a RR of 1.9 (95% CI: 1.7-2.1). The association was strongest for cystocele (RR 2.3, 95% CI: 2.0-2.7) and uterine prolapse (RR 4.0, 95% CI: 2.5-6.5). The authors concluded that women with levator avulsion defects were about twice as likely to show pelvic organ prolapse of stage II or higher than those without, with an increased risk of cystocele and uterine prolapse. A cystocele with an intact rectovesical angle is more likely to be associated with avulsion injury of the LAM and thus more likely to be caused by birth-related trauma [175]. Puborectalis avulsion injury and levator hiatal ballooning are independent risk factors for symptoms and sign of prolapse. The role of avulsion in the pathogenesis of prolapse is not fully explained by its effect on hiatal dimensions. It likely that avulsion implies not only muscular trauma but also damage to structures impossible to assess clinically or by imaging, i.e. myofascial and connective tissue [176]. Pelvic organ prolapse has a considerably lower incidence after caesarean section [26, 57]; however pelvic organ prolapse has been described in 35% of 26 women after caesarean section during active labour in comparison to 32% of 41 women who had spontaneous vaginal deliveries [118]. On the other hand, one epidemiological study using validated questionnaires negated the influence of labour versus no-labour pure caesarean delivery on pelvic organ prolapse [124] (LEVEL OF EVIDENCE: II-2). Others studies [156, 177] reported cases of early levator abnormalities after emergency caesarean section, and hypothesized a possible role of the active labour in the occurrence of lesions of the pelvic muscular floor.

A recent study of Leijonhufvud *et al.* [126] considered a cohort study of all women having their first and all subsequent caesarean deliveries (n = 33,167), and an age-matched sample of women having only vaginal deliveries (n = 63,229). Women who had only vaginal deliveries had an overall increased risk of prolapse surgery (HR, 9.2; 95% CI: 7.0-12.1) compared with women who had only having caesarean deliveries. They con-

clude that having only vaginal childbirths was associated with a significantly increased risk of pelvic organ prolapse surgery later in life compared with only having caesarean deliveries. There seems to be sufficient proof that pelvic organ support can be impaired by vaginal childbirth. It is unclear whether this effect is due to stretching or avulsion of structures and whether the observed changes are primary (i.e. directly due to childbirth) or the medium-term or long-term consequence of the levator impairment. Several mechanisms may well coexist in one individual [178].

Furthermore, it has been shown that any delivery-related changes occur against the background of marked variations in pelvic organ support in young nulliparous women [179]. As the most significant changes are observed in those with the least antenatalorgan mobility [180], the effect of childbirth may be a partial equalization of those interindividual differences.

A recent systematic literature review confirmed that the PMFT during pregnancy shortened the second stage of labor and reduced the urinary incontinence, whereas the perineal massage reduced perineal pain. [173]

3.3.4. Perineal trauma

Since the current literature suggests that childbirth and in particular vaginal childbirth has the strongest association with PFD and childbirth is significantly associated with POP, the identification of modifiable risk factors such as obstetric interventions during vaginal childbirth is of the utmost importance.

The role of episiotomy in the prevention of future PFD is still controversial.

The study of Sartore *et al.* [181] showed that mediolateral episiotomy does not protect against genital prolapse and is associated with a lower pelvic floor muscle strength compared with spontaneous perineal lacerations.

However, a recent systematic review of Frigerio *et al.* [144] reported that episiotomy does not seem to negatively influence genital prolapse development and might even be protective with respect to prolapse severity and prevalence without affecting surgery rates.

The episiotomy, a surgical incision in the perineum made to enlarge the vaginal opening and facilitate delivery, was originally introduced as a method assumed to improve maternal and neonatal outcomes and rapidly became a part of standard obstetric care. However, since the 1980s, routine use of episiotomy has been challenged, based on the lack of evidence of benefits of the procedure [182] and the publication of multiple studies reporting increased blood loss at delivery, perineal scar breakdown and infection, postpartum pelvic pain, and dyspareunia [183-186]. . Various types of episiotomy have been described in the past (median, modified median, J-shaped episiotomy, mediolateral, lateral, radical lateral and anterior) in papers and textbooks. Routine episiotomy is no longer recommended

Some studies deal with the different use of various episiotomies in different countries (e.g. UK, Finland and Greece) [188-191]. However randomized trials comparing alternative methods or position of episiotomy are lacking, resulting in Level 2b or Level 3 of evidence. To ensure Level 1 evidence from randomized trials, a standardization of the practice and reporting of the episiotomy incision is required . However, a standardized classification system has not been introduced yet, making it difficult to compare the various techniques. Even in the last Cochrane review of episiotomy, an exact classification or definition of episiotomies is lacking [192].

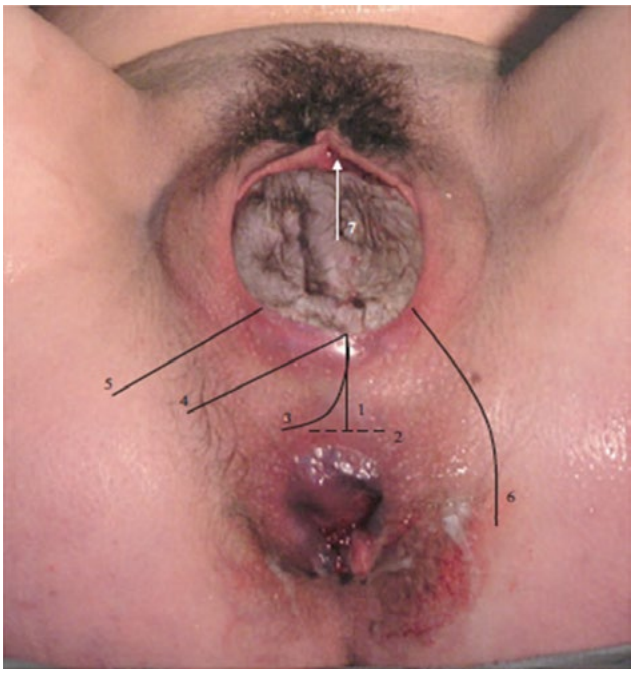


Figure 7: The description of mediolateral episiotomy (the most frequently used in Europe) in standard obstetrics textbooks differs widely: some publications provide only descriptive terms, the angle of incision varies between 31° and 63°, suggesting the wide potential variation in the practice of episiotomy worldwide.
Types of episiotomy. 1: median episiotomy, 2: modified median episiotomy, 3. 'J'- shaped episiotomy, 4: mediolateral episiotomy, 5. lateral episiotomy, 6: radical lateral (Schchardt incision), 7: anterior episiotomy (white arrow). From Kalis et al. Classification of episiotomy: towards a standardization of terminology. BJOG 2012 [187].

Some studies have demonstrated increased incidence of third and fourth-degree lacerations associated with the use of midline episiotomy [193, 194]. The resulting damage to the internal and external anal sphincters can lead to devastating long-term sequelae, including faecal incontinence and rectovaginal fistulae [195].

To support the benefits of episiotomy, some clinicians have claimed that meticulous repair of a surgical episiotomy yields improved wound healing when compared with an unpredictable spontaneous laceration [183]. This assertion has not been substantiated by empiric evidence [196].

Kalis *et al.* [197] evaluated the results of mediolateral episiotomy with incision angle of 60°: the study group comprised 60 consecutively recruited primiparous women who required episiotomy during delivery. The results showed that the angles differed significantly among the incision (60°), repair (45°), and 6-month (48°) measurements ($P < 0.001$). There was a poor correlation between the suture angle and the angle measured at 6 months postpartum. No severe perineal tear was diagnosed in the cohort. At 6 months postpartum, only one woman reported mild symptoms of de novo anal

incontinence, whereas seven women reported perineal pain related to episiotomy.

Many institutions and individual obstetric practitioners have decreased their performance of episiotomy over the past 20 years, most likely as a result of practicing evidence-based medicine.

An electronic audit of the medical procedures database at Thomas Jefferson University Hospital from 1983 to 2000 was completed to determine if practice patterns have been altered by the large body of literature strongly advocating the selective use of episiotomy. Overall episiotomy rates in 34,048 vaginal births showed a significant reduction from 69.6% in 1983 to 19.4% in 2000. Significantly decreased risk of episiotomy was seen based upon year of childbirth (OR 0.87, 95% CI: 0.86-0.87), black race (OR 0.29, 95% CI: 0.28-0.31), and spontaneous vaginal delivery (OR 0.40, 95% CI: 0.36-0.45). Increased association with episiotomy was seen in forceps deliveries (OR 4.04, 95% CI: 3.46-4.72), and with third or fourth-degree lacerations (OR 4.87, 95% CI: 4.38-5.41). This study demonstrated a statistically significant reduction in the overall episiotomy rate between 1983 and 2000 [186].

A population-based register of 514,741 women with singleton vaginal deliveries recorded in the Finnish Medical Birth Register was reviewed. Primiparous and multiparous women who had undergone episiotomy were compared to women who had not undergone episiotomy, for possible risk factors. The occurrence of episiotomy decreased from 71.5% in 1997-1999 to 54.9% in 2006-2007 among primiparous women, and from 21.5% in 1997-2001 to 9.2% in 2006-2007 among multiparous women. The use of episiotomy decreased not only in low-risk but also in high-risk women who had operative vaginal or breech deliveries, macrosomic newborns, and oxytocin augmentation. The ratio of episiotomy use remained relatively unchanged in different subgroups even though episiotomy policy became increasingly restrictive over time. The authors concluded that the spectrum of episiotomy indications has not changed over time, and use of episiotomy has declined arbitrarily to a similar extent among high and low-risk women [198].

To identify the risk factors for obstetric anal sphincter rupture (OASR), a retrospective population-based register study was carried out. A total of 514,741 women with singleton pregnancy and vaginal delivery between 1997 and 2007 in Finland were recruited. Episiotomy decreased the likelihood of OASR for the primiparous [OR 0.83, 95% CI: 0.75-0.92], but not the multiparous women (OR 2.01, 95% CI: 1.67-2.44). Episiotomy was associated with decreased risks for obstetric anal sphincter rupture in vacuum assisted deliveries (OR 0.70, 95% CI: 0.57-0.85). These results support the restrictive use of episiotomy, since 909 episiotomies appear to be needed to prevent one OASR among primiparous women. The equivalent estimate in vacuum assisted deliveries among primiparous women was 66, favoring routine use of episiotomy in such cases [190].

Robinson *et al.* [199], carried out a study to identify factors associated with the use of episiotomy at spontaneous vaginal delivery. They studied 1576 consecutive term, singleton, spontaneous vaginal deliveries; the association of demographic variables and obstetric factors with the rate of episiotomy use were examined. The overall rate of episiotomy was 40.6% (640 of 1576). Midwives performed episiotomies at a lower rate (21.4%) than faculty (33.3%) and private providers (55.6%) (P =0.001). After controlling for confounding factors with logistic regression, private practice provider was the strongest predictor of episiotomy use (OR 4.1, 95% CI: 3.1-5.4) followed by faculty provider (OR 1.7; 95% CI:1.1-2.5), prolonged second stage of labor (OR 1.8; 95% CI: 1.2-2.7), fetal macrosomia (OR 1.6; 95% CI: 1.1-2.5), and epidural analgesia (OR 1.4 95% CI: 1.1-1.8). The authors conclude that the strongest factor associated with episiotomy at delivery was the category of obstetric provider. Obstetric and demographic factors evaluated did not readily explain this association.

A study was carried out to lower the episiotomy rate through physician education and to document the indication when episiotomy was performed. The intervention consisted of an evidence-based lecture recommending limited usage of episiotomy and requesting documentation of any indication for episiotomy. Data 3 monts prior to the intervention were compared to those of the following year. For all vaginal deliveries, there was a 17% decrease in the rate of episiotomy, from 46.9% to 38.8%. For spontaneous vaginal deliveries, there was a 25% decrease in the episiotomy rate, from 40.8% to 30.8%. The most common indications for episiotomy reported were routine/elective, 41.0%; vacuum, 18.6%; forceps, 16.4%; and nonreassuring fetal heart tracing, 10.9% [200].

A review was conducted of women with consecutive vaginal deliveries at Magee-Women's Hospital between 1995 and 2005 to evaluate the episiotomy exposure at first vaginal delivery. A total of 6,052 patients were included, of whom 47.8% had episiotomy at first delivery. Spontaneous second-degree lacerations at the time of second delivery occurred in 51.3% of women with history of episiotomy at first delivery, compared with 26.7% without history of episiotomy (P<0.001). Severe lacerations (third or fourth- degree) occurred in 4.8% of women with history of episiotomy at first delivery compared with 1.7% without history of episiotomy (P<0.001). Prior episiotomy remained a significant risk factor for second-degree (OR 4.47, 95% CI: 3.78-5.30) and severe obstetric lacerations (OR 5.25, 95% CI: 2.96-9.32) in the second vaginal delivery after controlling for confounders. Based on these findings, for every four episiotomies not performed, one second-degree laceration would be prevented. To prevent one severe laceration, performing 32 fewer episiotomies is required. Episiotomy at first vaginal delivery increases the risk of spontaneous obstetric laceration in the subsequent delivery. This finding should encourage obstetric providers to further restrict the use of episiotomy. LEVEL OF EVIDENCE II [201].

In a biomechanical analysis on the impact of episiotomy during childbirth, Oliveira *et al.* [202] demonstrated that a mediolateral episiotomy has a protective effect, reducing the stress on the muscles, and the force required to delivery successfully up to 52.2%. The intervention also has benefits on muscle injury, reducing the damage to a small zone.

Handa *et al.* [141] demonstrated that forceps deliveries and perineal lacerations, but not episiotomies, were associated with pelvic floor disorders 5–10 years after a first delivery. Women with perineal lacerations in two or more deliveries were at significantly higher risk of prolapse. In contrast, even among women with multiple episiotomies across multiple pregnancies, the odds for incontinence and prolapse were not elevated. The data do not suggest a "dose response" relationship between perineal laceration and prolapse. Specifically, the increase in prolapse was statistically significant only in women with at least two lacerations. The observed association between spontaneous laceration and the later development of prolapse is biologically plausible, given recent evidence of the role of levator ani injuries in the genesis of prolapse. Magnetic resonance imaging suggests that avulsion of the levator from the pubis is associated with prolapse later in life [2]. Biomechanical models of the pelvic floor predict that avulsion of the levator ani occurs with

excessive stretching of the levator hiatus during crowning of the fetal head [203]. The hypothesis that spontaneous perineal laceration may be a marker of excessive stretch at the time of delivery has been later demonstrated by Shek *et al.* [171]: vaginal sidewall and third-/fourth-degree perineal tears were found to be independent clinical indicators of an increased risk of levator trauma, as diagnosed by 4D translabial ultrasound 3-6 months postpartum. Such clinical markers may become useful in the identification of women at high risk of levator trauma and future pelvic floor disorders.

Lisankova *et al.* [130] showed that the decline from 1987 through to 2009 in instrumental vaginal delivery and obstetric trauma may have contributed to the reduction in surgery for pelvic organ prolapse.

A recent review and meta-analysis by Driusso *et al.* showed that there was no difference in short-term PFM strength after childbirth between primiparous women who underwent caesarean section or vaginal delivery, as assessed through vaginal manometry. However, they identified reduced PFM strength in women who underwent an episiotomy or instrumented vaginal delivery compared with those who underwent caesarean section. [204] Eisenberg *et al.* aimed to verify the functional interaction that exists between the pelvic floor and the abdominal wall. The study was aimed to investigate the clinical and morphological relationships between diastasis rectus abdominus (DRA) and pelvic floor trauma in primiparous women. Their results showed that the diastasis rectus abdominus does not correlate with morphological changes in the pelvic floor, but does correlate with higher scores in the urinary symptoms portion of the PFDI-20. Women suffering from DRA do not endure more pain or greater lumbar disability than non-DRA women. In extended DRA, the abdominal muscles are significantly compromised and weaker. [205]

3.4. Age

Both incidence and prevalence of pelvic organ prolapse increase with advancing age. In a cross-sectional study of 1004 women (age 18–83 years) who came for their yearly examination, the relative prevalence of this disorder rose by about 40% with every decade of life [20]. In the Women's Health Initiative, American women aged 60–69 years (OR 1.2; 95% CI: 1.0–1.3) and 70–79 years (OR 1.4; 95%CI: 1.2–1.6) had a higher risk of prolapse than did those aged 50–59 [28]. Similarly, findings of a cross-sectional study of 21449 menopausal Italian women showed an augmented risk of pelvic organ prolapse in women aged 52–55 years (OR 1.3; 95% CI:1.1–1.5) and those 56 years or older (OR 1.7; 95% CI: 1.5–2.0) compared with those younger than 51 years [122]. Surgery for prolapse is uncommon in people younger than 30 and older than 80 years; for women between these ages, incidence rises steadily [21].

A recent nationwide epidemiological survey on 55477 Chinese women confirmed that the odds for each type of symptomatic POP increased with age (>50 vs 20-29 years old in symptomatic POP-Q stage II or higher, OR increased from 1.34 [95% CI 1.32-1.45] to 7.34 [95% CI 4.34-12.41]) [206].

3.5. Hormones

As age has been clearly shown to affect the prevalence and progression of POP, it is intuitive to believe that declining sex hormone levels observed with ageing may contribute to biochemical changes observed within tissue. However, several researchers studying hormonal status and prolapse have failed to find an association between oestrogen status and the disorder [27, 35, 57, 122].

The female lower urinary tract is a target organ for the action of the two sex steroid hormones, oestrogen and progesterone.

Steroidal hormones exert their effect on tissue through an interaction with specific intracellular receptors. Hormone receptor affinity may be at the root of the differences between women with pelvic floor diseases and normal controls. Progesterone receptors have been found to be more expressed in women with POP than in women without POP [207]. Several polymorphisms are present in the progesterone receptor gene that can alter its expression. A specific genotype (PGR rs484389) was significantly associated with the risk of having POP [208]. Similarly, the oestrogen receptor β gene also contains multiple single nucleotide polymorphisms that affect its expression. A case-control study of 69 women with POP and 141 control subjects found that a specific haplotype for the estrogen receptor β gene was associated with an increased risk of POP [209].

Studies have shown lower serum oestradiol (E2) levels in premenopausal women with SUI, with [210] and without concurrent POP [211], compared with control subjects. The impact of oestrogen on tissue may be related to its systemic or local levels, or altered sensitivity from a decreased amount of receptors noted in genitourinary tissues [210, 212].

Skala *et al.* [213], evaluates the expression of oestrogen receptor (ER) alpha (α) and beta (β) and progesterone receptor (PR) in vaginal and periurethral tissue in women with genital prolapse. The expression of PR and ER varied with the extent of prolapse. For patients with prolapse >stage 1 (n=32), there was a significantly greater amount of PR in periurethral tissue (p=0.007) and a significantly lower expression of ER β in vaginal tissue (p=0.008) compared to patients with a low stage prolapse (n=15). Patients with stage II and III prolapse did not differ in their amount of receptor expression. The authors concluded that the expression of PR in periurethral and ER in vaginal tissue varied with prolapse extent.

In a cross-sectional study aiming to determine whether there is a change in the number of vessels in the lamina propria of the vagina after menopause in parallel to ER- α expression on the vaginal wall, Lara *et al.* [214] showed that postmenopausal women with genital prolapse have a smaller number of vessels and a lower ER- α expression on the vaginal wall compared to normoestrogenic premenopausal controls.

Recent findings showed that the significant low hormonal levels in cases with high POP-Q stage as well as the significant higher estradiol levels in patients with strong Oxford Grading Scale may indicate that endogenous circulating sex steroids might have a potential role in the severity and progression of POP [215].

Oestrogen seems to have a profound influence on the synthesis and metabolism of pelvic connective tissues, and may have the ability to both prevent POP and improve prognosis if used therapeutically [216].

The current status of the literature is controversial: if some results suggest a hormonal impact on pelvic floor disease, recent findings suggest that hormone deficiency following menopause is unlikely to play a major role in pelvic organ prolapse sup-

port and levator ani function [217]. The weak level of evidence emphasizes the necessity for future research endeavors in this field to elucidate these complex relationships.

Moreover, there is limited research regarding the role of androgens and progesterone and their receptors in POP and results so far have also been contradictory, warranting further study to determine whether changes in androgen and progesterone receptor expression are a cause or effect of POP [216].

3.6. Obesity

Elevated BMI is an important lifestyle factor affecting pelvic prolapse. The most probable mechanism of POP development among obese women is the increase in intraabdominal pressure that causes weakening of pelvic floor muscles and fascia. Obesity is associated with significant pelvic floor symptoms and impairment of quality of life. Weight loss is likely not associated with anatomic improvement, but may be associated with prolapse symptom improvement. Weight loss should be considered a primary option in obese women for its beneficial effects on multiple organ systems and reducing pelvic floor disorder symptoms. Although the operation time in obese women is significantly longer than in healthy weight women, the complication rate of surgery has not been shown to be increased compared to nonobese patients, regardless of route of surgery. There are data to support the vaginal approach in obese women. Some studies have shown that women with high body weight are associated with an increase in the risk for both anatomical and functional recurrence, and other studies have shown no difference [218].

An high BMI increases the risk for prolapse [20, 27, 136, 219, 220] and specifically for progressive rectoceles [221]. Increased waist circumference was associated with more pelvic organ prolapse in some studies [57, 221]. Handa et al. [221] demonstrated this for cystoceles. Women who are overweight (body mass index 25–30 kg/m²) and obese (>30 kg/m²) are at high risk for developing pelvic organ prolapse [28, 135]. Similarly, women with a body mass index of more than 26 kg/m² are more likely (OR 3.0; 95%CI: 1.6–5.7) to undergo surgery for prolapse than are those with a lower value [136].

A review of 22 studies reported that women in the overweight and obese categories had meta-analysis risk ratios of at least 1.36 (95% confidence interval, 1.20-1.53) and at least 1.47 (95% confidence interval, 1.35-1.59), respectively. Subgroup analyses showed effect estimates for objectively measured clinically significant pelvic organ prolapse were higher than for self-reported pelvic organ prolapse [222].

Obesity is a prevalent modifiable condition that impacts PFDs including pelvic prolapse. Patients should be counseled using clinical judgment, knowledge of the literature and with the goal of improving QOL [218].

3.7. Previous surgery

Although hysterectomy might heighten the risk of subsequent POP, prolapse symptoms typically develop many years after this procedure [21, 27, 136, 223, 224]. In the Oxford Family Planning Study, surgical incidence for prolapse in women who had under gone a previous hysterectomy was 29 per 1000 women-years versus 16 per 1000 women-years for the entire cohort [27]. The cumulative risk of surgery for pelvic organ prolapse rose from 1% at 3 years after hysterectomy to 5% at 15 years. Risk was highest in women who had undergone a previous hysterectomy for prolapse (158 per 1000 women-years). In a retrospective cohort study of 149.554 women aged 20 and older, the mean interval between hysterectomy and surgery for pelvic organ prolapse in those who developed the disorder was 19.3 years [21, 225]. Contrary to findings of many other studies, the prevalence of prolapse in women with a uterus in the Women's Health Initiative was slightly higher than for those who had undergone hysterectomy, suggesting that previous prolapse of pelvic organs might have been repaired at the time of the procedure in this study population [28]. The surgical technique performed during hysterectomy, including performance of prophylactic culdoplasty, can lessen the development of a subsequent prolapse [226].

3.8. Chronic pelvic floor stress

Low socioeconomic status [227] and a labour-intensive occupation [35, 227, 228] are two demographic factors identified as risk factors for the development of POP. Housewives, who perform more physically demanding work, seem more likely to have prolapse (OR: 3.1; 95% CI: 1.6–8.8) than do professional managerial women [35]. Similarly, people with occupations involving heavy lifting might have a higher chance of undergoing surgery for pelvic organ prolapse [228].

A recent study on 448 Nepali women [229] showed that using a patuka (a special piece of cloth worn around the waist by heavy workers and mountain porters in Nepal), occupation and body position during work significantly associated with uterine prolapse.

3.9. Constipation and anorectal function

Repetitive straining, such as that seen in patients with chronic constipation or workers whose jobs entail heavy lifting, has also been associated with pelvic organ prolapse. Spence-Jones *et al.* [230] reported that stool straining as a young adult was more typical in women with prolapse than in those without the disorder (61% vs 4%; p<0.001). Individuals with stage II or greater pelvic organ prolapse had an increased risk of constipation (OR 3.9; 95% CI: 1.4–11.9) compared with women with stage 0 or 1 prolapse [231]. However, findings of larger studies have disputed this association, and several groups have shown that neither overall stage of prolapse nor stage of the posterior vaginal wall correlate with bowel function [232-234]. Additionally, women with only urinary incontinence and no prolapse seem to meet Rome II criteria for constipation with the same frequency as those with advanced pelvic organ prolapse [234].

Prolapse of the posterior vaginal wall, alone or in combination with other compartment defects, can be challenging for the pelvic surgeon. Pelvic pressure, vaginal/ perineal splinting to defecate, difficult defecation, faecal incontinence and impaired sexual relations are some of the symptoms associated with posterior POP. Whether the prolapse is the cause of the symptoms or is a result of straining and stretching of support structures in women with defecation disorders, remains unclear.

Bowel symptom like incontinence of flatus and obstructed defecation are common in women with POP. In several surveys, the incidence of anal incontinence ranges from 15-50% [232, 235-243]. Faecal incontinence was reported in 5-22% of women with prolapse [39, 235, 242] which was significantly more than bowel symptoms in a control group [242]. There were no associations found between prolapse stages and symptoms after adjusting for age and BMI [232, 241].

Meschia *et al.* [237] reported that among 881 women with symptoms of urinary incontinence and pelvic organ prolapse, the prevalence of anal incontinence was 20%. Urinary incontinence and severe rectocele were found to be associated with anal incontinence.

Disparities have been shown between the degree of pelvic organ prolapse, pelvic floor symptoms and defecography results [39, 244]. Two series of defaecographies in consecutive patients with prolapse and/or evacuation disorders described defaecographic findings that changed the patients diagnosis (though not always the management) in 46 of 62 of cases and noted enteroceles that were not found on physical exam in approximately 50% of cases [245-247]. Sigmoidoceles are present in 4-11% of reported series, and are nearly always missed on physical examination [247, 248]. Their clinical impact and management remain however unclear. Defaecography is not a routine investigation in women with POP and interpretation may be difficult in some cases since normal asymptomatic women may have focal defecographic abnormalities [244]. The prevalence of abnormal colonic transit time is approximately 20% in patients presenting with evacuation disorders [249]. An abnormal preoperative colonic transit study is the most consistently cited risk factor for failure of rectocele repair to relieve evacuatory symptoms, regardless of the surgical technique [250-252]. Goh *et al.* [253] reviewed the management of rectocele and clearly describe the complexity of clinical conditions resulting from the possible combination of various gynaecological and colorectal symptoms with anatomical abnormalities and the different surgical approaches.

Ramanah *et al.* [254] evaluated changes in anorectal symptoms before and after pelvic organ prolapse surgery, using laparoscopic sacrocolpoperineopexy. Preoperative and postoperative anorectal symptoms, colorectal-anal distress inventory (CRADI) and colorectal-anal impact questionnaire (CRAIQ) scores were prospectively compared from 90 consecutive women undergoing laparoscopic sacrocolpoperineopexy. After a median follow-up of 30.7 months, laparoscopic surgery significantly worsened CRADI (p=0.02) with no effect on CRAIQ (p=0.37) scores. Post-operative and *de novo* straining (27%) and the need for digital assistance (17%) were the most frequent anorectal symptoms. No correlation was found between laparoscopic surgery and anorectal symptoms after multivariate analysis (OR 2.45, p=0.05). The authors conclude that anorectal symptoms are not improved after POP surgery by laparoscopic sacrocolpoperineopexy.

Anorectal symptoms do not correlate with the degree of posterior vaginal wall prolapse, nor does the presence of prolapse equate to abnormal objective measures of anorectal function [255].

Recently Groenendijk *et al.* [256] studied the pathophysiology of defaecation disorders in patients with primary POP and the diagnostic potential of anorectal function testing including endosonography in the work-up of these patients. They concluded that anorectal function testing indicates the presence of neuromuscular damage of the anorectal region in patients with POP. Anorectal function testing is not useful in the work-up of patients with POP and constipation, because it fails to discriminate between symptomatic and asymptomatic patients. In cases of faecal incontinence, anorectal function testing and endosonography are helpful to distinguish between functional and anatomical problems.

3.10. Bony pelvis

There is evidence from several case control studies that variations in axial and pelvic skeletal structure can be associated with increased POP risks. These include increasing severity of thoracic kyphosis, a decrease in lumbar lordosis and in vertical orientation of the pelvic inlet, and an increase in the transverse diameter of the pelvic inlet [257-259]. In a case control study, Handa [260] compared 59 women with pelvic floor disorders with controls using standardized pelvimetry techniques during MRI. After controlling for age, race and parity and using a multiple logistic regression analysis, pelvic floor disorders were significantly associated with a wider transverse inlet (OR 3.4) and a shorter obstetrical conjugate (OR 0.23). The association between early age, advanced stage POP and severe disruption of pubic bone and pelvic muscle structure in women with bladder exstrophy is well recognized [261].

Recently Yang *et al.* [262] investigated the association between bony pelvis dimensions and anterior, apical, and posterior compartment POP: women with apical compartment POP are more likely to have a smaller anteroposterior diameter. Larger interspinous and intertuberous diameters were associated with anterior and apical POP, and smaller intertuberous diameter was associated with posterior POP.

3.11. LUTS and bladder function

So far, the relationship between LUTS and pelvic organ descent however, are not completely understood. Costantini et al. [263] retrospectively reviewed 256 patients presented with POP and LUTS and underwent POP surgery. Most of 50% of patients reported two or more symptoms and only 4.2% were asymptomatic for LUTS. 73.8% patients had voiding symptoms, 15% a urodynamic detrusor overactivity, 5% suffered from hydronephrosis. 57.8% showed SUI. The authors concluded that urologists and gynecologists should be aware of the high frequency of the association of POP and LUTS. POP repair my restore a normal anatomical situation but LUTS symptoms may last after the surgery or develop “de novo.”

In a large community-based questionnaire survey, 44% (104/239) of women who had prolapse symptoms (239/3799) also complained of SUI and 37% of overactive bladder [240]. SUI can be functionally masked by POP. SUI may be uncovered by POP surgery and clinically continent women are at risk for developing symptomatic postoperative SUI.

The role of urodynamic studies (UDS) before prolapse surgery is contentious and a hotly debated topic in urogynaecology. Previous studies in women with prolapse and women with uncomplicated SUI have focused on women without preoperative incontinence. Currently, it has not been possible to reach a universal consensus on the role of UDS before prolapse surgery in women with concomitant symptomatic or occult SUI. It is clear that UDS could add some information in women undergoing pelvic organ prolapse surgery and could facilitate counselling of patients. However, there is no evidence that the outcome of surgery is altered by prior UDS [264]. In fact, *Weber et al.* [265] showed that urodynamic testing before surgery in women with prolapse and stress urinary incontinence symptoms is not cost-effective relative to basic office evaluation. It is possible that UDS could better identify and define some urinary dysfunctions, such as a preoperative detrusor overactivity or occult SUI, but this information rarely leads to a change in the management plan or the type of surgical procedure. We have no data to show that the UDS can improve subjective or objective outcomes of

surgery for prolapse. New well-designed randomized studies are necessary to improve our understanding of this topic.

Evidence of reduced peptide-containing innervation of perineal and periurethral muscles in women with SUI and POP has emerged [78], suggesting a neural abnormality in their pathogenesis. Connective tissue alterations such as decreased a-1 antitrypsin expression and altered elastin metabolism [78], decreased collagen concentration [266], and decreased oestrogen receptors [212, 267] have been described in women with UI and/or POP.

Failure of bladder, bladder neck, and urethral support is often part of a more extensive defective pelvic organ support. Poor pelvic organ support can lead to pathological pelvic relaxation in one or more compartment(s). Marinkovic and Stanton [268] published a review of 97 articles regarding incontinence and voiding difficulties associated with POP: they described the incidence, pathophysiology, anatomical changes and resultant consequences, evaluation and imaging of cystocele, rectocele, enterocele, and uterine and vaginal vault prolapse in combination with UI. The authors concluded that POP appears to have significant clinical effects on urethral and voiding function that should be quantified preoperatively to allow appropriate surgical intervention, with the aim of restoring vaginal function and correcting concurrent incontinence, whether overt or occult. Not uncommonly, POP can lead to bladder outlet obstruction, detrusor instability, and latent SUI that is unmasked only with reduction of the POP (potential, latent, or unmasked SUI) [269]. It is recognized that POP surgery can improve voiding dysfunction and unmask occult SUI by alleviating the urethral kinking causing outlet obstruction [270].

Burrows *et al.* [271] described symptoms of bladder, bowel, and sexual function in 330 women with POP, comparing different degrees of prolapse staged by POP-Q system. Women with SUI symptoms had less advanced prolapse (median 5 cm less prolapse in apical compartment) than those without SUI. Women who needed to manually assist urination had more advanced prolapse (median 3.5 cm more prolapse in the most severe compartment) than those who did not. Women with urgency and urgency incontinence had less advanced prolapse (median 3 cm or less) but the differences were smaller than those for SUI. Severity of prolapse was not associated with bowel or sexual symptoms in this study. The most important finding is that there are few strong associations between specific symptoms and severity of prolapse. LEVEL OF EVIDENCE: II-2.

Women without anterior prolapse on POP-Q exam rarely (<10%) report urinary splinting but ranged between 23 and 36% for stage III and IV. Urinary splinting is 97% specific for anterior prolapse. Seventy-seven percent of women with stage II POP report a symptomatic bulge, and report of a bulge has an 81% positive predictive value and a 76% negative predictive value [272]. It seems therefore that if women present with symptoms of vaginal/perineal bulge, then careful assessment for POP is warranted. If a woman with SUI, however, presents with no symptoms of POP, then surgical treatment of asymptomatic and incidental anterior POP does not seem to be indicated.

Ramanah *et al.* [273] compared changes in urinary symptoms before and after POP surgery, using either laparoscopic sacrocolpopexy (LSC) or transvaginal porcine dermis hammock placement with sacrospinous ligament suspension (VS). Out of the 151 patients included, 87 patients underwent LSC, and 64 VS. Overall, after a median follow-up of 32.4 months, POP surgery improved urinary frequency ($P = 0.006$), voiding difficulty ($P = 0.001$), stress urinary incontinence ($P = 0.001$), but not urgency ($P = 0.29$). VS was more effective in treating SUI ($P < 0.001$ vs. 0.52) while LSC more effective on voiding difficulty ($P = 0.01$ vs. 0.08). Postoperative *de novo* symptoms were observed in 35.8% of patients with no difference between the groups ($P = 0.06$). UDI ($P = 0.04$) and UIQ ($P = 0.01$) scores were significantly lower after surgery. However, LSC significantly improved UDI ($P = 0.03$) with no effect on UIQ ($P = 0.29$) scores while VS significantly improved both scores (P=0.02 and 0.001, respectively). Upon multivariate analysis, only the improvement in the impact of urinary symptoms on daily living was independently associated to VS (OR 5.45, P=0.01). The authors concluded that most preoperative urinary symptoms decreased after POP surgery with equivalent proportion of *de novo* symptoms after vaginal and laparoscopic approaches.

The surgical management of women with POP and with latent SUI remains controversial and challenging. Maher *et al.* [274] aimed to determine the effects of surgery in the management of POP by searching the Cochrane Incontinence Group trials register (as on June 2004) for randomized or quasi-randomized controlled trials that included surgical procedures for POP. The metanalysis on the impact of POP surgery on continence was 'limited and inconclusive', but they report that 10% of women developed new incontinence symptoms postoperatively. Levin *et al.* [275] prospectively evaluated 313 women who underwent TVT procedure for overt (228 women) or occult (85 women) SUI. About 50% women also underwent POP surgery concurrently. Overall, for 241 women with at least a follow-up of 12 months, 6.6% had persistent mild SUI, an additional 7% had urodynamic evidence of asymptomatic sphincteric incontinence, whereas 8% developed *de novo* urgency incontinence.

Among 130 women who underwent surgical treatment for an enterocele (75% the vaginal wall protruded through the introitus), 77% presented with SUI or detrusor instability. Sixty-seven percent patients underwent Burch colposuspension with enterocele repair. Postoperative SUI requiring further treatment occurred in 10% after a mean period of follow up of 10 months, and cystocele developed in 1.5% [276].

Urologists and urogynaecologists are faced with the challenge of determining which women with POP associated with SUI will benefit from concurrent surgical intervention for POP. A comprehensive and anatomical approach to pelvic floor reconstruction is recommended. The intended goal of surgical correction of SUI and POP is durable restoration of normal anatomy and function, with symptomatic relief and avoidance of morbidity.

At present, the conclusions based on 19 RCTs (2717 women) are summarized in the Cochrane Systematic Review of Baessler *et al.* [277]: in women with POP and SUI (symptomatic or occult), a concurrent mid-urethral sling probably reduces postoperative SUI and should be discussed in counselling. It might be feasible to postpone the MUS and perform a delayed (two-stage) continence procedure, if required. Although an abdominal continence procedure (Burch colposuspension) during abdominal POP surgery in continent women reduced *de novo* SUI rates in one underpowered trial, another RCT reported conflicting results. Adding a mid-urethral sling during vaginal POP repair might reduce postoperative development of SUI. An anterior native tissue repair might be better than use of transobtu-

rator mesh for preventing postoperative SUI; however, prolapse recurrence is more common with native tissue repair.

The prevalence of OAB symptoms in relation to POP is reported to be between 22.5-36.8% in community based studies [240, 278-280] and between 16-88% in hospital based studies [269, 281-283]. By and large, the prevalence of OAB with POP is greater in the hospital-based studies than in the community-based studies, which is not surprising, given the selected nature of the hospital samples. Only three studies, one community-based and two hospital-based, were identified that presented data specified per compartment and showed conflicting results: in the study by Miedel *et al.* [280], there is a clear relationship between anterior and posterior compartment prolapse and OAB symptoms, in contrast to central compartment prolapse. In the studies by Bradley and Nygaard [284] and Sobhgol and Charandabee [285] such a relationship could not be identified. In a study by Ellerkmann *et al.* [286] no correlation between worsening of the anterior compartment and urgency incontinence could be found. Data regarding the relationship between the stage of prolapse and OAB are very sparse. Burrows *et al.* [271] found that urgency and urgency incontinence occurred more often in women with a less advanced overall prolapse. Another study using ultrasound reached the same conclusion; women with a higher grade of bladder descent were less likely to suffer from urgency incontinence [287].

The pathophysiology of OAB in women with POP is unclear. Several theories exist: bladder outlet obstruction; release of various chemical factors (ATP, Ach, and P2X3) by bladder distension stimulating the detrusor receptors; traction on the urethra due to prominent cystocele resulting in an open urethra with urine entering the urethra that causes detrusor contractions. Bladder outlet obstruction is likely to be the most important mechanism by which POP induces OAB symptoms and DO signs. However, several other mechanisms might also play a role. However, strong indications show a causal relationship between OAB and POP [288].

Pelvic organ prolapse is a common condition that often leads to lower urinary tract symptoms (LUTS) and may require surgical intervention to alleviate those symptoms. Therefore, the clinical evaluation of the women with POP symptoms also requires necessarily the assessment of urinary symptoms. Physicians, who examine women seeking care for one condition, should inquire about the symptoms of other disorders.

3.12. Neurological factors

Integrity of the pelvic innervation is essential to the normal pelvic function. The changes in neurophysiological parameters seen after childbirth were interpreted to reflect neuromuscular injury caused by forces exerted on the sacral plexus, pudendal nerves, and pelvic floor muscles.

Abnormal tests have also been found in women with prolapse or stress incontinence. Histologically, there are smaller and fewer nerve bundles in women with posterior vaginal wall prolapse compared with women without prolapse [289]. The density of peptide-containing nerves in the periurethral tissue and in the levator ani muscle in women with prolapse is reduced [290, 291].

Between 1985 and 1987, Allen *et al.* [292] found that 80% of primigravidae developed evidence of partial denervation of the pelvic floor following delivery. However, evidence of reinnervation and increased fibre density 2 months after vaginal delivery has been detected [292, 293]. Snooks *et al.* investigated 14 multiparous women from their previous studies [293, 294] 5 years after first vaginal delivery and demonstrated that pelvic floor striated sphincter musculature denervation progressed, indicating that age is a contributory factor [295]. Similarly, progressive denervation with time up to 15 years postpartum was found in another prospective study, corroborating the ageing factor [296].

The pudendal nerve innervates the voluntary urethral and anal sphincters, but it does not innervate the levator ani muscles, which receive their own nerve supply from the sacral plexus. Therefore, there is currently no clear evidence whether the neurological damage is responsible, together with the mechanical damage of stretching, of the visible levator defects.

Information from electrodiagnostic studies has demonstrated that birth causes changes in mean motor unit duration after vaginal birth and changes in pudendal nerve conduction patterns [292, 295, 297-299]. Prolongation of the pudendal nerve terminal motor latency (PNTML) is thought to be a result of pudendal nerve damage during vaginal delivery. Significantly prolonged mean PNTMLs have been found in women two to three days after vaginal delivery, compared to a multiparous [294] and a nulliparous control group [293]. At follow-up five years later, prolongation of PNTML persisted [295]. Two prospective analyses demonstrated a prolongation of PNTML antenatally to six to eight weeks after vaginal delivery, particularly after the first delivery [300, 301]. But, again, many of these changes seem to be temporary, as two-thirds of the women with an abnormally prolonged PNTML after delivery had normal measurement six months later [300]. Little recent electrophysiological work has been added in literature, probably due to the technically difficulty of the nerve function tests in clinical practice.

Although it has not been proven, it is reasonable to assume that periods of pain and discomfort after childbirth (e.g., due to perineal tears and episiotomy) and especially the pain related to attempted PFM contraction, could lead to a temporary non-activation of the PFM. This could be the origin of disturbances in behavioural patterns, which would need to be readjusted. In combination with a particularly vulnerable pelvic floor neural control, whose complexity only evolved phylogenetically after the attainment of the upright stance, such a temporary disturbance of neural control after childbirth may persist, although the lesion(s) would have fully recovered. Therefore, the effects of vaginal delivery on pelvic floor nerves remain not fully understood. While it seems logical that vaginal delivery causes some neuromuscular injury and this would be at risk for development of pelvic organ dysfunctions, many details are far from be resolved.

Due to weakened pelvic floor muscles, the risk of POP may increase after SCI; Elmelund *et al.* [302] investigated the occurrence of POP after SCI and evaluated the need for urogynecological consultations offered to women with spinal cord injury. From their results women with spinal cord injury are not in increased risk of developing anatomical POP. Nonetheless, the high occurrence of other urogynaecological issues supports the need for specialized urogynaecological consultations offered to women with SCI.

3.13. Sexual function

Sexual dysfunction associated with POP motivates women to seek medical help. Women with POP are likely to restrict sexual activity owing to a perceived of loss of attractiveness and fear of incontinence. Patients who present with pelvic organ prolapse symptoms should be questioned about their sexual function. Surgical treatment in these patients may cure their sexual disorders (e.g., by solving incontinence in patient with coital incontinence) but may also have undesired effects on sensation, blood flow, and anatomy. These effects can affect sexual arousal and orgasm or cause dyspareunia.

Dyspareunia, coital incontinence and vaginal dryness are common complaints in women with pelvic floor disorders [303, 304]. Although sexual dysfunction appears to be more frequently observed in these women, pelvic organ prolapse seems not negatively impact on sexual satisfaction when controlled for confounders like age [304-306].

Clinical populations are likely to have more severe pelvic floor symptoms and more advanced pelvic organ prolapse, with a greater potential for discernible impact on sexual function, whereas community populations may have mild symptoms and prolapse, with minimal impact. These conflicting results may also be the result of population differences in other related factors, such as age, menopause, or the status of the woman's intimate relationship. Other challenges in studying the factors associated with sexual function in women with POP include a limited characterization of female sexual function in some studies and difficulties assessing sexual function among women who do not have intercourse.

Handa *et al.* [307] reported that, with respect to anatomical prolapse, women with stage III–IV prolapse were more likely to report decreased libido and infrequent orgasm than women with stage 0 support. Adjustment for other characteristics attenuated the strength of these associations, although the association between prolapse and infrequent orgasm remained statistically significant. In the final adjusted model, the odds of infrequent orgasm were increased more than three times for women with stage III–IV prolapse (P=0.02). The authors conclude that women the anatomical prolapse (stage III–IV) were more likely to report infrequent orgasm but they were not at increased risk of other sexual problems. An important observation is that women with stage II support were not more likely to report any sexual complaint than women with stage 0 support. This suggests that the physical presence of stage II prolapse alone is not associated with sexual dysfunction. In contrast, women with prolapse symptoms (as reflected by a high score on the prolapse scale of the Pelvic Floor Distress Inventory) were much more likely to report sexual complaints.

Sexual function is worse in women with symptomatic prolapse. LEVEL OF EVIDENCE II.

In 305 women over 40 years seeking outpatient gynaecologic care the association between sexual complaints and perceived sexual distress has been investigated. Women with sexual distress were also more likely to report sexual difficulty related to pelvic floor symptoms, sexual avoidance due to vaginal prolapse (13.9% vs. 1%, P=0.001) [308].

Conservative (pelvic floor muscles training or pessary) or surgical management (transabdominally or transvaginally) can be offered to treat POP but questions remain regarding sexual outcome. Recent findings showed a significantly improved sexual function 1 year after pelvic floor surgery, and the improvement was predicted by other social and physical factors in addition to normal functional anatomy [309].

Despite the usual improvement in sexual function after surgery, a risk of *de novo* dyspareunia exists irrespective of the procedure used with slightly increased risk after transvaginal repair. Preoperative patient counselling, ideally with a cross-disciplinary approach is an important part of management of POP [310].

A better understanding of the anatomy of this area and of the sexual function it is necessary for a more targeted approach to manage these conditions.

4. CONCLUSIONS

The aetiology of POP is multifactorial. Vaginal delivery is the major risk factor but growing evidence underlines the possible genetic influence and familial predisposition in the aetiology of POP. LEVEL OF EVIDENCE II

Even though vaginal delivery is the major traumatic event for the pelvic floor during lifespan, caesarean section seems not to be completely protective. LEVEL OF EVIDENCE II.

Hormonal and mechanical physiological alterations during pregnancy affect the pelvic floor support. LEVEL OF EVIDENCE III

Forceps, vaginal parity, prolonged second stage of labour, and fetal macrosomia are obstetric risk factors for development of POP. LEVEL OF EVIDENCE II

Declining sex hormone level, ageing, obesity, constipation, chronic pelvic floor stress are associated with pelvic organ prolapse. LEVEL OF EVIDENCE III

The evaluation of POP requires the assessment of urinary, anorectal and sexual functions. LEVEL OF EVIDENCE II

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VI. MICROBIOTA IN INCONTINENCE AND PELVIC FLOOR DYSFUNCTIONS

1. INTRODUCTION

For a long time, urine was thought to be sterile. It has only been recently understood that the bladder contains its own microbiome. Consequently, a whole novel field of research within urology has opened up with regard to the physiological role of the lower urinary tract microbiome and its pathophysiology. Over 50% of women will experience at least one urinary tract infection (UTI) during their life, with a yearly prevalence of 11% [1]. In addition, UTIs are responsible for substantial morbidity in frailolder adults. Amongst community dwelling older women, UTIs compromise the second most common cause of infection. In long-term care facilities and hospitalised subjects, UTIs represent the most common cause of infection [2]. Aside from the patient's burden this results in significant health care expenditure. UTIs are estimated to be responsible for more than 100,000 hospital visits and $3.5 billion annually in the United States of America [3]. An analysis 456,586 German patients with Type 2 diabetes mellitus showed a prevalence of 48,337 UTI episodes over a mean observation period of 665 days. Additional multivariable cost analysis in this group showed a UTI cost-increasing effect of 3.916 euro per patient year [4]. These UTI related additional costs might even be higher in frail older adults; UTIs in this group led more often to hospitalisation [5]. During a 90-day follow-up period Turner *et al.* showed that in-hospital treatment led to significantly more costs during treatment but also at follow-up 90 days post-treatment [5].

1.1. Terminology

Microbiome: The microbiome represents the genes and genomes of the microbiota. In addition, it represents the products of microbiota and the host environment. The microbiome incorporates biotic and abiotic factors (including archaea, viruses and fungi and products of microbiota) and refers to the whole environment including [32].

Metagenome: The metagenome refers to the genes and genomes of the microbiota and highlight the genetic potential of a population.

Microbiota: Identification of the microorganisms in an environment by the use of molecular techniques (such as 16S ribosomal RNA sequencing). The term microbiota refers to the microbial taxa associated with an environment [32, 33].

Table 1: Registration of Urinary tract microbiota in different studies. The presented strains are highlighted by the authors of the original studies as predominant or more prevalent than other populations. The microbiota are listed as genera unless otherwise specified. STI: sexually transmitted infection, NBD: neurogenic bladder dysfunction, IC: interstitial cystitis, POP: pelvic organ prolapse, OAB: overactive bladder, MUI: mixed urinary incontinence; UUI: urgency urinary incontinence, UTI: urinary tract infection, UCPPS: urological chronic pelvic pain syndrome, SUI: Stress Urinary Incontinence.

	Patient groups	n	Predominant strains	Urine Sample collection
Nelson et al. 2010 [6]	Men with STI Men without STI	10 9	Lactobacillus, Sneathia, Gemella, Aerococcus, Corynebacterium, Streptococcus, Veillonella, Prevotella, Anaerococcus, Propionibacterium, Atopobium, Staphylococcus	First-void
Dong et al. 2011 [7]	Men with STI Men without STI	10 22	Lactobacillus, Sneathia, Gemella, Aerococcus, Corynebacterium, Streptococcus, Veillonella, Anaerococcus, Propionibacterium, Atopobium, Staphylococcus, Ureaplasma, Mycoplasma, Enterococcus, Finegoldia, Neisseria, Ralstonia	First-void
Siddiqui et al. 2011 [8]	Healthy women	8	Lactobacillus, Prevotella, Gardnerella, Peptoniphilus, Dialister, Finegoldia, Anaerococcus, Allisonella, Streptococcus, Stahpylococcus	Clean-catch midstream
Fouts et al. 2012 [9]	Healthy controls Patients with NBD	26 (58% women) 27 (48% women)	Lactobacillus, Enterobacteriales, Actinomycetales, Bacillales, Anaerococcus, Allisonella, Clostridiales, Bacteroidales, Burkholderiales, Pseudomonadales, Bifidobacteriales, Coriobacteriales	Midstream, catetherisation
Nelson et al. 2012 [10]	Healthy adolenscent men	18	Lactobacillus, Streptococcus, Sneathia, Mycoplasma, Ureaplasma	First-void
Siddiqui et al 2012 [11]	Women with IC	8	Lactobacillus, Gardnerella, Corynebacterium, Prevotella, Ureaplasma, Eterococcus, Atopobium, Proteus, Cronobacter	Clean-catch midstream
Wolfe et al. 2012 [12]	Healthy women Women with POP/UI	23 11	Lactobacillus, Actinobaculum, Aerococcus, Anaerococcus, Atopobium, Burkholderia, Corynebacterium, Gardnerella, Prevotella, Ralstonia, Sneathia, Staphylococcus, Streptococcus, Veillonella	Clean-catch midstream, Suprapubic
Lewis et al. 2013 [13]	Healthy men Healthy women	6 10	Jonquetella, Parvimonas, Proteiniphilum, Saccharofermentans Phyla: Actinobacteria, Bacteroidetes	Clean-catch midstream
Fricke et al. 2014 [14]	Patients receiving 1st renal transplant	60 (37% women)	Lactobacillus, Enterococcus, Pseudomonas, Streptococcus Families: Bifidobacteriaceae, Corynebacterineae	Not described
Hilt et al. 2014 [15]	Healthy women Women with OAB	24 41	Lactobacillus, Corynebacterium, Streptococcus, Actinomyces, Staphylococcus, Aerococcus, Gardnerella, Bifidobacterium, Actinobaculum	Transurethral catheterisation
Pearce et al. 2014 [16]	Healthy women Women with urgency UUI	58 60	Gardnerella, Lactobacillus, Actinobaculum, Actinomyces, Aerococcus, Arhrobacter, Corynebacterium, Oligella, Staphylococcus, Streptococcus	Transurethral catheterisation
Willner et al. 2014 [17]	Patients with uncomplicated UTI	50 (76% women)	Anaerococcus, Peptoniphilus, Streptococcus, Lactobacillus, Staphylococcus, Escherichia, Pseudomonas	Midstream
Pearce et al. 2015 [18]	Women UUI	182	Lactobacillus, Aerococcus, Bifidobacterium, Enterobacterium, Prevotella, Staphylococcus	Transurethral catheter
Nickel et al 2015 [19]	Men UCPPS Aged-matched controls	110 115	Lactobacillus, Listeria, Staphylococcus, Streptococcus, Propionibacterium, Finegoldia, Burkholderia, Bifidobacterium	Initial stream urine, midstream, after prostate massage
Nickel et al 2016 [20]	Women UCPPS and flare Women UCPPS without flare	127 86	Lactobacillus, Staphylococcus, Streptococcus, Finegoldia, Bifidobacterium, Corynebacterium, Escherichia	Initial stream urine, midstream
Karstens et al 2016 [21]	Women UUI Healthy controls	10 10	Lactobacillus, Lachnospiria, Enterobacterium, Comamonadacium, Micrococcus, Bifidobacterium, Provotella, Flavobacterium	Transurethral catheter

	Patient groups	n	Predominant strains	Urine Sample collection
Thomas-White et al 2016 [22]	Women UUI Healthy controls	74 60	Lactobacillus, Streptococcus, Enterobacterium, Staphylococcus, Actinobaculum, Bifidobacterium, Alloscardovia, Atopobium, Micrococcus	Transurethral catheter
Thomas-White et al 2016 [23]	Women with SUI	197	Lactobacillus, Streptococcus, Bifidobacterium, Corynebacterium, Atopobium, Prevotella,	Transurethral catheter, midstream
Curtiss et al. 2017 [24]	Women with OAB Controls	60 35	Staphylococcus, Streptococcus, Corynebacterium, Lactobacillus, Escherichia, Peptoniphilus, Fusobacterium, Enterococcus, Anaerococcus, Campylobacter, Bifidobacterium, Serratia, Proteus, Gardnerella, Prevotella	Midstream
Chen et al. 2018 [25]	Refractory DO and rUTI	39	Anaerococcus, Atopobium, Bifodobacterium, Corynebacteriaceae_family, Eneterobacteriaceae_other, Enterococcus, Escherichia, Finegoldia, Gardnerella, Janthinobacterium, Lactobacillus, Prevotella, Pseudomonas, Staphylococcus, Streptococcus	Midstream
Komesu et al. 2019 [26]	MUI Controls	123 84	Lactobacillus, Gardnerella, Prevotella, Tepidomonas, Serratia, Streptococcus	Transurethral catheter
Meriwether et al. 2019 [27]	UCPPS Controls	23 18	Lactobacillus, Prevotella, Shuttleworthia, Bifidobacterium, Streptococcus, Coriobacteriaceae, Dialister, Megasphaera, Anaerococcus, Rhodococcus	Midstream
Bresler et al. 2019 [28]	UCPPS Controls	18 20	Lactobacillus, Bifidobacteriaceae, Bifidobacterium, Corinebacterium, Megasphhera, Prevotella, Streptococcus	Midstream
Price et al. 2020 [29]	Women with UUI Women with SUI Continent Controls	61 54 47	Lactobacillus, Streptococcus, Staphylococcus, Aerococcus, Gardnerella, Actinotignum, Corinebacterium	Transurethral catheter
Garretto et al. 2020 [30]	Women with UTI Wonen with OAB Women with UUI Women without LUTS	42 5 13 6	Escherichia, Lactobacillus, Staphylococcus, Streptococcus, Klebsiella, Gardnerella,	Transurethral catheter
Jacobs et al. 2020 (31)	UCPPS Controls	15 13	Lactobacillus, Streptococcus, Gardnerella, Actinomyces, Staphylococcus, Enterobacteriaceae	Transurethral catheter

2. MICROBIOTA AND URINARY TRACT: PHYSIOLOGY

The significance of microbiome in maintenance of health and development has been extensively explored in organ systems other than the urinary tract and it has only been recently accepted that most of the human body is colonised with bacteria. The Human Microbiome Project (HMP) is a large mapping study of the human microbiome sampling 300 individuals at five body sites (gastrointestinal tract, mouth, vagina, skin and nasal cavity) using culture independent methods [34]. Specific microbial sites have been linked to diseases,for example, gastrointestinal misbalance in microbiota has been related brain abnormalities [35], problems in the musculoskeletal system [36] and linked to metabolic processes [37].

In addition to the Human Microbiome Project multiple studies have suggested that the lower urinary tract contains a unique microbiome that is vastly different from gastrointestinal and vaginal colonisation (Table 1) [12, 15, 38]. In contrast to traditional bacterial culturing of urine which only allows identification of fast-growing pathogens, progress has been made possible by advanced culture and molecular techniques (PCR and 16S ribosomal RNA sequencing). The initial disadvantage of the molecular techniques was that they were unable to distinguish live from dead bacteria. However, by combining RNA sequencing with expanded cultures Hilt *et al.* were able to show that most bacteria in the bladder were alive [15].

Is there a “core” set of microbiota? In 2013 Lewis and colleagues presented a catalogue of bacterial DNA from a small cross-sectional sample of healthy adults. In addition, they proposed the concept of a set of bacteria that exist across different age groups but may fluctuate in association with age [13]. However, with regard to the variations in detected microbiota amongst the different studies presented in Table 1, larger longitudinal studies will be needed to confirm the existence of a core set of microbiota in the bladder. Moreover, evolvement of the bladder’s microbiome over time and factors influencing these specific microbiota need further investigation.

The specific role of microbiota and the microbiome in the urinary tractremains unclear. In contrast to other organ systems

the homeostatic role of bacteria in the lower urinary tract has only received minimal attention. However, specific key roles of the urinary tract's microbiome have been suggested, based on research in other organ system: 1) Regulation and maintenance of barrier function of the bladder wall and functioning as the prime urothelial defence mechanism. For example, through competition with pathogens for common resources. This is true for other sites of the body such as the gut and vagina [39, 40]. 2) Products of microbiota may kill pathogens and degrade certain harmful compounds. 3) Involvement of microbiota in the development of the urinary tract, including the connected peripheral nervous system. There is only little known about the link between microbiota and development of the nervous system. Through production of neurotransmitters microbiota might be needed for correct development the bladder's signalling system. Incorrect development of these signalling systems might be related to lower urinary tract dysfunctions such as OAB or DUA. Gastrointestinal studies on germ-free mice show that absence of microbes correlated with behavioural and neurological disorders [27]. However, the exact role of microbiota in the bladder and its relation to signalling systems in the bladder-brain axis is still unknown due to the lack of studies in this specific area of research.

3. THE PATHOPHYSIOLOGICAL ROLE OF MICROBIOTA IN THE URINARY TRACT

Acknowledgement of the suggested physiological role of the urinary tract microbiome does raise questions about the pathophysiological role of microbiota in different urological entities. For example, microbiota have suggested to be involved in development of urolithiasis and as treatment for recurrent superficial bladder cancer. However, both of these topics are beyond the scope of this chapter. Here, the link between microbiota and functional lower urinary tract disorders will be furtherdiscussed.

3.1. Stress Urinary Incontinence

To date only one study considers relationship between urinary microbiota and the characteristics of women with stress urinary incontinence. This cross-sectional study in 197 women showed no association between stress urinary incontinence symptoms and the bacterial diversity [23]. Based only on these results, the involvement of the urinary microbiome in SUI seems of lesser importance compared to other lower urinary tract dysfunctions. However, more research is needed to confirm these initial conclusions.

3.2. Urgency Urinary Incontinence

Urgency urinary Incontinence is a widespread disorder affecting many adult women. It is only recently that the potential role of the microbiome has been explored. In 2014 Pearce *et al* compared microbiota of women with and without UUI using molecular sequencing. Results showed that women with UUI had decreased Lactobacillus taxa and higher Gardnerella presence. In addition, Actinobaculum, Actinomyces, Aerococcus, Arthrobacter, Corynebacterium, Oligella, Staphylococcus and Streptococcus were found more frequently in the UUI group [16]. Curtiss *et al*. too showed Lactobacillus to be less common in patients with OAB compared to controls, with Proteus found statistically more commonly in patients with OAB. No difference in microbial diversity was found [24].

Thomas-White demonstrated how 12 weeks of vaginal oestrogen treatment resulted in a significant increase in Lactobacillus in postmenopausal women's urine, with a modest but significant improvement in OAB symptoms. However, also in this case, no difference was found in microbial diversity [41].

Komesu *et al.* showed how Lactobacillus predominance did not differ between women affected by Mixed Urinary Incontinence (MUI) and controls, but it did distinguish between MUI and controls in women younger than 51 years. Indeed, younger MUI patients more commonly had Moderate-Lactobacillus or Mixed communities rather than a High-Lactobacillus community. Whether the high preponderance of health-associated bacteria (Lactobacillus) or the shift in the balance of MUI-associated bacteria (e.g., Gardnerella, Prevotella) contributes to bladder symptoms warrants further investigation [26].

In one of studies describing the variability in female microbiota in patients with UUI, an association between certain microbial characteristics (i.e. taxa and variety of microbes) and symptom severity was found. An increase in UUI symptom severity may be associated with a loss of microbial diversity in women with UUI [21]. Price *et al.* showed how, in adult women, the detection and richness of culturable urobiome was associated with UI, regardless of incontinence subtype (SUI or UUI) in comparison with the continent cohort. Furthermore, the two UI groups were more similar to each other than the control cohort, and each UI cohort differed significantly from the control cohort. Moreover, the richness indices were associated with worsening of incontinence symptom severity [29].

In a follow-up study, Pearce *et al* compared sequencing in positive and negative UUI groups before oral drug treatment for UUI. They found that positive sequencing was associated with more severe UUI and a better response to treatment [18].

In 2016 Thomas-White *et al* reported a 12 weeks anticholinergic follow-up study in women with UUI suggesting that less diversity in microbiota tended to be associated with fewer UUI symptoms and with better treatment response to an anticholinergic drug [22]. Non-responders had a more diverse microbial population than population found in responders. An additional study in women with stress urinary incontinence showed consistent results. Increased microbial diversity was associated with a higher urgency index score [23]. In addition to finding differences between women with UUI and healthy controls several studies have shown a relationship between urinary microbiota and response to oral drug treatment. The variations in outcome between the studies might be related to the sampling method. However, in general the results highlight the potential clinical importance of the urinary microbiome in UUI.

Chen and Phan demonstrated that rUTI are common in patients with refractory urgency incontinence, with either the same persistent strain or a new infecting strain. This may suggest the existence of a chronic reservoir (i.e. bladder, urethra, vagina or bowel flora) and that the composition of the microbiota might have an impact on the incidence of rUTI and the refractoriness to antimuscarinics drugs on DO patients [25].

A genomic survey of *Escherichia coli* bladder colonization in individuals with or without LUTS (OAB, UUI and UTIs), showed no correspondence between different genomic content of different types of E. coli and symptoms. Furthermore, the presence of E. coli alone was not sufficient to distinguish between the

urobiomes of patients with and without LUTS, making E. coli a weak predictor of LUTS, highlighting that symptoms are more likely to be a result of urobiome composition [30].

Hence, recent research gives clues regarding the potential role of urinary microbiota diversity in the aetiology and treatment of women with UUI. However, a major flaw in research is the variability in sampling methods between the different studies. This makes replication and clinical utility difficult[42].

3.3. Urological Pain Syndromes Painful Bladder Syndrome(PBS) / Interstitial Cystitis (IC)

The role of microbiota in different urological pain syndromes has been explored, for example in PBS/IC and chronic pelvic pain syndrome (CPPS). Saddiqui *et al.* collected urine samples of women with interstitial cystitis and compared this with healthy volunteers. They were able to show that IC patients had lower bacterial diversity and an increase in Lactobacillus compared to healthy volunteers (92 vs 57%) [11]. Reduction of bacterial diversity in general is seen in chronic inflammatory states such as inflammatory bowel disease [43]. Although, Jacobs *et al.* showed Lattobacillus to be the most common urotype, without any difference between IC/PBS individuals and controls. Presence of Lattobacillus or not did not affectIC/PBS symptoms. Furthermore, bacteria were not isolated from most of the IC/PBS patients, suggesting that bacteria may not be an aetiological factor for IC/PBS [31]. Furthermore, Bresler *et al.* compared the urinary microbiota of women affected by IC/PBS with a group of asymptomatic controls, highlighting that IC/PBS symptoms may not be related to differences in the female urinary microbiota, at least not its bacterial components [28].

In one study, premenopausal women with IC/BPS were not found to have significantly different urinary and vaginal microbiomes compared to women without IC/BPS andLactobacilli was the most abundant genus in both cohorts, while anaerobic or fastidious predominance was similar between groups [27]. The relative abundance of Lactobacillus however is yet to be confirmed in other studies and the question is whether this is truly associated with IC in women.

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) research network compared women with Urological Chronic Pelvic Pain (UCPPS), a group in which they gathered women with IC/PBS, with and without flare to examine differences in microbiota. The results revealed no difference in bacterial prevalence in the urine samples. However, the group with flare had a significantly greater prevalence of fungi (Candida and Saccharomyces sp.) [20]. This agrees with an earlier study from the same group in which they performed a 2-year follow-up of IC/PBS patients to identify bacterial culture status using only standard culture techniques [35]. The same MAPP research network studied male PBS/IC/chronic prostatitis patients and compared the microbiota with aged-matched controls. The study group showed higher presence of *Burkholderia cenocepacia* in the UCPPS group of patients in the initial stream urine [19]. However, these differences were not reproducible for the midstream urine samples or after prostate massage.

A recent study examining stool samples of female UCPPS patients identified potential stool-based microbial and metabolome markers for UCPPS, with specific interest for *Colinsella aerofaciens* and the metabolite glyceraldehyde. In this pilot study these biomarkers were altered in the gut of 18 women with UCPPS compared to 16 healthy controls [44]. Shoskes *et al.* analysed gut microbiota in men with UCPPS and showed a decreased microbial diversity in the gut in men with UCPPS compared to controls [45].

In theory the bladder microbiome might be involved in aetiology or development of IC/PBS/UCPPS, however different studies show largely varying results. Up until now there is no compelling evidence to support the specific role of the microbiome in patients with urological pain syndromes and more research is needed in this specific area.

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VII. CHILDBIRTH AND FAECAL INCONTINENCE

1. INTRODUCTION

Pregnancy and childbirth have a significant impact on the emotional and physical wellbeing of a woman. As many as 91% of women report at least one new symptom eight weeks post-partum [1.]. A fall in maternal mortality accompanied by an increase in female life expectancy (86 years in Japan) has now shifted the focus of attention towards identification of factors that may minimise morbidity. Although pre-existing bowel symptoms may be aggravated during pregnancy and childbirth, the development of symptoms *de novo* is a more frequent occurrence. Obstetric trauma is the most common cause of FI. However, the onset of symptoms may occur many years after delivery with a peak incidence in the perimenopausal years. This may reflect the effect of contributory factors such as aging, the effect of menopause or progression of neuropathy. This section focuses on the association between obstetric trauma and FI. The term 'anal incontinence' is used to include incontinence to flatus, liquid and solids.

Anal incontinence (AI) has been reported to occur between 5 [2,3] to 26 [4] percent of women during the first year following vaginal delivery. In a Canadian study [5] involving 949 consecutive women who delivered vaginally, 26% reported AI while 3% reported FI. They identified forceps delivery and third/fourth degree tears as independent risk factors. In a population based study of 8774 women in Oregon, USA, more than 25% reported FI within 6 months of childbirth [6].

The prevalence of anal incontinence among women who sustained OASIS 1–5 years previously has been found to be 18–53% for flatus and 3–23% for stools [7-11]. Among parous women without OASIS, the prevalence of incontinence to flatus was 15–32% and incontinence to stools 5–7% at 4–5 years postpartum [7,8]

2. NEUROGENIC TRAUMA

The mechanism that maintains continence is complex and affected by various factors such as mental function, lack of a compliant rectal reservoir, rectal hypersensitivity, enhanced colonic transit and changes in stool consistency and volume. However, the ultimate barrier is the anal sphincter. AI may ensue if there is mechanical disruption to the anal sphincter muscles, disturbance in neurological function or a combination of both factors. In about 80% of women with presumed "idiopathic" anorectal incontinence there is histological evidence of denervation of the striated pelvic floor muscles, particularly the puborectalis and external anal sphincter (EAS) [12]. This feature has also been demonstrated electro-physiologically by means of an increased fibre density in patients with idiopathic FI indicating re-innervation following denervation [13]. Another finding in these patients is a conduction delay in pudendal nerves as measured by pudendal nerve terminal motor latency (PNTML) [14].

Hertz in 1909 suggested that pelvic floor damage may result from a normal vaginal delivery, objective scientific evidence for this was only produced in 1984 [15] and a follow-up of 14 patients 5 years later [16.]. These authors studied 122 women, 71 after delivery with manometry, perineometry, PNTML and EMG, and 51 before and after delivery with EMG. This study demonstrated an increase in anal sphincter striated muscle fibre density in the vaginal delivery group at 2 months post-partum indicating evidence of re-innervation following denervation. The fibre density was not altered following elective caesarean section. Thirty three percent of primiparae and 50% of multiparae had prolonged PNTML within 48 hours of delivery. However, by 2 months, the PNTML had returned to normal in 60% of these women, indicating that damage to pudendal nerve conduction is reversible. Multiparity, forceps delivery, increased duration of the second stage of labour, third degree perineal tears and high birth weight were important factors leading to pudendal nerve damage. In the five year follow-up study of 14 women, only multiparae who did not have a forceps delivery were selected; the denervating process was found to be progressive in the majority of women and 5 women suffered from stress incontinence of urine, 3 of whom were also incontinent to flatus.

In another prospective neurophysiological study, Allen *et al.* [17] studied 96 nulliparous women with EMG, PNTML and vaginal pressure measurements during pelvic floor contraction. They found evidence of re-innervation in the pelvic floor muscles of 80% of primiparae 2 months after vaginal delivery. The only obstetric factors associated with re-innervation were a high birth weight and a longer active stage of labour. Forty five of the original 96 women were studied again 6 years later and they concluded that changes in pelvic floor neurophysiology occur with time and do not appear to be related to further childbearing [18].

A third prospective study [19] measured anal pressures, anal sensation and the perineal plane in 72 antenatal women and repeated 72 hours post-partum and in 41 women 2 months postpartum. Anal sensation was unchanged. Cornes *et al.* [20] measured anal sensation in 96 primiparae within 10 days after delivery and measurements were repeated in 74 women 6 months after delivery. They found that at 6 months anal sensation had returned to normal. Anal sensation remained unchanged after caesarean section. In women who had a torn EAS, only impairment of sensation in the upper anal canal persisted at 6 months. More than half the women who admitted to persistent anal incontinence had normal anal sensation. Chaliha *et al.* [21] measured anal electro-sensitivity before and after childbirth and found it unchanged. Anal sensation in isolation therefore probably plays a minor role in the development of obstetric related faecal incontinence.

A cross-sectional study of 175 women with FI and 19 healthy volunteers [22] concluded that fa

Faecal incontinence in women is mainly associated with mechanical sphincter dysfunction related to either muscle damage or, to a lesser extent, impaired efferent conduction at pudendal nerves. Impaired conduction through afferent anorectal pathways is also very prevalent in women with FI and may play an

important role as a pathophysiological factor and as a potential therapeutic target.

Broens *et al.* [23] reported that the puborectal muscle is able to contract involuntarily during rectal dilatation and described a new regulatory mechanism "puborectal continence reflex", which controls faecal continence by involuntary contraction of the puborectal muscle. It seems to be initiated by dilatation at the level of the puborectal muscle. Presumably, the puborectal continence reflex protects many patients with anal sphincter dysfunctions from faecal incontinence.

Jonker *et al*. [24] showed that voluntary contractions of the puborectal muscle are significantly decreased in patients with pudendal nerve damage, while involuntary contractions of the puborectal muscle are comparable to those of patients without nerve damage. They concluded that the puborectal continence reflex, which controls involuntary contractions of the puborectal muscle, is not regulated by the pudendal nerve. Although there are no relevant studies on women with postpartum faecal incontinence, it is possible that puborectal continence reflex plays a part in faecal continence women with pudendal neuropathy following childbirth.

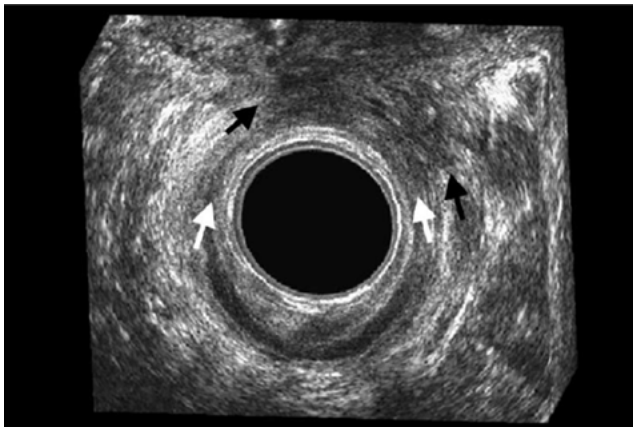

Figure 1: Anal ultrasound image of the mid anal canal. EAS = external anal sphincter. IAS = internal anal sphincter. The area between the black arrows at 11 and 2 o'clock represents an external anal sphincter defect while the area between the white arrows between 9 and 3 represent an internal sphincter defect.

3. MECHANICAL TRAUMA

Until the advent of anal endosonography, mechanical trauma to the anal sphincters was only suspected when there was a history of third or fourth degree tears collectively known as obstetric anal sphincter injuries (OASIs). Consequently, when anal endosonography was performed in patients believed to be suffering from "neurogenic" FI unsuspected internal anal sphincter (IAS) and EAS defects were identified [25]. The sonographic appearance of EAS defects has been verified histologically to represent fibrosis [26.] while the appearance of IAS defects have been validated prospectively in patients undergoing lateral internal anal sphincterotomy [27]. Trauma as identified by ultrasound may represent unrecognised OASIs (previously referred to as occult) or the consequence of recognised and repaired OASIs.

3.1. Unrecognised ("occult") anal sphincter trauma

Sultan *et al.* [2] performed the first prospective study (before and after childbirth) to demonstrate both "occult" anal sphincter trauma (**Figure 10**) and pudendal nerve damage during childbirth in both primiparous and multiparous women (n=150). In 35% of primiparous and 44% of multiparous women anal sphincter defects were identified at 6 weeks postpartum by anal endosonography that were not present before vaginal delivery. Thirteen percent and 23% respectively developed defecatory symptoms (faecal urgency and/or AI) after delivery. Only two of the 150 women (both primiparous) had recognised tears of the anal sphincter at the time of delivery. A strong association was demonstrated between the presence of any defect and the development of symptoms. Only 4% of multiparous women sustained new sphincter damage following a subsequent delivery. The single independent factor associated with anal sphincter damage was forceps delivery. The 23 women delivered by caesarean section remained asymptomatic and none developed sphincter defects. No relationship was demonstrated between PNTML measurements and defecatory or urinary symptoms.

Donnelly *et al.* [28] interviewed 219 nulliparae in the third trimester regarding bowel habits and performed anal vector manometry. At 6 weeks postpartum, 184 women returned and the same bowel symptom questionnaire was completed and anal vector manometry plus PNTML measurements were performed. Anal endosonography was performed in 81 women with altered faecal continence or abnormal physiology. Instrumental vaginal delivery and a passive second stage of labour prolonged by epidural analgesia were significantly associated with the greatest risk of anal sphincter trauma and impaired faecal continence. As instrumental delivery is a known risk factor (8 fold increased risk of sphincter trauma), early use of oxytocin was recommended to shorten the second stage. A continuation of the same study [29.] reported that PNTML was prolonged and the squeeze pressure increment was reduced in women who had a caesarean section in the late first stage (>8cm cervical dilatation) or second stage.

Chaliha *et al.* [21] measured anal sensation and manometry in 286 nulliparae during the third trimester and repeated in 161 women postpartum when anal endosonography was also performed. Anal endosonography revealed sphincter defects in 38% of women and this was associated with the presence a lowering of anal squeeze and resting pressures. Threshold anal electrosensitivity remained unchanged and bore no relationship to symptoms. Postpartum sphincter defects were associated with perineal laceration and vaginal delivery.

Abramowitz *et al.* [30] performed a prospective study of 233 women who had anal endosonography performed before and 6 to 8 weeks after childbirth. Of the 233 women (118 primiparae), 202 had a vaginal delivery. Postpartum AI in the 233 women was reported by 13% of primiparae and 8.5% of multiparae and anal sphincter defects in 21% and 12% respectively. However, the prevalence of anal sphincter defects amongst those who had a vaginal delivery (n=202) was 26% and 13% respectively. Previous studies [31,32] including others mentioned in **Table 3** and **7** have shown that the first delivery is at greatest risk for anal sphincter trauma but this study is at variance as it claimed that secundiparous females have the same risk as primiparous women. However, this finding remains unsubstantiated and is further disputed by a subsequent prospective study [32].

Fynes *et al.* [33.] undertook a prospective study of 59 previously nulliparous women through 2 successive pregnancies and found that 34% had anal sphincter injury after their first delivery but only 2 new injuries occurred after the second delivery confirming the findings in Sultan's study [2.]. An important finding in this study was that 42% of women (5 of 12) who had a severe 'occult' sphincter injury during their first delivery (squeeze pressure increment < 20mmHg or anal sphincter defect > one quadrant) developed AI after the second delivery.

Willis *et al.* [34] performed anal vector manometry, endosonography, PNTML and rectal sensibility at the 32 weeks and 6 weeks postpartum. Using the Kelly-Holschneider score they reported AI in 5% and identified occult injuries in 19%. PNTML and rectal sensibility was unaffected by vaginal delivery.

Nazir *et al.* [35] performed vector manometry and endoanal ultrasound in 73 nulliparous woman at 25 weeks and 5 months postpartum (**Table 3**). There was no correlation between vector manometry and anal endosonography or clinical variables.

Belmonte-Montes [36] performed anal endosonography in 98 nulliparous women 6 weeks before and 6 weeks after delivery and after excluding 20 third degree tears found occult sphincter injuries in 13%. Seventy five percent of women with defects were symptomatic and there was a good correlation between defects and symptoms. However, it is not clear as to how many with 'occult' defects were symptomatic (**Table 3**).

In 3 further studies [37, 40, 41] anal ultrasound was performed only after delivery and defects were identified in 11.5 to 34% (**Table 4**). Varma *et al.* [37] studied 159 postnatal women (105 primiparous and 54 secundiparous) and found occult anal sphincter defects in 11.5% of primiparous and 19% of secundiparous vaginal deliveries but 80% of forceps deliveries. None of their patients suffered FI but only 72% of questionnaires were returned. However, their cohort was recruited before 1998 and had a high caesarean section rate (25%) and a low forceps rate (4%).

Williams *et al.* [42] performed a prospective study in 45 nulliparous women before and after vaginal delivery using 3 dimensional endosonography. There was evidence of perineal trauma in 29% (external sphincter 11%, puboanalis 20%, transverse perineal muscle 7%). Sudoł-Szopińska *et al.* [43] performed 3 dimensional endoanal ultrasound in 112 primiparous women and found only 2.6% sonographic injuries. However, their obstetric practice was different in that they had a 77% episiotomy rate and a 59% epidural rate.

Oberwalder *et al.* [44.] performed a meta-analysis of 717 vaginal deliveries and found a 26.9% incidence of anal sphincter defects in primiparous women and an 8.5% incidence of new sphincter defects in multiparous women. Although two thirds of these women with "occult" defects were asymptomatic in the postpartum period, the probability of FI associated with a sphincter defect was 76.8 to 82.8%.

Some 15 years after having first coined the term "occult" OASIs based on anal endosonography, Sultan [2] began questioning whether the 28% sonographic anal sphincter defects (**Table 5**) identified some weeks after delivery were really genuine occult defects that were unidentifiable clinically at delivery. They therefore conducted a prospective study [49.] in which 241 women having their first vaginal delivery had their perineum re-examined by an experienced research fellow and endoanal ultrasound was performed immediately after delivery and repeated 7 weeks postpartum. When OASIs were identified by the research fellow, the injuries were confirmed and repaired by the duty registrar or consultant. The prevalence of clinically diagnosed OASIs increased from 11% to 25% (n=59). Every clinically diagnosed injury was identified by postpartum endoanal ultrasound. However, there were three women with sonographic defects in whom the injury was not identified clinically. Two of these had only small IAS defects that were not considered clinically significant. The other was a combined defect of both the IAS and EAS and while this could be classified as an occult tear, it is most probably a tear that was not recognised by the research fellow. At 7 weeks postpartum, no *de novo* defects were identified by ultrasound. This study concluded that virtually all sphincter defects that have previously been designated as "occult" injuries (**Table 5**) were in fact OASIs that could have been identified by a trained clinician [50] and that less than one percent are genuine occult OASIs (if indeed they exist). Interestingly, 87% of midwives and 27% of junior doctors failed

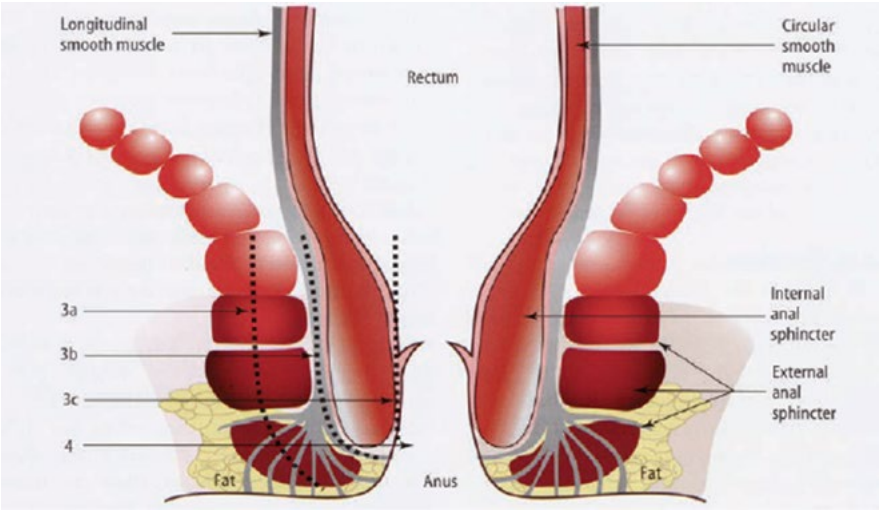

Figure 2: Schematic representation of the classification of 3rd and 4th degree tears (with permission from Springer)

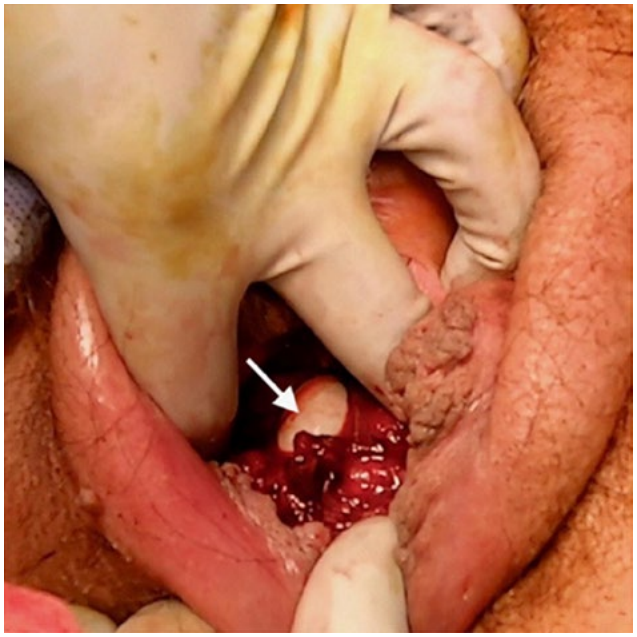

Figure 3: An isolated "buttonhole" tear of the rectal mucosa (arrow) inferior to which is an intact anal sphincter. (From 65. Roper, J.C., Thakar, R. & Sultan, A.H. Isolated rectal buttonhole tears in obstetrics: case series and review of the literature. Int Urogynecol J (2020)

to recognise OASIs clinically. Although it is likely that some of these injuries would have been detected at the time of suturing the tear, it is concerning that clinical recognition of OASIs is suboptimal [50.]. However, this finding is not unique as Groom and Patterson [51] also found that the rate of third degree tears rose to 15% when all "2nd degree tears" were re-examined by a second experienced person.

These studies [49, 51] confirm the lack of adequate training as previously highlighted by Sultan *et al.* [52] who reported that 91% of doctors who had done at least 6 months of training in obstetrics and 60% of midwives indicated inadequate training in perineal anatomy and 84% and 61% respectively reported inadequate training in identifying 3rd degree tears. Another possible reason for under-diagnosis is that tears of the anal sphincter have been wrongly classified and therefore anal sphincter tears have been under-reported. Any involvement of the anal sphincter should be classified as a third degree tear. However 41% of doctors and 16% of midwives classified a torn anal sphincter as a 2nd degree tear [52]. Sultan and Thakar [53] reviewed every relevant text book (n=65) in the library of the Royal College of Obstetricians and Gynaecologists (RCOG) and found that there was a lack of consistency in classification and in about 40% the classification was omitted or wrong. Furthermore, previous classifications were incomplete because they did not incorporate depth of EAS rupture or involvement of the IAS. This therefore has epidemiological, clinical and medicolegal implications. If a third degree tear is incorrectly classified as second degree, then inappropriate repair could result in sub-optimal outcome (see below). Sultan [54] therefore proposed the following classification (**Figure 11**) that has been incorporated into the 29th RCOG green top guidelines

Table 1: Prospective studies before and after vaginal delivery of "occult" anal sphincter injury (using 2d ultrasound) and anal incontinence but excluding fecal urgency.

Study	Parity	Vaginal delivery (n)	FU in weeks postpartum	Sphincter Defects	Anal Incontinence
Sultan et al 93[2]	Primi Multi	79 48	6 6	33% 44%	5% 19%
*Donnelly et al 98[28]	Primi	168	6	35%	25%
Rieger et al 98[38]	Primi	37	6	41%	8%
Zetterstrom et al 99[39]	Primi	38	9	20%	18%
*Fynes et al 99[33]	Multi	59	6-12	37%	17%
Abramowitz et al 00[30]	Primi Multi	202 including multi	8	26% 13%	15% 10%
Chaliha et al 01[21]	Primi	130	12	19%	13%
Belmonte-Montes et al 01[36]	Primi	78	6	13%	?
Nazir et al 02[35]	Primi	73	20	19%	25%
Willis et al 02[34]	Primi +Multi	42	12	10%	5%
MEAN (excluding Willis et al)	**Primi Multi**			**28% 31%**	**16% 15%**

**modified continence score questionnaire used and may include urgency*

Table 2: Postnatal studies of "occult" anal sphincter injury (using 2d ultrasound) sustained during vaginal delivery and anal incontinence excluding fecal urgency.

Study	Vaginal delivery	Parity	FU Postpartum	Defects	Anal Incontinence
*Varma et al 99[37]	78 31	Primi Multi	4 weeks 4weeks	11.5% 19%	0% 0%
Damon 00[40]	197	Primi	3 months	34%	6%
**Faltin 00[41]	150	Primi	3 months	28%	15%

**Ultrasound performed < 1 week after delivery ** anal ultrasound performed immediately after delivery before perineal repair*

Table 3: Prevalence of anal incontinence and fecal incontinence following primary repair of obstetric anal sphincter rupture. (predominantly end-to end repair of external sphincter).

Authors (n=42)	Year	Country	N	Follow-up Months	Anal(Fecal) incontinence
Bagade & MacKenzie[45] Sangali et al[60] Wood J et al[80]	2010 2000 1998	UK Switzerland Australia	79 177 84	>6 13 years 31	10% (111%) 15% (10%) 17%* (7%)
Walsh et al[81]	1996	UK	81	3	20% (7%)
Sander et al[82] Pretlove et al[83]	1999 2004	Denmark UK	48 41	1 ?	21% (4%) 22% (22%)
Crawford et al[84]	1993	USA	35	12	23% (6%)
Sorensen et al[78]	1993	Denmark	38	3	24% (?)
Mackenzie et al[85]	2003	UK	53	3	25% (7%)
Nichols et al[86] Shek et al[46]	2005 2014	USA Australia	56 140	3 2	25% (11%) 25% (3%)
Nielsen et al[87]	1992	Denmark	24	12	29% (?)
*Go & Dunselman[88]	1988	Netherland	20	6	30% (15%)
Fenner et al[89]	2003	USA	165	6	30% (?)
DeLeeuw et al[90]	2001	Netherland	125	14 years	31% (?)
Wagenius et al[91] Vaccaro & Clemons[92]	2003 2008	Sweden USA	186 60	4 years 3	33% (25%) 33% (12%)
Kumar[47] Huebner et al[48] Uustal Fornell et al[93]	2012 2013 1996	UK Germany Sweden	41 99 51	52 28 years 6	37 (25%) 39% (13%) 40% (16%)
Poen et al[75]	1998	Netherland	117	56	40% (?)
Sultan et al[58]	1994	UK	34	2	41% (9%)
Zetterstrom et al[63]	1999	Sweden	46	9	41% (2%)
Sorensen et al[94]	1988	Denmark	25	78	42% (?)
Tetzschner et al[95]	1996	Denmark	72	24-48	42% (17%)
Williams et al[96]	2003	UK	124	?	42% (?)
Norderval et al[97]	2004	Norway	156	25	42% (17%)
Garcia et al[98]	2005	USA	26	3	42% (15%)
Kammerer-Doak et et al[77]	1999	USA	15	4	43% (13%)
Haadem et al[79]	1988	Sweden	62	3	44% (?)
Rieger et al[99]	2004	Australia	51	3	45% (25%)
Bek & Laurberg[100]	1992	Denmark	121	?	50% (?)
Davis et al[101]	2003	UK	52	3.6	50% (?)

Authors (n=42)	Year	Country	N	Follow-up Months	Anal(Fecal) incontinence
Fitzpatrick et al[61]	2000	Ireland	154	3	53% (6%)
Samarasekera et al[102] Nazir et al[103]	2007 2003	UK Norway	53 100	15 18	53% (32%) 54% (17%)
Gjessing H et al[64]	1998	Norway	35	12-60	57% (23%)
Savoye-Collet et al[104]	2003	France	21	4	57% (29%)
Goffeng et al[76]	1998	Sweden	27	12	59% (11%)
Nygaard et al[105]	1997	USA	29	30 years	59% (28%)
Pinta et al[106] †Sakse et al[107]	2004 2009	Finland Denmark	52 33	15 5	61% (10%) 67% (42%)
Mean					**37% (12%)**

**Includes 2 with secondary sphincter repair † includes only 4th degree tears*

Table 4: Summary of studies using Sultan classification of OASIS and anal incontinence symptoms score following primary repair.

Authors, year and country	n	FU	Mean AI Score according to degree of OASIS				Questionnaire used and statistical significance
			3a	3b	3c	4th	
Patton et al [68] 2019 Australia	265	6m	1.2	2.1	3.3	2.9	Mean St Mark's score Significant
Ramage et al [69] 2017 UK	117	6-12m	4.1	5.1	5.2	4.6	Mean Wexner score Not significant
*Linneberg et al [70] 2014 Denmark	54	7 Yrs	1	1.5	Not documented	3	Median St Mark's Not significant
*Visscher et al [71] 2014 Netherlands	16	3m	4.4 (combined 3a & 3b)		9.7	-	St Mark's (3a & 3b) v 3c Significant
			3.5 (combined 3a & 3b)		8.3	-	Wexner (3a & 3b) v 3c Significant
*Cerro et al [72] 2017 Spain	95	6m	1.8	1.6	6.7 (3c + 4)		Mean Wexner (3a &3b) v (3c & 4) Significant
*Anglim et al [73] 2019 Ireland	437	12m	0 (0-2) 3a+3b		2 (0-5) 3c+4		Median St Mark's (IQR) Significant
*Roos et al [74] 2010 UK	531	9 w	Faecal urgency - 2.24 (SD, 0.94)		2.04 (SD, 0.94),		Mean Manchester Significant
			Flatus inc (1.95 (SD, 1.14)		1.66 (SD, 0.92),		Significant
			Loose FI 1.12 (SD, 0.44)		1.05 (SD, 0.30),		Significant
			Solid FI (1.04 (SD, 0.25)		1.02 (SD, 0.21),		Not significant

**Linneberg did not document 3c tears where as Vicscher, Cerro, Anglim and Roos combined different degrees of OASIS due to small numbers.*

[55.], adopted by The American College of Obstetricians and Gynecologists (ACOG) [56.] and included in this ICI textbook since it first edition in 2002,:

First degree: laceration of the vaginal epithelium or perineal skin only.

Second degree: involvement of the perineal muscles but not the anal sphincter.

Third degree: disruption of the anal sphincter muscles and this should be further subdivided into:

3a: <50% thickness of external sphincter torn.

3b: >50% thickness of external sphincter torn.

3c: internal sphincter torn also.

Fourth degree: a third degree tear with disruption of the anal epithelium.

Isolated tears of the rectal mucosa without involvement of the anal sphincter (Figure…) is a rare event but the true incidence is not reported. By definition, it is not a fourth-degree tear because the anal sphincter muscles are not torn and therefore should not be labelled as such. It can also occur concurrently with an OASIS, i.e. an isolated rectal tear occurs in conjunction with a separate tear involving the anal sphincter. However, this is extremely rare. Usually, the presentation is with an intact perineum at delivery or a first/second-degree tear, and consequently it can remain undiagnosed, without a structured and careful combined vaginal and rectal examination [65] If unrecognised and therefore unrepaired, a rectovaginal fistula can persist [66,67].

Since the introduction of new classification in 1999 there have been several studies looked at the anal incontinence rates with 3a, 3b, 3c and 4th degree tears. Table 6 summarises the anal incontinence rates with different degrees of OASIS

Table 6 shows that except for Ramage *et al.* [69] and Linneberg *et al.* [70] all the other studies which used the Sultan classification showed a significantly worse Anal Incontinence score with higher degrees of OASIs.

Ramalingam and Monga [108] analysed 255 patients' symptoms at 6 months classified according to the Sultan classification. Twenty-three patients (9 %) reported symptoms at 6-month follow-up. Eight patients reported anal incontinence of liquid or solid stool. Among patients who sustained 3a tears, 8 patients were symptomatic: 7 had urgency and 1 had flatus incontinence. None of the patients who sustained 3a tears reported incontinence of solid/liquid stool. They concluded that as the vast majority of patients are asymptomatic irrespective of the degree of OASIs, with effective primary care follow-up, there may be a place to follow up patients with 3a tears in the community during the routine 6- week postnatal check and refer the symptomatic patients to the hospital for further review.

Reid *et al.* [109] analysed 344 women who had OASIs classified using the Sultan classification followed up at 3 years showed that compared to 9 weeks, there was a significant improvement in urgency and flatus incontinence for both minor (3a & 3b) and major tears (3c & 4) at 3 years. There was no significant change in presence of faecal incontinence in women sustaining minor and major tears. However, they did find that 10% of women developed symptoms for the first time between these two time periods and all these women had persistent sphincter defects

A meta-analysis of 103 studies involving 16,110 women [110] showed that in those who delivered vaginally, OASIS were diagnosed on ultrasound in 26 % (95 %CI, 21–30, I 2 = 91 %), and 19 % experienced anal incontinence (95 %CI,14–25, I 2 = 92 %). In women without clinical suspicion of OASIS (n = 3688), sphincter defects were observed in 13 % (10–17, I 2 = 89 %) and anal incontinence experienced by 14 % (95 % CI: 6–24, I 2 = 95 %). Following primary repair of OASIS, 55 % (46–63, I 2 = 98 %) of 7549 women had persistent sphincter defects with 38 % experiencing anal incontinence (33–43, I 2 = 92 %). There was a significant association between ultrasound diagnosed OASIS and anal incontinence (RR 3.74, 2.176.45, I 2 = 98 %). However this meta analysis did not specify the type of OASIS classification used.

4. RECOGNISED OBSTETRIC ANAL SPHINCTER INJURIES

4.1. Introduction

The rate of OASIs is increasing and in England alone there has been a 3 fold increase between 2000 and 2012 from 1.8 to 5.9% in primiparous vaginal deliveries [57]. This has been attributed to improvements in understanding anal sphincter anatomy and clinical diagnosis [50]. Primary repair of OASIs are usually performed by obstetricians using the end-to-end repair technique [58]. However, as shown in **Table 5**, AI occurs in 37% (range 10 to 67%) and in addition, urgency can affect a further 6 [58] to 28% [59]. Frank FI affected 12% (range 2 to 42%). The reasons for persistent symptoms are unclear but there are at least six studies [58, 59, 61, 63, 64, 76.] demonstrating anal sphincter defects following repair in 40 to 91% of women. Although the extent of the sphincter injury appears to be related to outcome of repair, in some studies (**Table 5**) the data was not interpretable [77], incomplete [76] or inclusive of symptoms other than anal incontinence [79]. Nulliparity, instrumental delivery especially forceps without episiotomy, large baby >4 kg, shoulder dystocia and a persistent occipito-posterior position and prolonged second stage of labour have been identified as the main risk factors for the development of OASIs [30, 31, 55, 58, 75].

Traditionally, the technique described to repair the torn anal mucosa (4th degree tear) was to insert interrupted sutures with the knot tied within the anal canal [58]. However, this was recommended when catgut was in use to minimise tissue reaction and infection. With the availability of polyglactin suture material this is no longer necessary as it dissolves by hydrolysis. Figure of eight sutures should be avoided during repair of the anal mucosa as they can cause ischaemia and therefore a continuous non-locking suture is adequate [58].

The most popular method of EAS repair is the end-to-end technique, but colorectal surgeons prefer the overlap technique for secondary repair because of a better outcome [111]. Similar to other operations for incontinence, the outcome can deteriorate with time and one study has reported continence in 50% of women at 5-year follow-up [112]. However, at least one third of women in this study had more than one attempt at sphincter repair and therefore these findings cannot be extrapolated to that following primary repair of acute injury [112]. In 1999,

Sultan *et al.* [111] were the first to explore the feasibility of the overlap technique of repair for acute EAS rupture but more importantly advocated the identification and separate repair of the torn IAS [55]. Until then, very little importance was given to the torn IAS during primary repair. However, subsequently in a study involving 500 consecutive women with OASIs it has been shown that sonographic evidence of IAS injury was predictive of FI [113]. Roos *et al.* [114] studied 531 consecutive women with OASIs and found that women who sustained an IAS tear were significantly more likely to suffer incontinence, have lower anal pressures, persistent IAS defects and a reduced quality of life. Increasing IAS defect size has also been shown to be related to symptoms of AI [92]. Reid *et al.* [115] performed a prospective study using validated outcome measures at 9 weeks and 3.2 years after primary repair involving 539 women with OASIs. All those who had an internal sphincter injury were classified as major tears (including 4th degree tears). There was no significant difference in outcome between minor and major tears in relation to urgency (10%), flatus (7%) or FI (0.9%). In fact there was a significant improvement in symptoms over time confirming that good outcomes can be achieved when the internal sphincter is repaired as a primary procedure. Oude Lohuis *et al.* [59] have shown that only 10% (26 of the 29) of women who sustained internal anal sphincter injuries (3c and 4th degree tears) had no persistent internal sphincter defects at 3 months follow up indicating adequate repair. Dickinson *et al.* [116] followed up 136 women who sustained OASIs (25 women sustained 3c/4th degree tears) and found internal sphincter defects in 32% of women but this could have included undiagnosed internal sphincter injuries.

When a patient presents with FI months or years after delivery, it is almost impossible to perform a successful IAS repair, highlighting the importance of identification and repair immediately after delivery [62, 111]. Compared to matched historical controls [58] who had an end-to-end repair, Sultan *et al.* [111] found that the rate of AI was reduced from 41% to 8% when the overlap technique was used for EAS repair with separate repair of the torn IAS [111] and therefore recommended the performance of a randomized controlled trial.

The first published randomised trial by Fitzpatrick *et al.* [61] reported no significant difference between end-to-end and overlap repair although there appeared to be trend towards more symptoms in the end-to-end group. However, there were methodological differences in that the torn IAS was not identified and repaired separately and they used a constipating agent for 3 days after the repair. Unfortunately, they included partial EAS tears in their randomised study. A true overlap [62, 111] is not possible if the sphincter ends are not completely divided and it would be expected that if an overlap is attempted, the residual intact sphincter muscle would have to curl up and hence there would be undue tension on the remaining torn ends of muscle that would be overlapped. This technique would therefore go against the general principles of surgery of deliberately placing tissue under avoidable tension [55, 62].

Garcia *et al.* [98] also performed a randomized trial of the two techniques and took great care to include only complete ruptures of the EAS (full thickness 3b,3c and 4th degree tears). There were 23 women in the end-to-end group and 18 in the overlap group. Unfortunately, only 15 and 11 women respectively returned for follow-up which was only at 3 months. No significant difference was found between the groups in terms of symptoms of FI or transperineal ultrasound findings. However, the authors have acknowledged that the major limitations of their study were that the randomization process was flawed and that their study was underpowered.

Williams *et al.* [117] performed a factorial randomized controlled trial (n=112) in which women were randomized into 4 groups: overlap with polyglactin (Vicryl; Ethicon, Edinburgh, UK); end-to-end repair with Vicryl; overlap repair with polydiaxanone (PDS; Ethicon, Edinburgh, UK); end-to-end repair with PDS. This trial was specifically designed to test the hypothesis regarding suture related morbidity (need for suture removal due to pain, suture migration or dyspareunia) using the two techniques. At six weeks, there were no differences in suture related morbidity. The authors claimed that there were no differences in outcome based on repair technique. Unfortunately, the majority of patients included in this trial were partial tears of the EAS (70% were 3a tears) and as mentioned above, a true overlap [62, 111] cannot be performed if the EAS is only partially torn. Furthermore, their follow up rate at 12 months was only 54%. This data therefore needs to be interpreted by caution.

Fernando *et al.* [118] performed a randomised controlled trial of end-to-end vs overlap technique. The study had adequate power (n=64) and the primary outcome was FI at one year. All repairs were performed by two trained operators and Grade 3a EAS were excluded. At 12 months (81% follow-up rate), 24% in the end-to-end and none in the overlap group reported FI (p=0.009). Faecal urgency at 12 months was reported by 32% in the end-to-end and 3.7% in the overlap group (p=0.02). There were no significant differences in dyspareunia and quality of life between the groups. At 12 months 20% reported perineal pain in the end-to-end and none in the overlap group (p=0.04). During the 12 months period 16% in end-to-end and none in the overlap group reported deterioration of defecatory symptoms (p=0.01). Further calculation revealed that four women need to be treated with the overlap technique to prevent one woman with OASIs developing FI. On the basis of this randomized trial it would appear that the overlap technique of EAS repair accompanied by separate repair of the torn internal sphincter, performed by trained clinicians is associated with a good outcome. In 2006, the Cochrane review [98] concluded that as the surgeon's experience was not addressed in two of the three randomised studies, it would be inappropriate to recommend one type of repair over the other.

Farrell *et al.* [119] performed a randomised controlled trial with a 6 month follow-up of end-to-end (n=62) vs overlap (n=63) EAS repair in primiparous women. They reported significantly higher rates of flatal but not FI in the overlap group. However, there were more 4th degree tears in the overlap group and therefore more IAS injury that could explain the increased flatal incontinence in this group [120]. At 3 year follow up there was no significant difference in AI between the groups [121]. This supports the findings of Fernando *et al.* [118, 122] who demonstrated a significantly higher risk of deterioration in AI over time in the end-to-end group and highlights the importance of longer term follow-up.

Rygh and Korner [123] performed another randomized controlled trial (n=101) with the primary outcome measure 'of at least weekly solid stool incontinence'. They concluded that the overlap technique was not superior to the end-to-end repair. However, there were more women with symptoms of AI with the end-to-end repair (34% vs 20%).

The Cochrane Review concluded, "The data available show that at one-year follow-up, immediate primary overlap repair of the external anal sphincter compared with immediate primary end-to-end repair appears to be associated with lower risks of developing faecal urgency and anal incontinence symptoms. At the end of 36 months there appears to be no difference in flatus or faecal incontinence between the two techniques. However, since this evidence is based on only two small trials, more research evidence is needed in order to confirm or refute these findings" [122]. Although there are indications from two studies [92, 121] that compared to the end-to-end technique, the overlap technique appears to be more robust over time, longer term follow up of a larger cohort is required.

More recently, 3 and 4 dimensional transperineal ultrasound techniques have been used to image the anal sphincter and 40% residual defects were identified following OASIs repair and levator avulsion in 17% [46].

4.2. Management of subsequent pregnancy after OASIs

All women who sustained OASIs should be assessed in hospital by a senior obstetrician 6 to 12 weeks after delivery. Some centres have established dedicated multidiscliplinary perineal clinics. In a survey conducted in 2010 [124], 30% of hospitals in the UK had such a dedicated clinic. It is important that a comprehensive history is taken regarding bowel, bladder and sexual function. As these symptoms are embarrassing, a structured questionnaire may be useful. A proper vaginal and rectal examination should be performed to check for complete healing, scar tenderness and sphincter tone [49, 62, 125]. Mild incontinence (faecal urgency, flatus incontinence, infrequent soiling) may be controlled with dietary advice, constipating agents (Loperamide or Codeine Phosphate), physiotherapy or biofeedback. However, women who have severe incontinence should, in addition, be offered secondary sphincter repair by a colorectal surgeon. Asymptomatic women must be advised to return if symptoms develop [62].

It is known that the risk of recurrence of anal sphincter injury in centres that practice mediolateral episiotomy is 4.4% [126, 109] to 7.1% [127 ,128]. Two large cohort studies showed the rate of recurrent OASIs to be 7.2% -10% [129] for women who had previously sustained OASIS during their first vaginal delivery, compared with a rate of 1.3% for women who did not sustain OASIS [130]

The management of a subsequent pregnancy after OASIs has been largely based on obstetrician opinion. It has been suggested that a caesarean section should be performed even after transient anal incontinence· but this has been questioned [131].

In order to counsel women with previous OASIs appropriately, Sultan *et al.* [62] find it useful to have a symptom questionnaire, anal ultrasound (**Figure 10**) and manometry results (**Figure 13**). It has been shown that clinical assessment alone has a poor sensitivity for detecting anal sphincter defects [132]. If vaginal delivery is contemplated then these tests should be performed during the current pregnancy unless performed previously and found to be normal. In a prospective study over a 5 year period, Scheer *et al.* [128] followed the protocol shown in **Figure 13** and found that when women who had no evidence of significant anal sphincter compromise based on anal endosonography and manometry were allowed a vaginal delivery (the others were offered caesarean section) there was no deterioration in symptoms, anorectal function or quality of life. Other units have also reported favourable outcomes when vaginal delivery and caesarean section were offered on selected criteria [133, 134, . 135]. Although 11% of textbooks recommend a prophylactic episiotomy [53] there is limited evidence that an elective episiotomy prevents subsequent anal sphincter disruption [90] while other studies have indicated that episiotomy may increase the prevalence of anal sphincter disruption. However, there is no study that has been done evaluating outcome in subsequent pregnancies in which the angle of episiotomy has been controlled for [136].

A RCT by Abramowitz *et al.* [137] where 222 women who had a 3rd degree tear and / or a forceps delivery in their first pregnancy with no symptoms of anal incontinence were randomised to have a vaginal birth or a planned caesarean section. The authors concluded that a caesarean section had no significant impact on anal continence 6 months after the second delivery in women with asymptomatic obstetric anal sphincter lesions diagnosed by ultrasound. However, in this study 49 of 222 women had OASIs diagnosed and repaired at the time of delivery and the rest were detected by endoanal ultrasound scan subsequently. In addition, the patients did not undergo anal manometry. In effect the RCT by Abramowitz does not fit in to the criteria recommended by the RCOG and difficult to make any recommendations.

A study of 74 women who sustained a 4th degree tear and a review of subsequent deliveries following previous OASIS by Taithongchai [138] concluded that as there are only a few units offer specialist investigations to their OASI cohort, it would be reasonable to offer caesarean section to all women who have sustained a fourth-degree tear and not base this on presence of symptoms alone. However, in centres where EAUS and AM are available, clinicians should offer these investigations for more individualized counselling. The women would need to understand the short- and long-term risks, including the recovery period of each mode of delivery, as well as the fact that a caesarean section would be a recurring indication for all subsequent pregnancies.

Women who have had a successful secondary sphincter repair for FI should be delivered by caesarean section [139]. Some women with FI may choose to complete their family prior to embarking on anal sphincter surgery. It would appear that these women could be allowed a vaginal delivery as the damage to the sphincter has already occurred and risk of further damage is minimal and probably insignificant in terms of outcome of surgery. The risk of worsening or *de novo* neuropathy has not been quantified and in practice, does not appear to be clinically significant.

5. INSTRUMENTAL VAGINAL DELIVERY

Although only 4% of women delivered by forceps sustain a 3rd/4th degree tear, up to 50% of those that do tear have an instrumental delivery [58]. Vacuum extraction is associated with fewer OASIs than forceps and this view is supported by two large, randomized studies [140, 141]. A UK study [140] where mediolateral episiotomy is practised reported severe vaginal lacerations in 17% of forceps compared to 11% of vacuum deliveries and a Canadian study [141] where midline episiotomy is practised reported OASIs in 29% of forceps compared to 12% of vacuum deliveries.

In a Cochrane review [142], forceps were less likely than the vacuum extractor to fail to achieve a vaginal birth (risk ratio 0.65, 95% confidence interval (CI) 0.45 to 0.94). However, with forceps there was a trend to more caesarean sections, and significantly more third- or fourth-degree tears (with or without episiotomy), vaginal trauma, use of general anaesthesia, and flatus incontinence or altered continence. [143]. Compared to vacuum delivery, 'occult' trauma to the anal sphincter has been identified more frequently in forceps delivery occurring in up to 80 percent of women [2, 37, 144]. A small randomized study (n=44) confirmed this by identifying occult anal sphincter defects in 79% of forceps compared to 40% of vacuum deliveries. Trauma occurs more frequently when a second instrument is used to attempt vaginal delivery [144] and therefore if no descent of the head occurs following appropriate cup selection and application technique of vacuum extraction, one should resort to a caesarean section. Metal cups appear to be more suitable for 'occipito-posterior', transverse and difficult 'occipito-anterior' position deliveries [145]. The soft cups seem to be appropriate for straight forward deliveries as they are significantly more likely to fail to achieve vaginal delivery. There was no difference between the two groups in terms of maternal injury. Farrell *et al.* [146] performed a prospective study of 690 primigravid women and found that forceps delivery was associated with a higher incidence of flatal incontinence (RR 2.6) compared to spontaneous vaginal delivery and a higher incidence of both flatal (RR 2.6) and faecal (RR 938.6) incontinence compared to caesarean delivery. Vacuum delivery did not increase the risk of flatus incontinence. MacArthur *et al.* [3] performed the largest questionnaire based multicentre study to establish the prevalence of FI at 3 months post-partum. They reported a prevalence of 9.2%, with 4.2% reporting it more often than rarely. Compared to vacuum extraction, forceps delivery was associated with almost twice the risk of developing FI. Thakar and Eason [147] performed a meta-analysis and demonstrated that one anal sphincter injury is avoided for every 18 women delivered by vacuum extraction instead of forceps. De Leeuw *et al.* [49] have shown that when a mediolateral episiotomy is performed during a forceps delivery, the risk of anal sphincter injury is reduced by almost 80%.

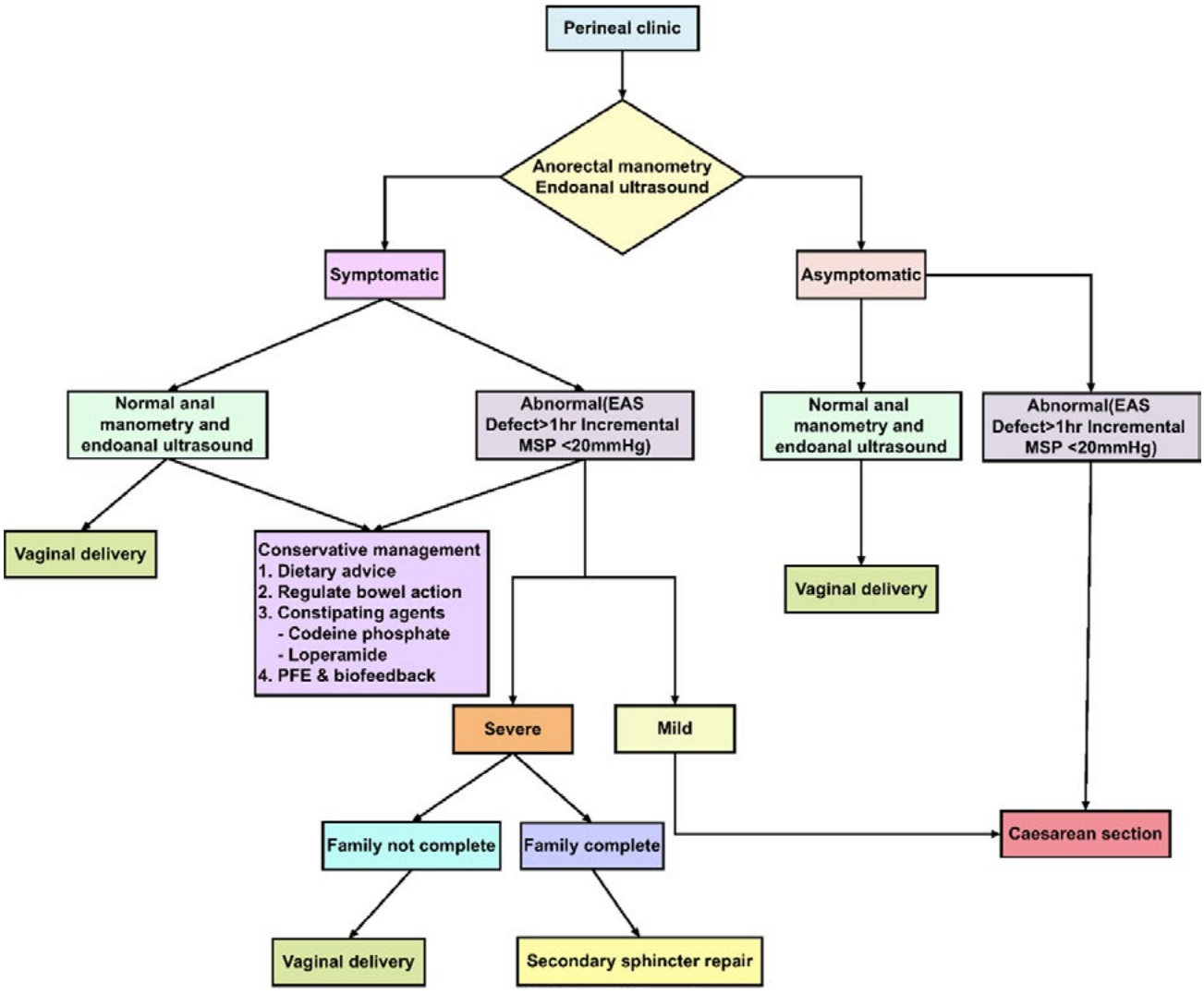

Figure 4. Flow chart demonstrating the Croydon pathway of the management of a subsequent pregnancy following OASIs (EAS = External Anal Pressure; MSP= maximum squeeze pressure)

The occipito-posterior position at delivery is a known risk factor for the development of a third degree tear and the risk of anal sphincter injury doubles with a vacuum delivery but trebles with the forceps [149]. It is strongly recommended that a liberal episiotomy should be performed in the presence of an occipito posterior position. When the baby's head is in the occipito-posterior position the diameter presenting at the outlet is larger than that of an occipito-anterior position. Therefore, it is more likely to cause a delay in progress and also more likely to result in a more extensive perineal tear particularly with an instrumental delivery.

5.1. Episiotomy

Observational data indicate that a reduction in episiotomy rate is not associated with an increase in OASIs. The Cochrane database [150] shows that restricting the use of episiotomy is associated with less posterior trauma. Although there was an increase in anterior perineal trauma it had no effect on the development of urinary incontinence. Henrikssen *et al.* [151, 152] performed an observational study in which they noted that when midwives who previously had a high episiotomy rate reduced their rate, the prevalence of OASIs also reduced. However, this beneficial effect was abolished when midwives with a low rate of episiotomy attempted to reduce it even further. Based on this evidence, it was suggested that the ideal episiotomy rate should lie between 20 to 30% and no more. Midline episiotomies are more popular in North America as it is believed that they are more comfortable, and recovery is less complicated. However, Coats *et al.* [153] performed a quasi-randomised study of 407 primiparae and found 24% of midline episiotomies extended into the anal sphincter (partial or complete tears) compared to 9% of mediolateral episiotomies. Although the perineum was significantly less bruised in the midline group and sexual intercourse commenced earlier, pain and wound breakdown was similar in both groups. Kudish *et al.* (154) performed an observational study in the USA of 46 239 singleton vertex vaginal deliveries and identified two modifiable risk factors for severe perineal trauma, namely, midline episiotomies and forceps delivery. They recommended the use of vacuum extraction and mediolateral episiotomy [154]. However, care needs to be taken to ensure that mediolateral episiotomies are performed correctly as Andrews *et al.* [155] have shown that only 22% of doctors and no midwife made the incision commencing from the posterior fourchette with a 40 to 60 degree angle from the midline. Another study demonstrated that for every six degrees away from the midline there was a 50% reduction in OASIs [156]. It has also been shown that the angle of incision when the head is crowning is underestimated such that a 60-degree angle measures 45 degrees after delivery [157].

Naidu *et al*. have shown that doctors and midwives were poor at cutting at the prompted episiotomy angle of 60° [158]. This highlights the need to develop structured training programmes to improve the visual accuracy of estimating angles or the use of fixed angle devices to help improve the ability to estimate the desired angle. There is evidence that the Episcissors 60 does cut at a 60-degree angle and its introduction in obstetric units is associated with a reduction in OASIs in nulliparous women undergoing spontaneous vaginal deliveries [136].

6. DELIVERY TECHINIQUES

Pirhonen *et al.* [159] compared the frequency of OASIs in low risk deliveries between two Scandinavian countries (26 541 vaginal deliveries) and found the risk to be 13 times higher in Sweden (Malmo) *vs* Finland (Turku). They speculated that the only explanation for this was a difference in manual support given to the baby's head during crowning and pushing the perineum under the chin. Jonsson *et al.* [160] performed a randomised trial between the Ritgen's manoeuvre and standard delivery but found no significant difference in OASIS rates. However, only 50% of the elligible women were assigned and almost 20% of the women randomized to the Ritgen's manoeuvre did not have this method of delivery. Hals *et al.* [161] provided the best available evidence, showing how an interventional programme in four Norwegian hospitals can reduce the frequency of OASIs. The programme involved a 2-3 day course at the delivery suite of each hospital that included training on delivery with perineal support and delivery of the neonate's chin. In addition, restrictive mediolateral/ lateral episiotomy was recommended. OASIs rates reduced from 4.16-5.25% before intervention to 1.73% during the last year of intervention. The following interventions with randomized controlled trials evidence regarding effectiveness demonstrated no effect on OASI: antenatal perineal massage, pelvic floor exercises in pregnancy, water births, positions during labour and birth, epidural analgesia, early vs delayed pushing with epidural and second stage pushing advice [1056]. Although one small randomized trial showed otherwise [5] other large observational studies, have shown that duration of the second stage of labour is an independent risk factor for the occurrence of OASIS [28, 31, 55, 161, 162].

6.1. Training

McLennan *et al.* [163] surveyed 1177 fourth year residents and found that the majority had received no formal training in pelvic floor anatomy, episiotomy or perineal repair and that supervision during perineal repair was limited. Stepp *et al*. found that textbooks used in American practice offered little in terms of prevention and repair of perineal trauma. [164] There is evidence from one study that perineal anatomy is poorly understood by midwives and trainee doctors, who perform the bulk of deliveries in the UK. [48] In this study, 41% of trainees and 16% of midwives incorrectly classified a partial or complete tear of the EAS as 'second degree'. Inconsistency in classification of tears would allow many injuries to pass unrecognised. In another USA study, the majority of residents demonstrated substandard skill in repairing OASIs [164]. It has been shown that hands-on workshops on perineal repair, such as that at (www.perineum.net) can change practice [165-168]. Intensive and focused training in perineal anatomy and repair should therefore become an essential module in the programme for trainees and midwives.

6.2. Inflammatory bowel disease (IBD)

The inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory diseases that commonly affect people of childbearing age [169] .The prevalence of IBD appears to be increasing worldwide, although the prevalence varies according to country and ethnicity.

A prospective study of 57 women, 17 (29.8 %) with ulcerative colitis, 23 (40.4 %) with Crohn's disease, and 17 (29.8 %) healthy controls showed that the incidence of postpartum anal incontinence is comparable across all groups; there was no statistically significant difference between the IBD and control groups. Postpartum anal incontinence was strongly correlated with the extent of perineal injury ($r = 0.80$; $p < 0.0001$). [170]

Donnelly *et al.* [171] recruited 312 primiparous women and reported that 11% of young primiparous women (n= 34 of 208) suffered from pre-existing IBS prior to their first pregnancy. Twenty four percent reported symptoms of impaired faecal con-

tinence in the puerperium but symptoms were found significantly more frequently in those with IBS compared to those with normal bowel habit (71% vs 18%). Women suffering from IBS were no more likely to incur mechanical or neurological injury to the anal sphincter. Women with IBS delivered by caesarean section did not have altered continence postpartum. However, 6 months postpartum there were no symptomatic differences between those with IBS and those without but only 90 of the 107 women who had either impaired faecal continence or abnormal anal manometry were studied. Treatment is directed towards the predominant symptom and although antispasmodics such as hyoscine, mebeverine and dicyclomine are used widely to relax intestinal smooth muscle, they should be avoided during pregnancy. Robinson *et al.* used validated questionnaires and bowel symptom diaries and found that the symptoms of urgency and diarrhoea in women with irritable bowel syndrome amplify the risk of anal FI in women who have sustained OASIs [172].

6.3. Evidence synthesis

a) Compared to forceps, the vacuum extractor is associated with less perineal and anal sphincter trauma. (LoE 1)

b) Compared to midline episiotomy, mediolateral episiotomy is associated with a significantly lower risk of 3rd/4th degree tears (LoE 1)

c) Liberal use of episiotomy is not beneficial (Level 1) and restricting the rate of episiotomy to about 30% may reduce the risk of trauma to the anal sphincter (LoE 4)

d) A prolonged active second stage of labour is associated with denervation of the pelvic floor and one study has suggested that this also occurs with a prolonged passive second stage of labour with epidural analgesia. In these circumstances, early use of oxytocics in the second stage of labour may be useful. (LoE 4)

e) Selective use of caesarean section may be beneficial, particularly in those who have evidence of compromised anal sphincter function and those who have had previous successful continence or prolapse surgery. (LoE4)

f) Modification in techniques of delivery of the baby, particularly appropriate perineal support ,may reduce anal sphincter injury ompared to midline episiotomy. (LoE 3)

g) A more focused training programme for doctors and midwives needs to implemented. There is a poor understanding of perineal and anal sphincter anatomy and hence identification of anal sphincter trauma, incorrect classification and poor outcome of repair (LoE4)

h) There is increasing evidence supporting the identification and repair of the internal anal sphincter. Outcomes of epair techniques of the external sphincter (overlap versus the end-to-end) for full thickness tears are inconclusive and more long term research is needed (LoE1)

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VIII. PATHOPHYSIOLOGY OF FAECAL INCONTINENCE

1. INTRODUCTION

Faecal continence is maintained by a complex, incompletely understood process involving the structural and functional integrity of the anorectal unit, the central and peripheral nervous system and pelvic structures. Continence requires a closed anal canal at rest, sensory function to detect the presence of flatus or stool in the rectum, intact reflex response of the appropriate muscles, cognitive recognition of the sensory signal, adequate storage capacity in the rectum and adequate function of the puborectalis and sphincter muscles. In addition, other factors such as stool consistency and physical mobility play a role. Disruption in the normal anatomy or physiology in any of these areas may lead to incontinence. Most often multiple factors are contributing in patients with significant faecal incontinence.[1-6]

2. STRUCTURE AND FUNCTION OF THE ANORECTUM

The anus is a muscular tube 2 cm to 4 cm long consisting of the internal anal sphincter, conjoined longitudinal muscle, external anal sphincter and puborectalis muscle. [7]

2.1. Muscles

2.1.1. Internal anal sphincter (IAS)

The internal anal sphincter (IAS), an involuntary smooth muscle, is a 0.3 cm to 0.5 cm thick expansion of the circular smooth muscle layer of the rectum. The IAS ends about 10 mm proximal

to the distal end of the external sphincter. It is primarily responsible for closure of the anal canal at rest through both myogenic and sympathetic excitatory activity. Studies disagree about the relative contribution of myogenic and nerve induced activity to the resting tone. [8, 9] The IAS generates slow pressure waves occurring 6-20 times per minute; about 10 % of asymptomatic people also have ultra-slow waves with pressures fluctuating between 20 mmHg and 50 mmHg. [10-12]. The internal anal sphincter contains non-adrenergic, non-cholinergic (NANC) fibres which contribute to contraction of the muscle mediated by nitric oxide. [13-15] Recent research focuses on the role the interstitial cells of Cajal as the generators of the slow waves which result in phasic contraction.[16-23] Other animal studies have focused on the cellular regulation of basal tone in the IAS. Up regulation of RhoA/Rho kinase in the smooth muscle cells of the IAS plays a significant role in the maintenance of the basal tone.[24] The RhoA/Rho kinase components are responsible for the inhibition of myosin light-chain phosphatase of resulting in a high level of myosin regulatory light chain. [25] At present the relative role of pure tonic contraction versus phasic contraction in inducing tone in the IAS is uncertain.

2.1.2. External anal sphincter (EAS)

The external anal sphincter, a 0.6 cm to 1.0 cm thick cylinder of striated muscle, covers the whole length of the internal sphincter and extends more distally into the subcutaneous tissue. The external sphincter contributes to the resting tone. Its primary function, however, is to contract to preserve continence when stool or flatus is present in the rectum or intra-abdominal pressure increases. The contraction may be voluntary or reflexive with increased abdominal pressure from coughing or distension.[26] The muscle also relaxes to facilitate evacuation. The separation of the external sphincter into sections is controversial. [27] Many authors describe three sections termed superficial, subcutaneous and deep but they have also been described as subcutaneous, main body and deep winged portion based upon MRI imaging.[28, 29] On MRI images, the subcutaneous portion is visibly distinct from the other portions with less clear separation between the middle and deeper portions.[28] Others argue the EAS functions as a single muscle unit. [30, 31] The EAS is a predominantly slow-twitch, fatigue resistant muscle with a majority of Type I fibres although there are also Type II rapidly contracting fibres as well. [32, 33] .

2.1.3. Conjoined longitudinal muscle

The outer longitudinal muscle layer of the rectal wall joins with fibres of the levator ani muscle to become the conjoined longitudinal muscle; it is primarily striated muscle with a few fibres of smooth muscle. [34] The muscle extends distally between the internal and external anal sphincter and then splits into extensions that traverse the superficial portion of the external sphincter to attach to the perianal skin and medially through the internal anal sphincter to join the submucosa smooth muscle.[35] Proposed roles for this muscle include provision of supporting meshwork for the anal sphincters and assistance in maintaining anal closure. The functional role is suggested by the differential response of the longitudinal muscle to neurotransmitters when compared to the internal anal sphincter. [15] Another possible role is that contraction of the muscle flattens the anal cushions and shortens the anal canal. [36]

2.1.4. Puborectalis muscle (PR)

The puborectalis muscle, the most medial portion of the levator ani muscle, is a U-shaped loop of striated muscle that encircles the anorectal junction and attaches to the posterior aspect of the pubis. The puborectalis muscle is a mixture of Type I and Type II fibres but has fewer Type II fibres than the EAS. [37] It functions to close the upper anal canal.[38, 39] It is situated immediately cephalad to the external sphincter. The configuration of the puborectalis muscle results in the anorectal angle between the distal rectum and anal canal. At rest, the anal canal forms an angle with the axis of the rectum of approximately 90°; during voluntary squeeze the angle becomes more acute, approximately 70°; during defecation, the angle becomes more obtuse, about 110° to 130°. Some data support the concept that the PR is part of the levator ani muscle (embryology, in vitro stimulation studies, innervation)[40-46] while other information suggests that it is part of the external anal sphincter (anatomic dissection, function during cough and straining [31, 47, 48] The puborectalis muscle responds increased abdominal pressure (coughing or straining) and rectal distension by contraction.

2.1.5. Levator ani

The levator ani muscles are a pair of broad sheets of striated muscle lying below the pelvic organs. There are three major components with different attachments. The iliococcygeus muscle arises from the ischial spine and attaches to the lateral aspect of the lower sacrum and coccyx. The pubococcygeus muscle runs from the posterior aspect of the pubis, mixes with fibres from the contralateral muscle at the anococcygeal raphe and inserts at the distal sacrum and coccyx. The third component is the puborectalis muscle which is described above. The urethra, vagina and rectum pass through an opening between the levator ani muscles called the levator hiatus.

2.2. Nerve structure and sensation

The somatic nerve supply arises from the second, third and fourth sacral spinal segments. The lower motor neuronal cell bodies for those nerves are located in Onuf's nucleus of those sacral spinal segments. The primary nerve is the pudendal nerve which has both motor and sensory functions.[49]. The pudendal nerve divides into three main branches. One branch, the inferior rectal nerve, supplies the external sphincter. The levator muscles including the puborectalis receive innervation directly from those spinal segments.[43, 44, 46, 50] However, ,the puborectalis muscle frequently receives an auxiliary supply from the inferior rectal and perineal branches of the pudendal nerve on its inferior aspect.[51] Both the EAS and levator ani muscles may be controlled voluntarily through corticospinal descending motor pathways.[37] They are also under reflex control through sacral reflex pathways. Pudendal nerve block creates a loss of sensation in the perianal and genital skin and weakness of the anal sphincter muscle, but it does not affect rectal sensation [52] It also abolishes the rectoanal contractile reflexes, suggesting that pudendal neuropathy may affect the rectoanal contractile reflex response.

The anorectum also has a rich nervous supply through enteric, sympathetic, parasympathetic and extrinsic spinal sensory neurons. Enteric motor neurons control most aspects of rectal motility; parasympathetic and sympathetic influence is mediated largely through modulation of the enteric neuronal circuits. [53] Within the myenteric plexuses there are motor, sensory and interneurons. The sympathetic supply of the rectum arises from the first three lumbar spinal segments. The innervation is carried through the preaortic plexus to the upper rectum and through the presacral nerves to the hypogastric plexus and then through the hypogastric nerves to the pelvic plexus. The parasympathetic fibres originate in the sacral parasympathetic nucleus in the sacral spinal cord and emerge through the sacral

foramen as the nervi erigentes. They join the sympathetic fibres at the pelvic plexus and pass-through rectal nerves to the rectal wall. The parasympathetic pathways have a role in propulsive activity of the colon and defaecation.

Extrinsic sensory innervation of the rectum seems to be responsible for sensory perception of rectal distension. Sacral afferents have cell bodies in the dorsal root ganglia of the sacral segments. Specialized sacral afferents have mechano-sensitive transduction sites within the myenteric ganglia of the rectum.[54, 55] These intraganglionic laminar endings are sensitive to distension and contraction of surrounding muscle layers. [56] Both thinly myelinated A fibres and unmyelinated C fibres are present in the rectal mucosa, and the myenteric plexus [57-60] The C fibres are mostly present in the wall of the rectum while the A fibres predominate in the rectal mucosa.[60] These nerves most likely mediate the distension or stretch-induced sensory responses as well as the viscero-visceral, [61] the recto-anal inhibitory, and the recto-anal contractile reflexes [59]. The sensation of rectal distension is most likely transmitted along the S2, S3, and S4 parasympathetic nerves [59] Clinical studies confirm that balloon distension is perceived in the rectum and that such perception plays a role in maintaining continence. [62, 63] Furthermore, sensory conditioning can improve hyposensitivity [64, 65] of the rectum.

Distal rectal and upper anal canal sensation is carried in the inferior rectal branch of the pudendal nerve. The upper anal canal particularly has a rich mixture of free and organized nerve endings such as the Krause end-bulbs,(cold) Goigi-Mazzoni bodies (pressure), genital corpuscles (friction), and the sparse Meissner's corpuscles (touch) [59, 66, 67] Specialized afferent nerves may exist that transmit the sensations of touch, temperature, tension, and friction, but are incompletely understood. [59] The role of anorectal temperature sensation is subject to debate. [68-72] The likely role of anal sensation is to facilitate discrimination between flatus and faeces and reflex maintenance of continence.

All of the sensory nerves reach the spinal cord through the mesorectum and then the brain to achieve perception. [73]The pudendal nerves run below the pelvic floor muscles and the remaining nerves above. The nerves are vulnerable to compression and stretching of the pelvic floor at that location.

2.3. Cerebral cortex

Rectal distension produces activation bilaterally in the secondary somatosensory cortex, sensory association cortex, the anterior cingulate cortex and insular cortex, as well as bilateral activation in the prefrontal cortex and extending from the peri-orbital cortex to the anterior temporal lobe. [74-78] Studies have identified activation in multiple areas of the cortex including those involved in spatial discrimination (secondary somatosensory cortex, sensory association cortex) and those that process affective and cognitive aspects of sensation (the anterior cingulate cortex, insula and prefrontal cortex.). While rectal and anorectal stimulation activated similar regions of the brain the locations within the regions varied. [79] Anal musculature is represented bilaterally on the superior motor cortex (Brodmann area 4); the degree of symmetry varies.[80]

2.4. Reflexes

Distension of the rectum results in contraction of the rectum, relaxation of the internal anal sphincter and contraction of the external anal sphincter.

2.4.1. Rectoanal inhibitory reflex (RAIR)

Rectal distension is associated with a fall in anal resting pressure known as the rectoanal inhibitory reflex. The amplitude and duration of this relaxation increases with the volume of rectal distension. [81] It has been suggested that bowel contents are periodically sensed by anorectal "sampling," [82-84] the process by which transient relaxation of the IAS allows the rectal contents from the rectum to come into contact with specialized sensory organs. This process allows discrimination between flatus and stool.

2.4.2. Cough reflex

Abrupt increases in intra-abdominal pressure, such as those caused by coughing or laughing, are associated with increases in anal sphincter pressure. [26, 85-88] The increased pressure may be achieved through multiple mechanisms, including reflex contraction of the puborectalis. [89] The response is relative to the intensity of the cough.[85]. It is unclear whether the response is a polysynaptic spinal reflex [26, 86] since it is preserved after spinal cord transection [90] or also requires central integrative centres. [87]

2.4.3. Rectoanal contractile reflex (sensori-motor response)

The rectoanal contractile reflex (or rectal anal excitatory reflex or inflation reflex) is the contraction of the EAS in response to rectal distension.[91-93] The amplitude and duration of the rectoanal contractile reflex increases with rectal distension up to a maximum volume of 30 ml [81]. This reflex persists despite damage to the pudendal nerve and does not change with age. [94]

2.4.4. Puborectal continence reflex

A reflex similar to the rectoanal reflex occurs with the puborectalis muscle. [95] While voluntary contractions of the muscle diminish with pudendal nerve damage, the involuntary contraction reflex does not. [96] Recent evidence suggests that the rectoanal reflex assists in control of both solid and liquid stool but the puborectal reflex contributes to continence of solid stool only. [97]

2.5. Rectum

The rectum is a hollow muscular tube, 12 cm to 15 cm long, composed of a continuous layer of longitudinal muscle that interlaces with the underlying circular muscle. These muscles are a mixture of smooth muscle cells and several types of interstitial cell of Cajal.[53] A network of interstitial cells of Cajal joined by gap junction connections coupled to smooth muscle cells trigger mechanisms that give rise to large, slow repetitive depolarization of the smooth muscle, the slow waves.[98] The proximal end is defined either as the sacral promontory, the third sacral vertebrae or the area where the colonic taenie splay out and end. The distal end is the dentate line or anorectal ring. The rectum serves as a reservoir for storage and a "pump" for evacuation of stool facilitated by several characteristics. The rectal walls are compliant maintaining a relatively low pressure with increasing volumes. Its innervation allows the sensation of increasing volume.[1, 53]

2.6. Rectosigmoid junction

Currently there is no standardized definition of the rectosigmoid junction. The possibility of a functional sphincter at the rectosigmoid junction has been debated for years. [99, 100] Recent manometry studies of healthy volunteers identified an intermittent high-pressure band at the rectosigmoid junction that relaxes or contracts in response to a high-pressure propagating wave

in concert with relaxation or contraction of the anal sphincter. [101] Lin and colleagues reviewed the existing evidence of a "rectosigmoid brake" in 2017.[102]

2.7. Anal endovascular cushions

The submucosa of the anal lining contains blood vessels, connective tissue, smooth muscle and elastic tissue. They typically form three separate complexes of smooth muscle fibres and vascular channels called the anal cushions.[103, 104] A study of women demonstrated the normal variation in size; the size did vary with posture and parity but not age, history of obstetrical trauma or mild haemorrhoid symptoms. [105] Differences between asymptomatic women and incontinent women were identified. Their contribution to continence is poorly studied and controversial.

2.8. Stool consistency

Considerable evidence exists that evacuation of formed stool is more easily deferred than loose stool (discussed in detail under diarrhoea). While theories exist about the reason, physiological proof is not available.

2.9. Physical mobility

The ability to defer evacuation until a socially acceptable time and place requires the physical mobility to reach a bathroom in the required time frame. The contribution of physical mobility to continence is largely inferred from studies identifying lack of physical mobility as a risk factor for incontinence.[106-108] There is limited information about the relative role for mobility in continent patients.

3. CONTINENCE MECHANISM

Complete continence depends upon normal transit of formed stool, anal closure at rest, sufficient reservoir capacity and sensation in the rectum, functional reflexes for sampling and sphincter contraction, adequate cognitive function to recognize the urge to defaecate and physical mobility to reach the bathroom in time.

The anus is normally closed by the tonic activity of the IAS with contribution from the EAS and PR at different levels of the anal canal. [39, 109]. Studies of the relative contribution of the IAS to the resting tone yield results varying from 55-85 % [9, 52] Some of that variation is likely related to the measurement technique utilized but it has also been found that resting pressure varies during the day [110] and with posture, increasing with the upright position. [111] The IAS contribution is also influenced by rectal distension. [52, 112] Some postulate that the anal cushions provide a tight seal based upon studies showing that the sphincter muscles in their circular configuration cannot contract sufficiently to provide complete closure. [113, 114]. An in vitro study showed that even during maximal involuntary contraction, the internal sphincter ring was unable to close the anal orifice completely and a gap of approximately 7 mm was left open. This gap was filled by the anal cushions.[115] Anal cushions may exert pressures of up to 9 mmHg and thereby may contribute 10% to 20% of resting anal pressure. [116] These barriers are further augmented by the puborectalis muscle, which pulls the anal canal forward forming the anorectal angle. The extent to which the anorectal angle contributes to continence is controversial.[109, 117-121] One study suggests that it is important to the control of semi-solid material more than the control of liquid.[122]

With rectal distension or increased intra-abdominal pressure, this barrier is reinforced by reflex or voluntary contraction of the EAS and PR. The contraction requires functional peripheral, spinal and cerebral function to sense and recognize the distension, as well as activate the reflex and voluntary responses. In addition, adequate muscular contraction to increase the anal pressure is required. The rectal wall must distend to allow accommodation to the increased pressure. Finally, the mobility to reach an appropriate setting before the muscle fatigues is required.

4. DEVELOPMENT OF INCONTINENCE

Faecal incontinence occurs when one or more mechanisms that maintain continence is disrupted to an extent that other mechanisms are unable to compensate. Hence, faecal incontinence is often multi-factorial.[1-5] In a prospective study, 80% of patients with faecal incontinence had more than one pathogenic abnormality. [2] The interaction of those factors and timing of the development of clinical incontinence is poorly understood.

Clinically, patients may have urgency, passive or mixed incontinence. A recent systematic review found that urgency incontinence was more frequent than passive.[123] However, the authors noted a lack of homogeneity in the definition of each type and lack of availability of validated instruments for research and limited studies of the mixed group. In most studies, the squeeze pressures were higher in the passive incontinence group but other testing results were discordant or the same. A retrospective study published since that review reported on the finding of dynamic ultrasounds in 145 patients with either urgency, mixed or passive faecal incontinence.[124] Sphincter defects were equally present in all groups. The urgency dominant group had a higher rate of loss of rectal support on Valsalva as measured by the dynamic ultrasound. Other investigators studied the role of postprandial and fasting retrograde colonic activity and found differences in patients with urgency incontinence compared to normal controls.[125, 126]

4.1. Passive incontinence

Compromise of anal closure and loss of sensation may result in soiling or incontinence without awareness. Prolapsing tissue (either mucosal or full thickness rectal prolapse, rectal lesions) prevents closure of the anus. Some believe that resection of the anal cushions may result in passive incontinence. [114] Injury secondary to trauma, surgery or childbirth and weakness of the IAS are other causes. IAS atrophy occurs in systemic sclerosis and likely contributes to faecal incontinence [127, 128] although neuropathy also appears to be a contributing factor. [129]. Loss of sensation occurs from peripheral neuropathy, spinal cord and cerebral cortex events or after transection of the nerve supply by surgical or other trauma. Increasing evidence suggests that rectal hyposensitivity significantly contributes to passive incontinence.[130-134] Interestingly faecal seepage in men occurs despite normal anorectal physiology testing. [130, 135, 136]

4.2. Urgency incontinence

Incontinence occurs when the ability to hold stool or flatus is overwhelmed. If the rectum cannot distend to hold stool or the muscles do not contract adequately incontinence results. Changes in the reservoir function of the rectum from disease processes, radiation therapy or surgical resection limit the abil-

ity of the rectum to distend to hold stool. Pelvic floor muscle dysfunction may result from direct injury causing a defect or weakness. Obstetric trauma is the most common cause of injury to internal and external sphincter muscles. The puborectalis and levator ani muscles may also be injured and the presence of defects appears to correlate with poor contractility and symptoms in several studies. [137-141] Major levator ani muscle injuries are more frequent in women with EAS obstetric injuries and those with combined injures are more likely to be symptomatic.[139] However, other investigators found no relationship between the presence of levator ani injuries and faecal incontinence. [142, 143]. Weakness of intact sphincter muscles may develop secondary to aging or neurological dysfunction.

Rectal hypersensitivity, a lower threshold for the urge to defecate, also contributes to urgency incontinence. [3, 4, 125, 144-147] Complex, poorly understood mechanisms mediate rectal hypersensitivity. Variables include decreased compliance, increased sensitivity of extrinsic peripheral pathways or central afferent mechanisms.[145]

5. RISK FACTORS FOR FAECAL INCONTINENCE

Many events and conditions impact the mechanisms of continence often in multiple ways. The next section covers the conditions that most frequently contribute to incontinence.

5.1. Aging

Multiple studies document the increasing incidence of faecal incontinence in association with with age in both men and women. [5, 148-154] One study of community dwelling women found that 70% of incontinence developed after the age of 40. [155] Another study of women in the United States documented an initial 15% prevalence of incontinence in women over 50 years old and onset rate of 7% over the next 10 years. [156]

While the rising incidence is well documented, understanding of the physiological impact of aging is less clear. Conflicting evidence exists about the effect of aging on anal resting pressure. While a number of studies report decreased anal resting pressures in older continent and incontinent adults [146, 157-160], some found lower pressures in patients with incontinence but not asymptomatic older adults.[161, 162] Increased thickness of the internal anal sphincter is associated with aging [146, 163-166]; the finding is thought to represent increased fibrosis although that hypothesis is not proven. Animal studies of smooth muscle contraction demonstrate decreased contractility with aging. [167] Studies of the internal sphincters of aging animals found changes in translocation of signaling molecules as well association and phosphorylation of contractile proteins. [167] Other investigators focus on the role of aging related oxidative stress through the RhoA/Rock pathway as a cause of decreased tone. [168]

Most studies of the effect of aging on anal squeeze pressures found decreasing pressures with advanced age [158-162, 169, 170] but not all. [146, 171-173] One report found decreasing anal squeeze pressures with age in women but not men.[170] The decrease in anal squeeze pressures does not correlate with easier fatigability of the external sphincter. Indeed, studies show no change with age [174] or that the external sphincter becomes more resistant to fatigue with age. [175] These findings are consistent with studies of skeletal muscle in general which show that reduction of muscle fibres with increasing age with a greater loss of Type II fibres which are less fatigue resistant. [176] The result is a weaker but more fatigue resistant muscle. One explanation of the change in the sphincter muscle is change in the neuronal control. A recent study compared motor unit action potential amplitude and firing rates in young and older women.[177] The investigators found a linear increase in amplitude and decrease in firing rates with age. One interpretation is that external sphincter weakness results from denervation of motor units and decreased upper neuron drive.

The decreased anal squeeze pressures might also be related to external sphincter atrophy. Thinning, presumed to be secondary to atrophy, of the external sphincter has been documented in both endoanal ultrasound and MRI studies. [163-165, 178-180] One study found excellent correlation of atrophy on imaging with the pathologic changes of atrophy.[181] Some studies found that atrophy is related to aging [165, 179] but not all. [146] Faecal incontinence did correlate with external sphincter atrophy. [146] Data from studies of nerve injury in animals reveals that sphincter atrophy and decreased function develops after nerve injury.[182-184] Muscle atrophy secondary to age related loss of anterior horn cell occurs.[185] Human studies demonstrate increased muscle fibre density suggesting reinnervation in the external sphincter with age.[162, 186]

Finally several studies found a decrease in rectal sensitivity with increasing age.[157, 169] One study found that decrease only in women.[160] The relationship of this finding to faecal incontinence is not clear.

5.2. Sex

Prevalence studies suggest that faecal incontinence occurs more frequently in young women but as people age, many studies report essentially equal incidence in men and women. [150, 152-154, 170, 187, 188] The mechanisms of faecal incontinence in men appear to differ from women. [5, 130, 135, 136, 189, 190]

Oestrogen and progesterone receptors are found in the IAS and EAS. Because of this finding, some proposed that menopause is a factor for incontinence in women. However, since aging and menopause are closely related, an independent relationship is difficult to prove. Symptomatic improvement from oral oestrogen replacement supports the proposed relationship; however a randomized trial comparing topical oestrogen to placebo showed no difference.[191] In addition one study found a 30% increased risk of incontinence in patients currently taking oral oestrogens.[192] At the present, the role of the hormone receptors and relationship of menopause to the onset of incontinence is uncertain. [193]

5.3. Diabetes

Diabetes is reported as a risk factor for faecal incontinence in several studies. [153, 154, 192, 194, 195] One study reported a 40% increase in the risk of faecal incontinence.[192] Another population based study found that both occasional and frequent episodes of incontinence were more common inpatients wiht diabetes (OR 2.7) [196] In a study of older Korean patients, diabetes was associated with faecal incontinence in women but not men. [197] A review of incontinence in community dwelling men did identify diabetes as a risk factor, however. [190] A case control investigation found that patients with diabetes had more frequent and severe episodes of faecal incontinence. [198]

Several reports found that incontinence was more frequent in patients with diabetic complications particularly neuropathy and retinopathy[198-200] It is uncertain whether longer duration of disease increases the likelihood of incontinence as one study found an association [199] but two did not.[198, 200] Faecal incontinence was associated with poor glycaemic control in one report, [198] but not another.[200]

The underlying mechanism (s) for faecal incontinence in diabetesis not clear. One likely contributor is oral medication taken for diabetic control. Metformin has been found to be independently related to faecal incontinence .[201] In addition, withdrawal of metformin was reported to eliminate the incontinence.[202] One confounding factor is that diarrhoea, a known risk factor for faecal incontinence, occurs in 5-35% of patients with diabetes. [196, 199, 203, 204]

Diabetes affects gastrointestinal functioning including functional and structural changes in the intestinal wall and central, sympathetic and parasympathetic nervous systems. [205] One hypothesis regarding the mechanism is that microvascular changes associated with diabetes result in damage to pelvic floor innervations and muscles.[206] . Another hypothesis is that poorly controlled hyperglycaemia results in formation of advanced glycation end products which can damage the structure of nerve cells. [205] A comparative study of anorectal physiology of controls, incontinent patients with diabetes and continent and incontinent patients with multiple sclerosis found that the incontinent, diabetic patients had higher sensory thresholds and lower resting and squeeze pressures. [207] An anal physiology study compared findings of patients with the diagnosis of diabetes for less than 10 years to those with the diagnosis for longer than 10 years. [208] Both groups of patients had lower resting and squeeze anal pressures ($P < 0.01$), impaired rectoanal inhibitory and anocutaneous reflexes, and reduced sensitivity in rectal distention. Although both groups had statistically significant differences from the control group, the patients with the longer duration of disease had lower sphincter pressures and more blunted sensation in addition to more frequent episodes of incontinence. The latter group also had more evidence of microvascular disease and neuropathy. Blunted rectal sensation and internal sphincter dysfunction were identified in patients with diabetes in two separate studies.[65, 209] These findings would be consistent with underlying neurological and/or microvascular changes as the underlying aetiology. It is unclear how to reconcile that hypothesis, however, with the lack of association of incontinence with neuropathy in some epidemiology studies. [203, 210]

5.4. Gastrointestinal disorders

5.4.1. Diarrhoea

Diarrhoea is consistently reported as a risk factor for faecal incontinence. For many patients, symptoms of diarrhoea include loose consistency of the stool and rectal urgency. Loose stool is an independent risk factor for incontinence and is additive to other risk factors such as obstetric sphincter injury.[5, 148, 150, 151, 156, 187, 190, 192, 211, 212] Diarrhoea has a significant impact on the development of incontinence with OR 53 in one study.[148] Loose stool is also reported to result in incontinence after pelvic irradiation. [213]

5.4.2. Rectal urgency

Rectal urgency is reported as an independent risk factor for faecal incontinence [150, 214] as well as a factor in worsening symptoms in patients with incontinence.[145] It is unclear whether the aetiology is rapid transit into the rectum overwhelming the reservoir function or hypersensitivity or some combination of factors.[150, 187] Several investigators found that rectal hypersensitivity to be a common finding but incontinence developed only in patients with associated sphincter weakness. [3, 145] Rectal urgency is often associated with diarrhoea but can occur in patients without diarrhoea. A recent study of patients who underwent anorectal physiology testing found that patients with diarrhoea and urgency demonstrated rectal hypersensitivity on testing but the patients with urgency without diarrhoea did not.[215] Urgency in patients without diarrhoea was significantly associated with urinary urgency incontinence. Rectal hypersensitivity has also been found to be associated with an abnormal colonic motility pattern in the sigmoid colon in incontinent patients.[126] The relationship of this finding to irritable bowel syndrome remains to be clarified.

5.4.3. Constipation/impaction

Constipation and incomplete evacuation of the rectum are associated with faecal incontinence in several studies.[149, 156] The combination of symptoms is often unrecognized; in one study 46.7% of patients referred for only faecal incontinence were found to have clinically significant constipation. [216] In a study of chronic constipation patients with and without faecal incontinence, the incontinent patients had a higher mean BMI and lower anal pressures and were less likely to have dyssynergia and rectocele. [217] In another comparison study, patients with isolated faecal incontinence to patients with both faecal incontinence and constipation, several significant differences were identified. [218]Patients with both symptoms had higher resting and squeeze pressures, were more likely to exhibit abnormal balloon expulsion tests and paradoxical EMG as well as higher rates of intra-anal intussusception.

A study of hospitalized older patients found that faecal impaction and diarrhoea were strongly associated with faecal incontinence. [219] Uncertainty exists regarding whether these two factors result in incontinence in patients with otherwise normal anorectal function. Overflow incontinence occurs in some patients with faecal impaction. The use of laxatives may exacerbate the problem. [220] One study of older patients with impaction compared to controls found that they had blunted rectal sensation and less frequent external sphincter contractions in response to rectal distension [221] In addition, the internal sphincter relaxed at lower levels of rectal distension. Studies of impacted patients without incontinence have not been reported.

5.4.4. Inflammatory bowel disease

A systematic review from 2018 identified studies of faecal incontinence in patients with inflammatory bowel disease without a history of ileoanal anastomosis. [222]There was a consistent prevalence of 24%; faecal incontinence was more common in inflammatory bowel disease patients than controls. In evaluation of pathophysiology, there were conflicting results about rectal compliance, anorectal sensitivity and sphincter function. Analysis of the National Health and Nutrition Examination Survey (N=5593) found an association of zinc intake with gas and liquid leakage. [223] A recent study of 500 patients found an equal incidence in ulcerative colitis and Crohn's patients.[224] Faecal incontinence was more likely in older patients and those with active disease. The rate did not differ by sex, location of disease or presence of perianal disease. In contrast, faecal incontinence was more common in patients with Crohn's disease than with ulcerative colitis in another study; active disease and

age remained risk factors. [225] With improvement in medical management of inflammatory bowel disease, more attention to associated functional disorders is necessary.

5.4.5. Irritable bowel syndrome

A number of studies found irritable bowel syndrome to be a risk factor for faecal incontinence. [148-150, 192, 226-228] Proposed mechanisms include age, loose stool consistency, rapid colonic motility and rectal hypersensitivity. [126, 229, 230]

5.5. Neurologic/psychiatric conditions

A recent review summarized the gastrointestinal neuromuscular and extrinsic and intrinsic nervous systems. [231] The author reviews specific altered mechanisms in a range of neurologic diseases associated with faecal incontinence and other gastrointestinal motility disorders.

5.5.1. Dementia

The prevalence of faecal incontinence is higher in patients with dementia compared to others of similar age. One study reported a prevalence of 32% in older patients with dementia.[232] Another study reported a rate of 34% in patients with dementia compared to 6.7% in those without dementia.[233] Although diarrhoea was the greatest risk factor for incontinence in a study of nursing home residents, dementia also contributed to the development of incontinence. [234] In the study of community-living older adults in the United States, the prevalence odds ratio of faecal incontinence decreased by 51% with each unit improvement in cognitive score.[235] Similarly, a higher Cognitive Dementia Rating score was predictive of incontinence in a study of East Asian long term care residents.[236] A Japanese study of community dwelling older adults found dementia to be a risk factor for double (dual) incontinence.[237] There is limited information available about the relationship of intellectual disability and faecal incontinence. [238] Proposed mechanisms for the specific contribution of dementia include lack of recognition or understanding of the urge to defaecate and lack of ability to articulate the need for the bathroom.

5.5.2. Depression

Several studies identified depression as a risk factor for faecal incontinence.[151, 153, 187, 190, 239] Many assume that the association occurs because of the psychological burden of the symptoms while it is also possible that side effects of anti-depressant medication contribute to the symptoms. Recently, however, an editorial challenged investigators to “clarify the link between the cerebral impact of neurotransmitters and anorectal physiology” given the role of serotonin in depression and gastrointestinal function.[240] Depression and faecal incontinence are both associated with poor nutritional status in older adults [241]; that association confounds understanding of any true causal relationship between any two of the conditions.

5.5.3. Spinal cord injury

Patients with SCI frequently report difficulty with both constipation and incontinence [242, 243]. The level of the injury determines the effect on continence. Supraconal lesions lead to delayed colonic transit and exaggerated rectal contractions and anal relaxation in response to rectal distension. Cauda equina lesions interrupt the efferent limb of the reflex arc which results in loss of rectal sensation and tone as well as impaired sphincter function [244] Paraplegics or persons with sacral neuronal lesions may retain some degree of sensory function, but virtually no sensation is felt if lesions reach the higher spine [63, 90]. Recent data suggests that spinal cord perfusion pressure in the immediate post-injury phase may influence the degree of impairment of anorectal function as measured by manometry, cough reflex and recto-anal inhibitory reflex.[245]

5.5.4. Stroke

In several large surveys, stroke is identified as a risk factor for incontinence.[153, 187, 190, 237] Studies of stroke patients demonstrate fairly consistent rates of faecal incontinence from 30-40% on admission.[232, 246-249] The rates decreased to 20% by the time of discharge [246, 248] and 7-11% at 6-12 months. [232, 247, 249]. The Copenhagen Stroke Study found that strokes in patients with incontinence were more likely to be haemorrhagic, larger in size and involve the cerebral cortex than in stroke patients without incontinence.[249] A population based study of over 32,000 people found the risk for incontinence is increased in both men and women up to 10 years after a stroke.[250]

5.5.5. Neurodegenerative disorders

Faecal incontinence is more common in several neurodegenerative disorders. Examples are multiple sclerosis[251, 252] and Huntington disease. [253] A study of multiple sclerosis patients found patient with incontinence had lesions in left supramarginal gyrus and the right parahippocampal gyrus and the amygdala. [254]

5.6. Nutrition

5.6.1. Obesity

Population based studies of faecal incontinence identify obesity as a significant risk factor. [148, 149, 192] In addition, studies of pelvic floor symptoms in obese patients find a higher incidence of faecal incontinence than generally found in the non-obese population with rates ranging from 16-68%. [255-262] A non-significant trend towards worsening incontinence was found in another study.[263] Four studies investigated the relationship between the rate of incontinence to the BMI; two found increasing rates of incontinence with increasing BMI. [192, 260, 264] Two did not. [262, 265] The relationship is further supported by data that weight loss after bariatric surgery decreases the incidence of faecal incontinence. [256, 260, 266, 267] While the findings of these studies are quite consistent a recent systemic review of obesity and pelvic floor disorders found the number of studies to be limited, primarily focused upon women, and usually lacking control groups and physiology testing. [268] A study published since that review did include men and anorectal physiology testing.[269] Obese patients were more likely to have a history of cholecystectomy and irritable bowel syndrome with diarrhoea as well as higher resting pressures, higher maximum tolerable volumes and abdominal pressure. Two confounding factors were noted in studies of this relationship. One is that diarrhoea, an independent risk factor for incontinence, is also frequently associated with obesity. [268] The second is the association of faecal incontinence with low fibre intake in obese women raising the question of dietary contribution to the increased incidence of faecal incontinence with obesity. [258] Chronically elevated intra-abdominal pressure, known to be associated with obesity, [270, 271] is typically proposed as the reason for pelvic floor dysfunction in obesity. Other factors including diabetes, neurological changes and intervertebral disc herniation, common in the obese population may very well contribute.

5.6.2. Vitamin D

Vitamin D deficiency is associated with urinary incontinence in men and women.[272, 273] One small study of ten patients with faecal incontinence found that all had either vitamin D deficiency or relative vitamin D insufficiency. [274]These rates are much higher than the 36-57% rate of deficiency or relative insufficiency from historical data of the general population. In a large study of 1881 women in the US, there was a non-significant trend towards an association between lower vitamin D levels and faecal incontinence. [272] It is known that vitamin D absorption and synthesis in the skin declines with age. [275, 276] Any association between lower levels of vitamin D and faecal incontinence may represent that both are common inolder adults. A randomized controlled study of post-menopausal women found that a low vitamin D level was associated with urinary but not faecal incontinence. The significance of vitamin D levels in patients with faecal incontinence is uncertain but potentially could represent an easily remediable factor.

5.7. Obstetrical injury

The impact of pregnancy and vaginal delivery on continence is described in the section on obstetric injury. While those injuries occur with reasonable frequency, quite often the patient does not develop clinical incontinence until later in life. The reasons for the onset of symptoms and the required combination of factors are poorly understood. Current thinking is that the main factors are pudendal and pelvic autonomic neuropathy and endo-pelvic fascial and ligamentous abnormalities. [73] However, the contribution of EAS defects to incontinence is supported by data demonstrating that clinical improvement after sphincteroplasty is more likely in patients with successful anatomical repair seen on ultrasound. [178, 277-279] The frequency of puborectalis or levator ani muscle injury as well as the degree to which it contributes to faecal incontinence is unclear but is being more actively investigated. [138, 140, 142, 280]

5.8. Physical mobility

Intuitively, adequate physical mobility to reach the toilet in a timely manner in response to the urge to defaecate is necessary for continence. Limited mobility was found to be a risk factor for incontinence in one population based study [187] and an investigation of nursing home residents [107]. In a study of urban dwelling older persons, the odds of prevalent incontinence increased by 20% for each unit decrease in the physical performance measure.[235] These findings were supported by data from the Nurses' Health Study.[265] , Immobility was one of the strongest predictors of incontinence in a study of long-term care patients. [281] In another study, the use of physical restraints (maximal limitation of mobility) was found to be the most significant cause of incontinence when the data were adjusted for other risk factors. [282] Even among women with spinal cord injuries, permanent use of a wheelchair significantly increased the odds of incontinence.[283]

5.9. Radiation

Faecal incontinence occurs after pelvic irradiation for prostate, gynaecological, anal and rectal cancer.[284-288] Radiation therapy adds to the risk of incontinence associated with rectal resection. [289-292] Comparisons of long and short course radiation therapy before surgery for rectal cancer have produced conflicting results. [293-296] Direct comparison trials powered to answer the question have completed recruitment. [297, 298]; oncologic but not functional results have been published. In a study of the relationship of radiation dosage to symptoms after prostate radiotherapy, faecal incontinence was associated primarily to radiation to the EAS and PR. [299] The exact mechanism(s) that radiation therapy causes incontinence is uncertain. The rectum may be stiffer and less compliant [300] and the anal pressures reduced either from muscle or nerve injury by the radiation.[290, 301, 302]

5.10. Mucosal, internal and full thickness rectal prolapse

A significant portion (48-63%) of patients with prolapsing haemorrhoids or mucosal prolapse report soiling.[303, 304] Symptoms resolve with successful treatment. [303-306]

External rectal prolapse is associated with faecal incontinence in up to 66% of patients.[307-310] Diminished anal resting tone commonly accompanies rectal prolapse [90, 308, 311]; that finding suggests that internal sphincter dysfunction perhaps from repeated stretching is one mechanism for incontinence. Other considerations include the presence of neuropathy; it is unclear if the prolapse results in prolonged pudendal nerve latencies [312, 313]or if both share a common etiology. The exact mechanism or combination of causes is uncertain. Other investigators, however, found that patients with rectal prolapse and persistent incontinence had evidence of sphincter defects either from surgical or obstetrical injury. [314, 315]

Internal rectal prolapse is also associated with faecal incontinence [316-319] and decreased anal pressures. [311] The risk of decreased resting tone is greater with recto-anal intussusception than recto-rectal intussusception. In addition, women with internal prolapse without a rectocele seem more likely to have reduced resting tone compared to ones with a rectocele. [320] While surgical intervention for internal rectal prolapse is controversial, several studies report improvement in their incontinence after rectopexy. [321-324]

5.11. Surgery

5.11.1. Anorectal surgery

Lateral internal sphincterotomy is the recommended surgical procedure for refractory anal fissures. Surgery involves division of the internal sphincter and may result in incontinence of flatus and stool. [325-330] Quite variable rates of post-operative incontinence from 0-36 % are reported. The definition of incontinence, type of follow-up and length of sphincterotomy contribute to the variability. Shorter length sphincterotomies are associated with reduced post-operative incontinence confirming that length of sphincterotomy is an important factor. [331, 332] Some authors suggest that pre-existing sphincter injury might predispose to incontinence [333, 334] Another author found evidence for increased sphincter asymmetry in the patients with incontinence after sphincterotomy compared to continent post-operative patients but no differences in pre-existing sphincter defects. [335] The development of symptoms of incontinence may be delayed similar to women with obstetric sphincter injuries. [336]

Incontinence is reported in 0-14% of patients after haemorrhoidectomy.[337-340] In the limited studies available, increased risk of incontinence has been related to previous vaginal deliveries [338], number of haemorrhoids excised [339] and post-operative internal sphincter defects. [338, 341] Some have argued that excision of the anal cushions is the reason for incontinence. [114]

Surgery for anal fistulae may result in faecal incontinence. The frequency depends upon the anatomy of the fistula, base-

line sphincter function and the surgical procedure performed. The reported rates of post-operative incontinence range from 0-50%. [342-354] The definition and measurement of incontinence varies among the studies. Treatment of high fistulae involving more sphincter muscle is more likely to be followed by incontinence.[326, 342, 349, 354] Injections of fibrin glue and endorectal advancement flaps have lower post-operative incontinence rates than other fistula procedures. [345] Age over 45 years old [342] sex[344, 353, 355] and previous anorectal surgery [355] were found to increase the risk in some studies. The mechanism appears to be iatrogenic (and sometimes intentional) sphincter injury.

5.11.2. Rectal resection

In a meta-analysis of functional outcomes after resection for rectal cancer from studies reported between 1978 and 2004, faecal incontinence of any kind occurred in 3-79% of patients. [287] Rates of incontinence of solid stool ranged from 0-40%, liquid stool 0-60% and flatus 9-76%. The pooled proportion of incontinence of solid stool was 14 % and liquid stool 29%. The risk of incontinence appears to depend upon the tumour location and level of the anastomosis [356] as well as occurrence of anastomotic leakage.[357] As surgical techniques evolve, new ones have been compared to existing techniques to determine if technical details impact functional outcomes. Transanal total mesorectal excision has recently been compared to laparoscopic total mesorectal excision, while some studies document higher incontinence [358, 359], a meta-analysis found no difference. [360] Theoretically, loss of the rectal reservoir is one contributor. The goal of replacing the reservoir function led to the development various types of reconstruction following resection (coloplasty, colonic J pouch, ileoanal reservoir). While long–term data are sparse, in the first 18 months post-operatively colonic J pouches result in lower rates of incontinence than straight anastomoses or coloplasty according to a Cochrane review.[361] Damage to the internal sphincter occurs during this type of resection presumably from transanal introduction of stapling devices and may contribute to incontinence as well. [362, 363] However a study comparing patients undergoing hand-sewn anastomoses to double stapled ones found no difference in faecal incontinence post-operatively or anorectal manometry results. [364] Another possible explanation for the incontinence after low resection is the disruption of the rectoanal inhibitory reflex. There is data to support the loss of the rectoanal inhibitory reflex post-operatively and its correlation with incontinence. [365-367] In a recent study 61% of patients who underwent an intersphincteric resection for rectal cancer recovered their rectoanal inhibitory reflex after 12 months; incontinence was significantly less common in that group compared to patients with a permanent loss. [365] It is interesting to note that recovery of the rectoanal inhibitory reflex did not correlate with the amount of internal sphincter resected. Diminished rectal sensation and changes in motility seen post-operatively indicate that nerve damage may also contribute. [364, 368, 369] Rectal sensation and the ability to defaecate can be abolished completely by resection of the nervi erigentes [370]. If parasympathetic innervation is absent, rectal filling is only perceived as a vague sensation of discomfort. Cadaver studies after total mesorectal excision reveal the close proximity of the levator ani nerve and pelvic splanchnic nerves to the plane of dissection particularly for low rectal resections. [371] Damage to those nerves would impact function of the sphincter mechanism. A recent small study found that approximately half of the patients with low anterior resection syndrome had qualitative changes in anal slow wave activity compared to healthy controls. [372] It is likely that multiple factors contribute to incontinence after rectal resection; more research is needed to understand the relative importance of each factor.

5.11.3. Hysterectomy

Several reports identified hysterectomy as a risk factor for faecal incontinence. [148, 187, 373] However several studies found either improvement or no association.[374] [192] [149] Gynecological cancer appears to have a more significant impact on pelvic floor symptoms including faecal incontinence than hysterectomy alone. [373, 375] However, it is not clear whether surgery or adjuvant therapies are responsible.

5.11.4. Cholecystectomy

Cholecystectomy results in diarrhoea in some patients. It is often assumed at incontinence occurring after cholecystectomy is related to the onset of diarrhoea. However, two studies identified cholecystectomy as a significant independent risk factor for incontinence. [148, 376]The underlying mechanism, if not associated loose stool, is uncertain but perhaps could be related to rectal urgency secondary to bile salt irritation.

5.12. Smoking

A study from the Mayo Clinic reported an association of incontinence in older adults with current smoking with an odds ratio of 4.7. [148] An earlier study reported the same finding in post-partum patients with faecal incontinence. The reason is unclear. [377] Chronic obstructive pulmonary disease has been associated with faecal incontinence [192] but in the Mayo Clinic study, pulmonary disease was not found to be a factor. Other proposed mechanisms include the anti-oestrogen effect of nicotine [378] or accelerated colonic transit secondary to nicotine induced high amplitude contractions in the colon.[379]

5.13. Trauma

Direct injury to the anal sphincter occurs in both military and civilian settings in addition to childbirth. However, there is limited literature about long term anorectal function of those patients. [380] Anal intercourse has been found to be a risk factor in both men and women, [381-383] In small studies of men with faecal incontinence and history of anal intercourse, reduced resting pressures were identified but no sphincter changes could be detected on ultrasound.[383, 384]

5.13.1. Urinary incontinence

Many studies report an association of urinary and faecal incontinence. It is likely that it is not a causative relationship but rather that the two conditions result from common aetiology.[148, 151, 154, 187, 192, 212, 385-387]

6. SUMMARY AND RESEARCH RECOMMENDATIONS

Multiple risk factors play a role in the development of faecal incontinence. As treatment patterns for diseases such a rectal cancer and inflammatory bowel disease change, early work on the functional consequences should be continued. Since the last report, increased focus has been placed on the role of rectal urgency, anorectal sensation and the involved nervous system. However, many questions remain. Understanding of the complex interaction of the pelvic floor musculature and nervous system in healthy patients and incontinent patients is incomplete.

Why some patients with similar risk factors are incontinent but not all is unclear. What combination of abnormalities is required for significant incontinence needs further investigation.

Clinicians need to know which of those abnormalities, including ones associated with aging, are remediable and if the possible remedies result in clinical improvement.

More detailed knowledge of the molecular pathways would be helpful in devising new treatment. Answers to those questions would might allow prevention, improve patient selection for various treatments and facilitate discovery of new treatment modalities

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COMMITTEE 4A

INITIAL ASSESSMENT OF URINARY INCONTINENCE IN ADULT MALE AND FEMALE PATIENTS

Chairs

Castro-Diaz, David. Chair (Spain)
Robinson, Dudley. Co-Chair (United Kingdom)

Members

Arlandis Guzman, Salvador (Spain)
Bosch, JLH (Netherlands)
Costantini, Elisabetta (Italy)
Cotterill, Nikki (United Kingdom)
Espuña Pons, Montserrat (Spain)
Lemos, Nucelio (Canada)
López-Fando Lavalle, Luis (Spain)
Shelly, Elizabeth (United States)
Yoshida, Masaki (United Kingdom)

COMMITTEE 4A

INITIAL ASSESSMENT OF URINARY INCONTINENCE IN ADULT MALE AND FEMALE PATIENTS

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ABBREVIATIONS

AHCPR Agency for Health Care Policy and Research's
AUA American Urological Association
BD Bladder Diary
BMI Body Mass Index
BOO Bladder Outlet Obstruction
BPE Benign Prostatic Enlargement
BPH Benign Prostate Hyperplasia
BPO Benign Prostatic Obstruction
CLSS Core LUTS Score
DAN-PSS Danish Prostatic Symptom Score
DO Detrusor Overactivity
DRE Digital Rectal Examination
EBM Evidence Based Medicine
FIGO International Federation of Gynaecology And Obstetrics
FVC Frequency-Volume Chart
GFR Glomerular Filtration Rate
GH Genital Hiatus
GSM Genitourinary syndrome of menopause
ICI International Consultation on Incontinence
ICIQ International Consultation on Incontinence Modular Questionnaire
ICIQ-MLUTS International Consultation on Incontinence Modular Questionnaire-Male LUTS
ICIQ-SF International Consultation on Incontinence Questionnaire-Short Form
ICS International Continence Society
ICUD International Consultation on Urologic Diseases
IHCIS Health Care Information Solutions Database
IPSS International Prostate System Score
IUGA International Urogynaecology Association
LR Likelihood Ratio
LUT Lower Urinary Tract
LUTD Lower Urinary Tract Disease
LUTS Lower Urinary Tract Symptoms
MOS Modified Oxford Scale
MSAM-7 Multinational Survey of the Aging Male
MUCP Maximum Urethral Closure Pressure
OAB Overactive Bladder Syndrome
OABSS OAB Symptom Score
PB Perineal Body
PFDI Pelvic Floor Distress Inventory
PFM Pelvic Floor Muscles
PGI-I Patient Global Impression of Improvement
PISQ12 Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire
PISQ-IR Pelvic Organ Prolapse/Incontinence, IUGA-Revised
POP Pelvic Organ Prolapse
POP-Q Pelvic Organ Prolapse Quantification
PPI Post-Prostatectomy Incontinence
P-QOL Prolapse Quality Of Life
PRO Patient Reported Outcomes
PSA Prostatic Specific Antigen
PVR Post-Void Residual
QOL Quality of Life
RALP Robot Assisted Laparoscopic Prostatectomy
RP Radical Prostatectomy
RRP Retropubic Radical Prostatectomy
RUTI Recurrent Urinary Tract Infection
SSC Standardisation Steering Committee
SUI Stress Urinary Incontinence
TOT Transobturator Tape
TVL Total Vaginal Length
UI Urinary Incontinence
UTI Urinary Tract Infection
UUI Urgency Urinary Incontinence
UWIN Urgency and Nocturia Scoring Tool
VLPP Valsalva Leak Point Pressure
VVA Vulvar and Vaginal Atrophy

I. INTRODUCTION

The aim of this report is to provide an update of the evidence-based recommendations from the 7th ICI regarding the initial assessment of urinary incontinence (Committee 5A) for adult men and women.

II. GENERAL INFORMATION

1. TERMINOLOGY

A critical step in the evaluation of urinary incontinence (UI) is the use of up-to-date terminology to describe different types of UI and their associated lower urinary tract symptoms (LUTS). LUTS includes both storage and emptying symptoms in contrast to overactive bladder syndrome (OAB) which describes a subset of storage symptoms (e.g., urgency, frequency, nocturia), with or without the symptom of UI. The use of standardised terminology during history taking of UI ensures an accurate characterisation of the type of UI experienced by each patient.

The ICS 2002 report (1) and the ICS /IUGA Joint Report (2) are recommended for reference, as well as an update of the terminology for nocturia (3). It should be noted however that a bibliometric and questionnaire analysis of the use of standardised terminology documents the low rate of acceptance of this terminology in both the literature and practice, and the slow abandonment of previously accepted common terms. (4)

The Standardisation Steering Committee (SSC) of the International Continence Society (ICS) "establishes terminology and methodology in the ICS's areas of activity, to underpin professional standards of clinical management and research. The value of the SSC is in promoting best standards when clinicians and allied professionals communicate with patients and colleagues, undertake diagnostic tests, proceed to therapeutic interventions and undertake research. Precise use of agreed terminology ensures clear understanding for collaborating centres and readers of publications. Adherence to the diagnostic testing standards gives patients and clinical colleagues confidence that conclusions on which important therapeutic decisions are reliable. Development of future insights into mechanisms and treatments of the disease areas relevant to the ICS is enhanced where research studies employ internationally standardised approaches.

The term "urinary incontinence" refers to the complaint of any involuntary loss of urine. The symptom of urinary incontinence can be volunteered by, or elicited from, the individual or may be described by the individual's caregiver. Urinary incontinence can be categorised into several distinct sub-types based on associated characteristics and circumstances surrounding episodes of urine leakage. Although defining the type of incontinence will not establish a definitive underlying diagnosis, it will ultimately guide investigation and treatment. The following are the accepted ICS definitions of these conditions unless referenced (1).

1.1. Types of urinary incontinence

a) Stress (urinary) incontinence: Complaint of involuntary loss of urine on effort or physical exertion e.g., sporting activities), or on sneezing or coughing. (Sporting activities)

b) Urgency (urinary) incontinence: Complaint of involuntary loss of urine associated with urgency.

c) Postural (urinary) incontinence: Complaint of involuntary loss of urine associated with change of body position, for example, rising from a seated or lying position.

d) Mixed (urinary) incontinence: Complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing.

e) Incontinence associated with chronic retention of urine: Complaint of involuntary loss of urine which occurs in conditions where the bladder does not empty completely as indicated by a significantly high residual urine volume and/or a non-painful bladder which remains palpable after the individual has passed urine. (Note: The ICS no longer recommends the term overflow incontinence. A significant residual urine volume denotes a minimum volume of 300 ml, although this figure has not been well established.)

f) Nocturnal enuresis: Complaint of involuntary loss of urine which occurs during sleep.

g) Continuous (urinary) incontinence: Complaint of continuous involuntary loss of urine.

h) Insensible (urinary) incontinence: Complaint of urinary incontinence where the individual is unaware of how it occurred

i) Coital incontinence (for women only): Complaint of involuntary loss of urine with coitus. This symptom can be further divided into that occurring with penetration and that occurring at orgasm.

j) Functional incontinence: Complaint of involuntary loss of urine that results from an inability to reach the toilet due to cognitive, functional or mobility impairments in the presence of an intact lower urinary tract system.

k) Multifactorial incontinence: Complaint of involuntary loss of urine related to multiple interacting risk factors, including factors both within and outside the lower urinary tract such as comorbidity, medication, age-related physiological changes and environmental factors.

Urinary incontinence can exist in isolation or may be associated with other lower urinary tract symptoms. The ICS classifies lower urinary tract symptoms (LUTS) into bladder storage, voiding and post-micturition, and pelvic organ prolapse symptoms. The following section summarises the definitions of LUTS described by the ICS-SSC.

1.2. Bladder storage symptoms

Bladder storage symptoms are experienced during the bladder filling phase:

a) Increased daytime urinary frequency: Complaint that micturition occurs more frequently during waking hours than previously deemed normal. Traditionally seven episodes of micturition during waking hours was considered as the upper limit of normal, although it may be higher in some populations.

b) Nocturia: Complaint of interruption of sleep one or more times because of the need to void. Each void is preceded and followed by sleep. The number of nocturia episodes and the degree of bother based on number has been questioned and the threshold of 2-3 per night has been suggested (5-10).

c) Urgency: Complaint of a sudden, compelling desire to pass urine which is difficult to defer. (Note: The ‘all or none‘ nature of ‘urgency’ has been questioned) (8).

d) Overactive bladder syndrome (OAB): Urinary urgency, usually accompanied by increased urinary frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.

1.3. Bladder sensation

Asking patients about bladder sensory symptoms during bladder filling may be helpful in characterising certain types of incontinence.

a) Increased bladder sensation: Complaint that the desire to void during bladder filling occurs earlier or is more persistent to that previously experienced. This differs from urgency by the fact that micturition can be postponed despite the desire to void.

b) Reduced bladder sensation: Complaint that the definite desire to void occurs later than that previously experienced despite an awareness that the bladder is filling.

c) Absent bladder sensation: Complaint of both the absence of the sensation of bladder filling and a definite desire to void.

1.4. Voiding and postmicturition symptoms

Voiding symptoms are experienced during the voiding phase and post-micturition symptoms are experienced immediately after micturition.

a) Hesitancy: Complaint of a delay in initiating micturition.

b) Slow stream: The individual’s perception of reduced urine flow, usually compared to previous performance or in comparison to others.

c) Intermittent stream (intermittency): Complaint of urine flow which stops and starts, on one or more occasions, during micturition.

d) Straining to void: Describes the muscular effort used to initiate, maintain or improve the urinary stream.

e) Spraying (splitting) of urinary stream: Complaint that the urine sprays or splits rather than coming out as a single, discrete stream.

f) Terminal dribble: is the term used when an individual describes a prolonged final part of micturition, when the flow has slowed to a trickle/dribble.

g) Feeling of incomplete bladder emptying: Complaint that the bladder does not feel empty after passing urine.

h) Need to immediately re-void: Complaint that further micturition is necessary soon after passing urine.

i) Postmicturition leakage: Complaint of a further involuntary passage of urine following the completion of micturition.

j) Position-dependent micturition: Complaint of having to take specific positions to be able to micturate spontaneously or to improve bladder emptying, for example, leaning forwards or backwards on the toilet seat or voiding in the semi-standing position.

k) Dysuria: Complaint of burning or other discomfort during micturition. Discomfort may be intrinsic to the lower urinary tract or external (vulvar dysuria in women).

l) (Urinary) retention: Complaint of the inability to pass urine despite persistent effort.

2. ASSESSMENT OF SUB-POPULATIONS REVIEWED BY OTHER COMMITTEES

The targeted assessments and specific outcome measures for conditions of UI in Children (Cmte.9), Neurogenic Patients (Cmte.10), Frail Elderly (Cmte.11), Painful Bladder Syndrome (Cmte.19) and Faecal Incontinence (Cmte.16) are presented separately in the respective reports. The requirements of specific sub-populations negate the ability to recommend a 'universal' initial evaluation. Within the initial assessment of UI, these sub-populations / subgroups are recognised because of the differences within patient groups or the interrelationship between the conditions. Congenital and developmental issues are critical considerations in children. Specific risks for combined storage and emptying abnormalities and upper urinary tract deterioration in the neurogenic population demand a more involved initial and complex evaluation. The effects of ageing on the lower urinary tract, altered toileting functions, and medical co-morbidities in the frail elderly group present unique challenges. These subgroups also include patients with LUTS with and without incontinence and with the presence of pelvic pain or faecal incontinence.

The sub-sections in this report should be utilised in conjunction with other population or condition specific Committee Reports of the Consultation and with the final recommendations of the Consultation which are presented in simplified form in Appendix (1. Definitions). Recommendations for initial evaluation have been developed by the International Scientific Committee and are also published in Appendix (2. Evaluation). In addition, History and Symptom Assessment recommendations are further detailed as the initial steps in the evaluation of the index adult male (3. Initial Management, II. Male), and adult female (3. Initial Management, III. Female). The reader is encouraged to refer to these recommendations and algorithms in combination with this report.

3. EVIDENCE BASED RECOMMENDATIONS

The recommendations presented in this report are evidence-based and utilise the ICUD-EBM grades. A search of the available literature in English obtained from Medline and Pubmed by the individual committee members employed multiple search terms related to the initial assessment of the patient with urinary incontinence and patient reported outcome assessment.

III. INTIAL ASSESEMENT

1. PURPOSE OF INITIAL ASSESSMENT (EXPERT OPINION OF THE COMMITTEE)

As will be noted, especially in this committee report (5A), the amount and sophistication of the literature that is applicable for the development of evidence-based guidelines is limited. For this reason, the grade of recommendation in the area of "initial assessment" will often rely on 'expert opinion of the panel'. For the purpose of subsection 5A, the 'initial assessment' represents the components of the history, physical examination, laboratory tests, and basic office testing to:

1. Establish a presumptive or condition specific diagnosis and exclude underlying organ-specific related or unrelated conditions that would require intervention.
2. Assess the level of bother and desire for intervention from information obtained from the patient or caregivers, utilising objective measures or patient reported outcomes.
3. Prepare for the institution of empirical or disease specific primary therapy based on the risk and benefit of the untreated condition, the nature of the intervention and the alternative therapies including Conservative (Cmte.12) or Pharmacological (Cmte.8) therapies.
4. Prompt the recommendation of additional more complex testing or specialist referral (when indicated).
5. Assess the level of improvement after intervention from information obtained from the patient or caregivers, utilising objective measures or patient reported outcomes (Cmte.5B).

Once the type of Urinary Incontinence (UI) with associated lower urinary tract symptoms (LUTS) has been established, there can be consideration of a differential diagnosis , and further investigations may be requested , and an eventual treatment plan can be formulated to address or modify the effects of the underlying cause(s). The success of the treatment plan can be measured by patient-reported outcomes (from a simple "yes" or "no" to more complex questionnaires), and/or other objective measures of urinary leakage events (including bladder diaries, pad tests, or urodynamics studies).

The initial assessment must consider the degree of bother, and the cost of further evaluation, balanced against the consequences of failure to diagnose an underlying condition, the risks and benefits of empirical conservative management or pharmacological therapy, and the need for an accurate diagnosis before more complex intervention or empirical therapy. The burden of these conditions and the availability of resources for individual patients, caregivers, physicians, and health care systems requires that primary intervention strategies be formulated from evidence-based findings and decisions emanating from the initial evaluation.

Of note, LUTS cannot be utilised with confidence to make a definitive diagnosis of a specific lower urinary tract condition or lower urinary tract disease (LUTD), as these symptoms may suggest and indicate pathologies such as urinary tract infection (UTI) or more

serious underlying conditions. Basic laboratory tests, such as testing for UTI or blood (haematuria), and appropriate screening for malignancy should be considered before the decision is made to choose therapy for incontinence. Urinary retention with overflow may present as urinary urgency, frequency, and nocturia with urinary loss mimicking OAB.

Concomitant pathology may affect urine production as a co-morbid contributory factor, by affecting fluid balance or renal function (fluid intake and output regulation) and may need to be addressed prior to or in combination with LUT or bladder outlet therapy. A thorough review of medications which alter fluid production or lower urinary tract function should be addressed. The physician should also seek a history of pelvic pathology or surgery and neurological symptoms and signs that may indicate alterations in the control of the lower urinary tract function or be responsible for the cognitive, motivational, or physical factors that determine the ability to perform toileting functions effectively. The physical examination and the appropriate laboratory tests are necessary to refine the differential diagnosis and therapeutic options.

The recent ICS report on the terminology for pelvic floor muscle (PFM) assessment lists symptoms a patient may use to describe a sensation which could be related to a disorder of PFM structure or function (11). Recognising the symptoms of possible PFM disorder can direct further assessment and guide intervention. PFM sensory symptoms may include numbness, reduced feeling, decreased sensation, tingling, pins and needles, sensitivity/hypersensitivity, or increased or unusual sensation in the region the patient perceives to be related to the PFM. Terms used to describe painful symptoms may include pain, tender, ache, burning or discomfort in the region the patient perceives to be related to the PFM. Further assessment of PFM function may be considered in patients describing these sensations (8).

2. INITIAL ASSESSMENT – GENERAL RECOMMEDATIONS

1. Lower Urinary Tract Symptoms (LUTS) cannot be used to make a definitive diagnosis; they may also indicate pathologies other than LUTD. Specific to this report, LUTS includes Overactive Bladder (OAB) a syndrome which may be associated with urgency incontinence (OAB-wet) or without incontinence (OAB-dry) (Level 4 - Grade D).
2. Urinary incontinence should be described by specifying relevant factors such as type, frequency, severity, precipitating factors, social impact, effect on hygiene and quality of life as well as the measures used to contain the leakage and whether or not the individual desires help (Level 4 - Grade D).
3. Urinary incontinence should be categorised by symptoms into urgency incontinence, stress incontinence or mixed incontinence and conservative (non-invasive) therapies may then be started based on this classification to treat the most troublesome component, or both components of the incontinence. More sophisticated testing (e.g., urodynamic studies) is not required prior to conservative therapy (see indications for urodynamics in the Committee Report on Dynamic Testing Committee 6) (Level 3 - Grade C).
4. Both objective (bladder diary) and subjective (patient reported outcomes – PROs) are recommended for assessment and measurement of the degree of symptoms and bother of UI at baseline, and for the assessment of the impact of therapy (Level 3 – Grade D).
5. Normal lower urinary tract function requires the ability of the bladder to adequately store urine at low pressure while the bladder outlet remains competent, and the bladder to contract until completely empty while the bladder outlet remains open. In addition to an evaluation of LUT function, a thorough evaluation for co-morbid conditions which affect fluid intake and output should be undertaken. Diseases of the nervous system and pelvic disorders, as well as medications which may affect the LUT should be addressed (Level 4 - Grade D).
6. Referral to a specialist is recommended for haematuria (visible or microscopic), urinary tract infection (persistent or recurrent), prolapse (symptomatic or below the introitus) , obstruction or retention (symptoms or findings of palpable bladder, hydronephrosis or obstructive renal insufficiency), suspected neurological disease, mass (urethral, bladder or pelvic - benign or malignant), fistula (urinary or bowel), faecal incontinence, a history of prior pelvic surgery or radiation (incontinence, oncologic), symptoms suggestive of possible PFM disorder (Level 4 - Grade D).

3. INITIAL ASSESSMENT – GENERAL RESEARCH RECOMMENDATIONS

1. Standardisation of the ‘definition of symptoms’ and the ‘measurements of symptom frequency, severity and bother’ are essential for patient care and research. Continued research into the appropriate scales and metrics should be accompanied by a significant attempt to establish best practice guidelines for their use and a consensus on the adoption of universal standards.
2. Recognition and resolution of the differences in common language usage and scientific utilisation of terms should continue. Resolution of the differences in definitions and metrics between recognised societies and organisations is essential for communicating data with respect to patient care, research, and treatment outcomes.
3. Research into the development of accurate measures to objectify subjective symptoms such as “urgency” and other bladder sensory symptoms.
4. Development, standardisation, and universal adoption of symptom assessment tools (questionnaires) to improve the diagnostic accuracy of lower urinary tract symptoms (Refer to section 5B of this committee’s report).
5. Validation of the accuracy of specific components of the history and physical findings to establish an accurate diagnosis and to initiate non-invasive conservative or pharmacological therapy. In addition, to further identify components that would indicate the need for more invasive testing, complex therapeutic interventions, and indications prior to / or as a result of referral.
6. Creation and institution of evidence-based guidelines for the referral of patients to a specialist are needed to improve the efficiency of the healthcare system in treating the large burden of disease (See Epidemiology, Committee 1). The institution of conservative measures and pharmacology are in the domain of the primary caregiver. Further improvement in the ability to define the index patient, but more importantly the sub-groups of patients who will require more complex specialist therapy, will aid in counselling and referral at the primary level. In addition, refining the true risks for significant underlying disease noted while obtaining the history, or during the examination or laboratory findings will improve resource utilization.

IV. GENERAL POPULATIONS

1. INITIAL ASSESSMENT OF URINARY INCONTINENCE

Individuals with UI can be identified through routine screening, or the patient may initiate discussion about incontinence problems. The initial assessment of UI should help the health care provider to understand the type of incontinence, while identifying potentially modifiable contributing factors. Most primary treatment options, such as lifestyle modifications and behavioural treatments, do not vary by type of UI. However, it is important to determine the type of UI since some treatment options do vary . Equally important, establishing the type of UI will lead the health care provider to a list of possible underlying causes, or differential diagnosis of the urinary symptoms. Most causes of UI are non-life threatening. However, symptoms of incontinence may also herald life-threatening or more severe disease such as bladder cancer when associated with haematuria, when more specialized testing will be required immediately. Finally, assessing the level or bother and desire for intervention from information obtained from the patient or caregiver is essential for guiding the nature of the treatment plan.

1.1. History

Taking a careful clinical history is fundamental to the clinical process. Some studies have indicated that patient history alone is not completely accurate as the sole determinant of incontinence type (12, 13). However, Martin et al. (14) in a systematic review and meta-analyses on the methods for diagnostic assessment of urinary incontinence, suggested that women with urodynamic stress incontinence (USI) can be correctly identified in primary care from clinical history alone with a sensitivity of 0.92 (95% C.I.: 0.91- 0.93) and specificity of 0.56 (0.53- 0.60); symptoms of urge incontinence were found to be 0.61 (0.57- 0.65) sensitive and 0.87 (0.85-0.89) specific for the diagnosis of detrusor overactivity.

Despite the lack of formal evidence, there is universal agreement that taking a history should be the first step in the assessment of anyone with UI (1, 15).

The general history should include questions relevant to establish the type of UI, timing and severity of UI, and some attempt to quantify symptoms should also be made. The history should help to categorise LUTS as storage, voiding and post-void symptoms (16).

The incontinence first should be characterized subjectively. Does the leakage occur: With physical activity? With a sense of urgency? Without sensory awareness? If the nature of the incontinence is mixed, does one component cause more bother or occur more frequently than the other? Secondly, the leakage should be quantified if possible. Appraisal of the degree of leakage before therapy can be helpful during postoperative assessment of treatment impact. For the purposes of routine outpatient assessment, this quantification can be achieved based on the number of pads used per day or the frequency of clothing changes because of urinary leakage. Medical practitioners should also be aware of symptoms of PFM disorder listed above.

Acute symptoms can be defined by documenting patterns of fluid intake and output, acute infection, recent surgery or trauma. Chronic symptoms should prompt queries about a history of congenital abnormalities, neurological disease, relevant surgery or general health issues. History should also identify patients who need rapid referral to an appropriate specialist. These include patients with associated pain, haematuria, a history of recurrent urinary tract infection (UTI), pelvic surgery (particularly prostate surgery) or radiotherapy, constant leakage suggesting a fistula, voiding difficulty or suspected neurological disease (Red Flag Symptoms).

The voiding pattern should also be defined. What is the frequency of micturition during the day and during the night? Are there any voiding symptoms and/or storage symptoms? Previous surgery such as pelvic or back surgery and, in males, prostate or urethral surgery for benign or malignant disease should be investigated.

Information should be obtained concerning medications with known or possible effects on the lower urinary tract. The general history in women should also include assessment of menstrual, obstetric, sexual, gynaecological and bowel function. It is also helpful to determine the impact that the leakage has on the patient's daily life and activities if incontinence limits the individual's activity and if the patient made lifestyle changes because of the threat of leakage. Finally, it is important to emphasize the importance of establishing patient expectation of treatment and an understanding of the balance between the benefits and risks/burden of available treatment options (see Committee Report 5B).

The reader is referred to the report on Epidemiology (Committee. 1) for specific risk factors to be considered during the medical history, and to the report on Frail Elderly (Committee. 11) for a list of co-morbidities and medications that can cause or contribute to UI.

A later section of this Committee Report (5B) presents a complete review and evaluation of questionnaires that are applicable for clinical and research use in evaluating patient symptoms. Structured condition specific questionnaires may be utilised and may be either clinician or self-administered. Use of questionnaires may facilitate disclosure of embarrassing symptoms, ensure that symptoms are not omitted and standardise information for audit and research.

In the absence of questionnaire use, Table 1 summarises key questions for the initial assessment of urinary incontinence based on the expert opinion of this committee. Note that the committee strongly encourages the use of standardised questions.

Table 1: Key Questions in the Initial Assessment of Urinary Incontinence

Stress urinary incontinence: Do you sometimes leak urine when you cough or sneeze or when you exert yourself, such as when lifting a heavy object?
Urgency urinary incontinence: Do you sometimes feel an urge to void that is so sudden and strong that you sometimes don't make it to the bathroom on time?
How long have the symptoms been present?
How often do you leak urine and how much do you leak? (Do you need protections and how many during day and night?
Circumstances surrounding urine leakage e.g. sexual activity, change in position, provocation by running
water or 'key in the latch'?
Nocturnal symptoms or enuresis?
Association with other lower urinary tract or pelvic organ prolapse symptoms?

Impact on personal and social life?
Amount and type of fluid intake e.g. coffee, tea, alcohol?
Episodes of urinary tract infection or haematuria?
Previous treatment attempts (successful and unsuccessful)?
Mobility problems?
Cognitive deficits?
Neurological deficits?
Problems with constipation or faecal incontinence?
Number of pregnancies and the type of delivery, with complications?
Previous prostate, pelvic or abdominal surgeries or radiation treatment?
Coexisting diseases (diabetes, heart disease, neurological impairment)?
Types of medications consumed?

1.2. Bladder diaries

The micturition time chart records the timing of voids in 24 hours. The term frequency-volume chart is used to describe a chart that records the time of each micturition and the volume voided for at least 24 hours. The bladder diary may include fluid intake, incontinence episodes, pad usage, the degree of incontinence as well as a record of episodes of urgency and sensation and activities performed during or immediately preceding the involuntary loss of urine. Therefore, bladder diaries are most suited for the purpose of comprehensive evaluation of urinary incontinence. However, documentation of the frequency of an individual's lower urinary tract symptoms and the voided volume for at least 24 hours can be extremely helpful in the initial assessment of urinary incontinence, although 2-3 days of recording generally provide more useful clinical data. Moreover, a diary may be therapeutic as it provides insight into bladder behaviour and it can be utilised to monitor the effectiveness of treatment during follow-up.

A frequency-volume chart or bladder diary, if properly completed, can provide all of the following information.

a) Daytime urinary frequency: Number of voids by day (wakeful hours including last void before sleep and first void after waking and rising).

b) Nocturnal frequency/nocturia: Number of times sleep is interrupted by the need to micturate. Each void is preceded and followed by sleep.

c) Twenty-four-hour frequency: Total number of daytime voids and episodes of nocturia during a specified 24-hr period.

d) Twenty-four-hour urine production: Summation of all urine volumes voided in 24 hr.

e) Maximum voided volume: Highest voided volume recorded.

f) Average voided volume: Summation of volumes voided divided by the number of voids.

g) Median functional bladder capacity: Median maximum voided volume in everyday activities.

h) Polyuria: Excessive excretion of urine resulting in profuse and frequent micturition, defined as greater than 2.8 L of urine during 24 hours for an individual weighing 70 kg.

i) Nocturnal urine volume: Cumulative urine volume from voids after going to bed with the intention of sleeping to include the first void at the time of waking with the intention of rising (excludes last void before sleep).

j) Nocturnal polyuria: Excess (over 20–35% age dependent) proportion of urine excretion (nocturnal voided volume/total 24 hr voided volume x 100% = Nocturnal Polyuria Index [NPI]) occurring at night (or when the patient is sleeping). Nocturnal polyuria is most often diagnosed using the Nocturnal Polyuria Index >0.33) (17).

However, it should be noted that there are some limitations to the use of a frequency-volume chart or bladder diary. There is no evidence that the results of these charts provide a valid prediction of the type of urinary incontinence experienced by each patient (18,19). Some patients may have difficulty completing the diary in a reliable, meaningful or timely fashion, especially when increasing the complexity or the amount of time (days) required to complete the diary (20). The bladder diary may not yield information about the evolution of incontinence episodes that occur less frequently than once per day (20,21). Furthermore, for therapy monitoring, the use of the pre- and post-treatment voiding diary for 3-7 days is not always acceptable to by patients. However, previous research has identified several challenges with using bladder diaries in clinical trials, including inaccurate completion and a bladder self-monitoring effect (22). Alternative tools have been introduced for the follow up of patients with OAB. Chapple et al have validated an overactive bladder assessment tool (OAB-BAT) in multiple stages with input from OAB patients. The eight-item OAB- BAT v3.0 is a psychometrically sound measure for determining OAB patients' perspectives on symptom bother and the impacts of their condition. It could complement the assessment made with the voiding diary or even replace it (23).

Several studies have compared patients' preference for, and the accuracy of, electronic and paper voiding diaries in voiding dysfunction (24-28), but the utility of electronic diaries has not been fully clarified yet.

Due to intraindividual variation, FVC recordings differ on different days. The more days recorded, the more likely it will be that the recordings will capture the whole spectrum of variation. Few data have been reported on the intraindividual variation of FVC parameters (29-31). However, these variations have been used in statistical analysis leading to statements on the optimal duration of FVCs. Recommendations for diary duration vary considerably including 24 hours, 3 days or 7 days; this inconsistency is partially explained by differences among study populations, based on diagnosis, age, sex, and geography, and by differences in methods of analysis and in interpretation of the results.

In a mini-review on the reliability of FVCs, it was argued that using FVCs of 3 days or longer might be the most acceptable policy, but there was no evidence that compliance rates had been accounted for in the studies reviewed (32). The authors concluded that reliability was overestimated in some reports. Another review by Bright et al focusing on the validation of FVCs summarised that excessive duration reduces patient compliance, but also a short duration may produce unreliable measurements (19). Van Haarst and Bosch found that with each additional day, FVCs showed a decrease in compliance but an increase in reliability (33). At day 3, a reliability of 80% was achieved for all FVC parameters, but compliance dropped to 73%. Beyond 5 days, the yield of additional recorded days was limited. They therefore advocated an FVC duration of 3 days but

added that the duration could be shortened or extended depending on the goal of the FVC.

The choice of diary duration may not only be based upon better validity or reliability but also on the possible behavioural therapeutic effect of keeping a diary (34). Recently, Bright et al have described the development of the first validated bladder diary for the assessment of LUTS in both male and female adults, using a psychometric validation methodology. The resulting bladder diary is recommended for use over a 3-day period and has been accepted as the ICIQ bladder diary. Urinary incontinence is assessed by the recording of pad use. The ICIQ bladder diary has been validated using a British English-speaking population and as with all such tools, will require cultural adaptation and linguistic validation for other languages using the formal ICIQ protocol [35,36].

In conclusion, voiding diaries generally give reliable data on lower urinary tract function. However, there remains a lack of consensus on diary duration and how well diary data correlate with some symptoms.

1.2.1. Bladder Diary Recommendations

1. Ask patients with urinary incontinence to complete a bladder diary to evaluate co-existing storage and voiding dysfunction. A bladder diary is recommended in order to document and communicate both objective information and to objectify observations by the patient during the diary period. Although never completely diagnostic, diary patterns may characterise normal and abnormal states (Level 2, Grade A).
2. A 1-day frequency volume chart (FVC) which includes the first morning void on the following day is a reasonable tool to gain insight into voiding habits during normal daily routine. A 3-day FVC or diary is recommended for accurate assessment of LUTS and for confirming a consistent clinical pattern in day-to-day practice. For atypical clinical patterns or clinical research, a 7-day diary might be recommended, although it should be realized that compliance decreases. Most pharmacological studies now employ a 3-day diary as a standard to optimize patient compliance (Level 2, Grade A).
3. The validated ICIQ bladder diary is recommended for use over a 3-d period. The inclusion of the diary in research studies is recommended and will provide ongoing evidence of validation, as well as the external validity of the diary (Level 3,Grade A).

1.2.2. Future Research

a) The ideal duration of a bladder diary based on the utility of the diary for diagnosis, the selection of therapy, and improving the outcomes of therapy requires further investigation.

b) The utility of paper versus electronic methods of recording voiding patterns requires further research.

c) The ICIQ bladder diary should be culturally and linguistically validated for as many other languages as well as British English and be included in research studies for further validation as well as determining external validity.

In conclusion, voiding diaries generally give reliable data on lower urinary tract function. However, there remains a lack of consensus on diary duration and how well diary data correlate with some symptoms.

1.3. Urgency scale

According to the IUGA/ICS definition urgency is ": Complaint of a sudden, compelling desire to pass urine which is difficult to defer" (2). However, in clinical practice, urgency is often accompanied by other symptoms. Urgency, with or without urgency incontinence, usually with frequency and nocturia, is the cornerstone symptom of overactive bladder syndrome (OAB) (37); while together with bladder pain, frequency and urgency are typical symptoms of interstitial cystitis or bladder pain syndrome (38). However, sometimes patients with lower urinary tract symptoms may not be able to differentiate between normal urge (desire) to void and urgency (difficult to postpone) (4). Furthermore, with history only, it may be difficult to define the severity, duration and frequency of urgency (39,40). Thus, it is important to have appropriate tools that allow accurate diagnosis, to establish tailored therapy and to assess the effectiveness of treatment. Severity questionnaires and scales have been developed specifically to assess urinary urgency, to help the patient to define the symptoms and severity and the physician to establish the therapy and its effects. Table 2 and table 3 show the validated questionnaires and scales respectively, used to assess the urinary urgency.

Table 2: Questionnaires To Assess Urgency

Questionnaire	Aim of tool	Items	Population sample	Reliability	Content Validity	Construct Validity	Concurrent Validity	Discriminant Validity	Respon-siveness	GR
UPS (Urgency Perception Score) [35]	Grading the urgency to void and assessing the reason why individuals usually void	5	Men Women OAB + LUTS LUTS (without urgency) Healthy	Yes	Yes	Yes		Yes		B
UQ (Urgency Questionnaire) [36]	Severity of urgency and urge incon-tinence Impact of urgency and urge inconti-nence on the quality of life Discomfort of urgency with VAS scale	15 + 10 VAS	Women OAB	Yes	yes	Yes	Yes	Yes	Yes	A
USIQ-QoL (Urgency Severity and Life Impact Questionnaire-Quali-ty of life) [37]	Impact of urgency on the quality of life	8	Women Men OAB	Yes	Yes	Yes		Yes		B
USIQ-S (Urgency Severity and Life Impact Questionnaire: Se-verity Symptsoms QQQ) [37]	Severity of urgency	5	Women Men OAB	Yes	Yes	Yes		Yes		B
UU Scale [38]	Monitoring efficacy treatment	10	Women Man • OAB	Yes		Yes			Yes	A

Table 3: Scales to assess the urinary urgency (39-43)

Scale	Aim of tool	Degrees of urgency	Population sample	Reliability Test-re test	Content validity	Construct Validity	Concurrent Validity	Discriminant Validity	Respon-siveness	GR
UPS (Urgency Perception scale) [39]	Severity of urgency	3	Men Women OAB		Yes	Yes	Yes		Yes	B
IUSS (Indevus urgency Severity Scale) [40]	Severity of urgency per void The ability to complete actives	4	Men Women OAB with urge Incontinence	Yes	Yes	Yes	Yes	Yes	Yes	A

Scale	Aim of tool	Degrees of urgency	Population sample	Reliability Test-re test	Content validity	Construct Validity	Concurrent Validity	Discriminant Validity	Respon-siveness	GR
PPIUS (Patients' perception of intensity of urgency scale) [41]	Severity of urgency Urgency incontinence	4	Men Women Urgency Urge incontinence	Yes	Yes			Yes	Yes	A
USS (Urinary Sensation Scale) [42]	Severity of urgency	5	Men OAB+LUTS Women OAB		Yes	Yes	Yes	Yes	Yes	A
URS(Urgency Rating Scale) [43]	Severity of urgency	5	Men	Na	Na	Na	Na	Na		C

1.4. Urinalysis

A screening urinalysis is generally recommended as part of the testing for urinary incontinence. Although in many instances a reagent strip (dipstick) urinalysis provides the necessary information, a complete urinalysis includes both chemical and microscopic analysis (49). In relation to urinary incontinence, dipstick urinalysis is not a diagnostic test. Dipstick urinalysis may indicate proteinuria, haematuria, glycosuria, pyuria and/or bacteriuria requiring further assessment (50).

Even in the absence of controlled studies, there is general consensus that the benefits of urinalysis clearly outweigh the costs involved, although the use of urinalysis should always be associated with prognostic significance (51).

The importance of urinalysis in the basic assessment of patients with urinary incontinence and lower urinary tract symptoms (LUTS) is not dependent on gender, age or aetiology. Indeed, it has been recommended in the evaluation of geriatric patients including nursing home residents who are incontinent (52), in peri and postmenopausal women (53), and in older women reporting urinary incontinence (54).

Urine dipstick testing is a useful adjunct to clinical evaluation in patients in whom urinary symptoms are suspected to be due to (UTI). Urinalysis negative for nitrite and leucocyte esterase may exclude bacteriuria in women with lower urinary tract symptoms (LUTS) (55), and should be included, with urine culture when necessary, in the evaluation of all patients with LUTS.

Pyuria and bacteriuria, detected from urinary dipstick leukocyte esterase and nitrite tests respectively, are important signs of urinary tract infection. The specificity and sensitivity of these latter tests for UTI is increased when used together compared to either individual test (56).

A positive dipstick urinalysis will prompt formal urine microscopy and culture to detect UTI prior to antibiotic treatment and/or the use of additional tests such as endoscopy and urinary tract imaging. Urinalysis negative for nitrite and leucocyte esterase reliably excludes UTI in people with UI (55) and should be included, with urine culture when necessary, in the evaluation of all patients with UI (Level 4, Grade A, based on expert opinion). Urinary incontinence may occur during symptomatic UTI (level 3) (57) and existing UI may worsen during UTI (level 3) (58).

UTI can cause irritative voiding symptoms and urgency incontinence. UTI can cause or contribute to urinary incontinence disorders in several ways. Local inflammation can serve as a bladder irritant, causing uninhibited bladder contractions. Endotoxins produced by some bacterial strains can have an alpha-blocking effect on the urethral sphincter, thereby lowering intraurethral pressures.

The clinical relevance of asymptomatic bacteriuria (without pyuria) and pyuria (without bacteriuria) in the elderly is controversial as the rate and severity of UI was unchanged after eradication of asymptomatic bacteriuria in nursing home residents (level 2; Grade B) (59). In this context, it has been observed that clinically significant urine samples can even be obtained from disposable diapers in elderly incontinent women (60).

Haematuria can indicate important pathology such as urothelial carcinoma in situ, leading to lower urinary tract storage symptoms including incontinence (61).

Glycosuria is relevant, as a potential indicator of diabetes mellitus. This can cause symptoms via several mechanisms including polyuria secondary to osmotic diuresis. Diabetic peripheral autonomic neuropathy affecting bladder innervation may be associated with impaired bladder emptying. The clinician should note that a patient does not generally demonstrate glucose into the urine until the blood glycaemia is >180 mg/dl. Consequently, a dipstick urinalysis may fail to reveal intermittently high sugars or mild diabetics. If diabetes is suspected, then a random or fasting blood sugar is preferred (62,63,64).

For many years, urine has been considered sterile, grounded on the lack of bacteria cultivated in urine samples using standard culture protocols (65). Recently, bacterial commu-

nities (microbiota) have been discovered in the female bladder and consequently, the sterile urine paradigm is no longer valid. Emerging evidence suggests that the female urinary microbiota may contribute to symptoms of urinary incontinence in women (66).

At this time, clinical use of improved culture techniques that provide additional microbial information may be of particular relevance for patients with persisting LUTS, whose standard urine cultures show no growth. While improvements in urine culture techniques offer an alternative that can be implemented immediately in most clinical laboratories, sequencing is not practical for most current clinical settings. To investigate urinary microbiota, many research groups have performed DNA sequencing analysis, in particular, 16S rRNA gene sequencing (67).

Analysis by 16S rRNA sequence and expanded quantitative urine culture provided evidence for the presence of live bacteria in urine, non-detectable by standard culture protocols. Moreover, differences in the urinary microbiota between healthy individuals and patients with LUT dysfunction were demonstrated. In the near future, urologists must consider urinary dysbiosis as a possible cause of different functional LUT disorders, with potential clinical implications in their diagnosis and treatment (67).

1.4.1. Urinalysis -Recommendation

1. Perform urinalysis as a part of the initial assessment of a patient LUTS (Level 4- Grade D).
2. Dipstick test including haematuria, glucose, leukocyte esterase and nitrite tests are recommended (Level 4 - Grade D).
3. Additional tests available on dipstick strips, such a protein, bilirubin, ketones and pH, are not essential in LUTS or incontinence context (Level 4 - Grade D).
4. Dipstick is not as accurate as urine culture, being specific for infection but not sensitive (Level 2 - Grade C).
5. Urinalysis negative for nitrite and leucocyte esterase may exclude bacteriuria in women with LUTS (Level 3, Grade C).
6. Urinary incontinence may be a symptom during a UTI, and LUTS may deteriorate during a UTI (Level 3- Grade C).
7. If a urinary tract infection is present with LUTS, reassess the patient after treatment (Level 3, Grade C). The presence of a UTI worsens existing symptoms of UI (Level 3, Grade C).
8. Do not routinely treat asymptomatic bacteriuria in elderly patients to improve urinary incontinence (Level 1; Grade A). Elderly nursing home patients with UI do not benefit from treatment of asymptomatic bacteriuria (Level 2, Grade A).

1.4.2. Future Research

Emerging evidence challenges the long-held paradigm that the healthy bladder is sterile and evidence indicates that the human urinary tract contains microbial communities; however, the role of these communities in urinary health remains to be elucidated (68). Further research to clarify the role of urinary microbiota in maintaining urinary health and inducing LUT dysfunction will help refine treatment algorithms and prevention strategies (67).

Certain microbes have characteristics that protect against uropathogens by producing antibiotics, antimicrobial peptides, and/or other antimicrobial compounds that inhibit or kill other pathogenic microbes (69).

In addition, it is well known that the vaginal and gut microbiota are able to rapidly change microbial composition, and these changes may affect urinary microbiota. Finally, urinary microbiota-based biomarkers might represent new diagnostic, therapeutic, and prognostic tools for LUT functional disorders (67). New diagnostic tools are developing: expanded quantitative urine culture and 16S ribosomal RNA gene sequencing and could give allow a greater insight into many lower urinary tract disease including incontinence (70).

1.5. Post voiding residual in the female and male patient

Post-void residual (PVR) volume (also known as residual urine, bladder residual) is the amount of urine that remains in the bladder after representative voiding. It indicates poor voiding efficiency, which may result from a number of contributing factors. It is important because it may worsen symptoms and, more rarely, may be associated with upper urinary tract dilatation and renal insufficiency. Both bladder outlet obstruction and low bladder contractility contribute to the development of PVR. PVR measurement can be accomplished within a few minutes of voiding either by catheterisation or by calculation of bladder volume using a portable ultrasound scanner.

It is difficult to determine the value of post-void residual determination in the initial assessment of urinary incontinence since most studies with data on PVR have not been performed in patients with UI. However, the populations studied have included some women with UI, and incontinent patients with neurogenic bladder disease.

Several studies have compared volumes measured with portable ultrasound scanners versus catheterisation and found portable scanners to be 85-94% accurate (71-72). A study has imaged the bladder volume after catheterisation and found that the volume of urine remaining in the bladder after catheterisation accounted for most of the difference between the two measurements (71). Bimanual palpation cannot reliably estimate the post-void residual urine volume (73). Since PVR may vary, one measurement of PVR may not be sufficient (74). PVR should probably be measured several times to increase its reliability. In geriatric patients, Griffiths et al found a significant variability in PVR measurement depending on the time of the day, with the greatest volume occurring in the morning (75). A non-representative PVR is particularly common if the patient's bladder is not full enough to yield an urge to void. Special consideration is required in male patients with incontinence and bladder outlet obstruction, in incontinent neurogenic patients who may demonstrate combined disorders of storage and emptying (76), and preoperatively in female patients being considered for incontinence surgery.

An increased PVR alone is not necessarily a problem, but if combined with high pressures it can lead to upper tract problems. If related to UTI's, PVR needs to be treated since UTI's cannot be eradicated in the presence of an infected residual. A significant PVR also decreases the functional bladder capacity and thus contributes to urgency/frequency, urgency incontinence and nocturia. However, a Scandinavian study in nursing home residents found that an elevated PVR was not associated with bacteriuria and incontinence (77). Since recurrent UTI's, due to elevated PVR, can be associated with urinary incontinence it remains necessary to measure PVR in incontinent patients with UTI.

Review of the literature fails to show an evidence-based specific maximum PVR that is considered normal, nor is there a minimal PVR that is considered abnormal. The amount of residual urine that precludes treatment by various therapies has also not been determined. The AHCPR guidelines state that, in general, a PVR less than 50 ml is considered adequate bladder emptying and over 200 ml is considered inadequate emptying (expert opinion of the panel members) (78).

"Normal values" of PVR have been determined in several groups of non-incontinent and incontinent women. Gehrich et al studied 96 women (mean age 60 ± 11 yrs) that were seen in a well-women clinic. These women had no history of incontinence, retention, symptomatic prolapse or neurologic disorders. Most (97%) had a minor (asymptomatic) degree of prolapse, 80% were post-menopausal and 30% had had a hysterectomy. The median PVR was 19 ml (range 0-145 ml; mean 24 ± 29 ml); only 5% had PVR > 100 ml. Only, age > 65 yrs was associated with higher PVR. This study gives some indication of what might be considered normal or relatively normal (79).

Tseng et al studied 107 women with urodynamic stress incontinence. They found a mean PVR of 62.5 ml by bladder scan and 38.5 ml by catheterization. Only 15.9% had a PVR greater than 100 ml. The PVR determined by bladder scan offered a sensitivity of 64.7% and a specificity of 94.3% in detecting PVR greater than 100 ml (80). Haylen et al studying women with lower urinary tract dysfunction found that 81% had a PVR of less than 30 ml (81). Fitzgerald et al studied women with urgency, frequency and urge incontinence: 10% had an elevated PVR of > 100ml. In these women with OAB, the following independent risk factors of increased PVR were found: vaginal prolapse, symptoms of voiding difficulty and absence of stress-incontinence (82). Lukacz et al found that only 11% of women with pelvic floor disorders had an elevated PVR (83). Wu and Baguley studied 319 consecutive patients (196 women, 123 men) in a subacute general, but predominantly geriatric, rehabilitation unit. 22 had been admitted with a catheter and were excluded. Of the 297 "asymptomatic" patients, 21.5% had PVR volumes of 150 ml or more. Patients with elevated PVR (> 150 ml) were significantly more likely to have a urinary tract infection at admission and have urinary incontinence on discharge (84).

Milleman et al retrospectively reviewed 201 women (mean age 55; range 20-90) who presented with complaints of urinary frequency, urgency and /or urge incontinence. 19% had an elevated PVR of more than 100 ml (mean 211 ml; range 100-997 ml). On multivariate analysis the following independent predictors of raised PVR were identified: age > 55 yrs [OR 3.71], prior incontinence surgery [OR 4.32], a history of multiple sclerosis [OR 15.32] and pelvic organ prolapse grade 2 or greater [OR 3.61] (85).

In summary, an elevated PVR > 100 ml was found in 5% of women visiting a well-women clinic, in 10-19% of women with OAB, in 11% of women with pelvic floor disorders and in 15.9% of women with urodynamic SUI. Overall, incontinent women have a slightly higher risk of elevated PVR compared to asymptomatic subjects. Does a significant PVR have an impact on the outcome of treatment in patients with incontinence? Nager et al studied the predictive value of urodynamic measures on stress continence outcomes after surgery for stress urinary incontinence. They found that urodynamic measures do not predict outcomes. However, since women with PVR > 150 ml were excluded in this study, one can only conclude that PVR volumes < 150 ml did not have an adverse impact on stress continence outcomes (86).

Since there is no consensus on what constitutes a significant PVR in women; therefore, the Panel suggests the additional use of Bladder voiding efficiency (BVE) which is the proportion of the total bladder volume that is voided by the patient. The BVE can be defined as a percentage: BVE = (voided volume/[VV]+PVR) x 100. This may be a more reliable parameter to evaluate poor voiding (87)

A PVR measurement is recommended in men with symptoms suggestive of bladder outlet obstruction. It is a well know clinical principle that chronic urinary retention can be associated with overflow incontinence [ischuria paradoxa]. Apart from this there are unfortunately insufficient data on the role of PVR and its significance in male urinary incontinence. Therefore, there are insufficient data to draw conclusions about the association of PVR and urinary incontinence in men as well as the association of PVR and the outcome of incontinence treatment in men.

In the geriatric patient, a PVR should always be measured since it decreases functional bladder capacity and contributes to urgency/frequency, urgency incontinence and nocturia. PVR should probably be measured several times to increase its reliability. In elderly patients, Griffiths et al found a significant variability in PVR measurement depending on the time of the day; the greatest volume occurred in the morning (5). Counter-intuitively, a Scandinavian study in nursing home residents was unable to show an association between an elevated PVR and bacteriuria and incontinence (77).

1.5.1. Recommendations

1. Varying degrees of decreased bladder emptying, or urinary retention, may be a cause of LUTS that are associated with symptoms of decreased urinary storage. The decision to perform a PVR in disease specific sub-groups of incontinent patients should be based on an association of the condition with poor bladder emptying, whereas in individual patients this decision may be based on symptoms or physical findings (Level 2, Grade B).
2. Female patients who present with storage specific symptoms, with normal sensation and no complaints of decreased bladder emptying, and no anatomical, neurological, organ-specific, or comorbid risk factors for retention may be assessed for bladder emptying by history and physical examination alone (Level 4, Grade B).
3. Due to the increased possibility of bladder outlet obstruction due to prostatic obstruction in the male patient, the threshold for investigating residual urine in the male is significantly lower (Level 4,Grade D).
4. A PVR should be performed in incontinent patients when decreased bladder emptying is suspected, especially if treatments that decrease bladder contractility or increase outlet resistance are being considered (Level 4,Grade D).
5. Non-invasive ultrasound measurement of PVR is as accurate as measurement by catheterization and is therefore the preferred method (Level 4,Grade A)
6. A palpable bladder on physical examination is an indication for referral to a specialist (Level 3, Grade D)

1.5.2. Future Research

1. Development of more specific indications for PVR testing for diagnosis and prior to instituting therapy based on history, physical examination and disease specific findings.
2. Further development of low cost, minimally invasive, and accurate means of measurement of PVR that do not require catheterisation.

V. SPECIFIC POPULATIONS: EVALUATION OF THE FEMALE PATIENT

1. ESTABLISHING THE TYPE OF URINARY INCONTINENCE IN WOMEN

The aims of the assessment of women with urinary incontinence are the documentation and characterisation of type of incontinence, its timing and its severity, the differential diagnosis, prognosis evaluation and planning of treatment (88). The classification of subjective diagnosis of urinary incontinence into stress, urgency and mixed incontinence is basically clinical. Generalist physicians may identify a woman with incontinence through the review of systems during a routine visit or the patient may initiate discussion about incontinence problems. If a woman reports leaking urine, she is incontinent, and the symptoms should not be ignored. Assessment should include history, symptom assessment, and physical examination. A careful urological history may be helpful to make a first subjective differentiation between the types of incontinence. In fact, as shown in Holroyd-Leduc's meta-analysis (18), simple questions to diagnose stress or urgency urinary incontinence have high reliability in women, with the percent agreement between repeated questioning estimated at 90% for stress, urgency and mixed urinary incontinence sub-types (18).

Further questioning on the frequency, severity of leakage and degree of bother, is essential for planning treatment and counselling of the women. The leakage should also be quantified if possible, by using voiding diaries (89, 90), pad tests (the 1-hour pad test the most used) (91), and evaluation of the number of pads used per day. Finally, a general history and medication review are helpful to classify the different types of incontinence into uncomplicated and complicated. The definition of complicated or uncomplicated SUI is not widely agreed. According to FIGO's consensus uncomplicated stress urinary incontinence (SUI) is UI without further storage symptoms, absence of voiding symptoms and without history of recurrent urinary tract infections (RUTI), no prior extensive pelvic surgery or prior surgery for stress incontinence and no medical conditions that can affect the lower urinary tract (92)). Complicated SUI does not fulfil the uncomplicated SUI criteria (92).

In a multicentre single nation database (93) SUI has been defined as uncomplicated when the presenting history of SUI has been present for at least 3 months, the post-void residual urine volume is < 150 ml, urinalysis or urine culture is negative and clinical assessment of urethral mobility, with an expressed desire for surgery for SUI, and a positive provocative stress test. Conversely complicated SUI has been defined as incontinence in women with previous surgery for incontinence, history of pelvic irradiation, pelvic surgery within the previous 3 months, and anterior or apical pelvic organ prolapse (POP) of 1 cm or more distal to the hymen (88). Nevertheless, several studies (12, 93) have shown that patient history alone is not completely accurate in determining the type of incontinence. Symptom assessment by validated questionnaires can provide a very helpful complement to the patient history, to assess the impact of urinary incontinence on quality of life, and the symptoms (94-98). In the literature there are no studies that prove the usefulness of physical examination to typify the urinary incontinence. However, it is recommended to identify risk factors as well as significant associated or underlying pathology, such as significant prolapse, obstruction, neurological disease and malignancy (18).

2. GENERAL MEDICAL HISTORY

The history should include the nature and impact of incontinence symptoms, gynaecological and obstetric history, relevant coexisting diseases, current medications, functional status, review of environmental factors and lifestyle factors, previous treatment history, and current goals and expectations of treatment. In fact, the main goal of the general medical history in women with urinary incontinence is trying to identify all comorbidities that could initiate or worsen UI or even those which could negatively impact treatment success rates. The main factors associated with urinary incontinence are: obesity (99,100), diabetes and other metabolic conditions (101), neuropsychiatric disorders (102, 103,104), occupations involving heavy lifting, smoking, previous pelvic surgeries and constipation (105-106).

Neurological diseases, pelvic neoplasms (malignant or benign) and radiation therapy can also lead to incontinence. Therefore, a careful surgical history should be taken, and specific attention should be given to pain and other sensory disturbances, especially on sacral nerve dermatomes, which could imply a neurologic disease or an intrapelvic entrapment.

Pelvic pain can also be associated with apical support defects (107), endometriosis (108) or pelvic congestion syndrome (109). The latter two, can be associated with neurogenic urgency/urge-incontinence, when endometriotic lesions and/or varicosities entrap sacral nerves or involve the inferior hypogastric plexus (110,111).

Anorectal dysfunction, such as anal incontinence and obstructed defecation must also be carefully assessed and treated simultaneously, as these symptoms are strongly associated with urinary incontinence and share a common aetiology – pelvic support defect.

A careful surgical history must be taken, especially for pelvic reconstructive procedures, radical treatment of pelvic malignancies or endometriosis, as such procedures are associated with a high risk of intrapelvic nerve damage (112,113,114,115,116). Understanding the details of previous incontinence procedures is also important to plan treatment of recurrent/de novo/persistent SUI and/or urgency incontinence (117).

3. SYMPTOM ASSESSMENT

Determining if urine is involuntarily lost with effort or exertion, or on coughing or sneezing, is commonly used to help identify stress incontinence (118)

For example, a woman can be asked, "Do you lose urine during sudden physical exertion, lifting, coughing, or sneezing?". To diagnose urgency incontinence, the women is asked about the association between involuntary urinary leakage and feelings of urinary urgency. An example of such a question is "Do you experience such a strong and sudden urge to void that you leak before reaching the toilet?" (119).

As classification of Urinary incontinence is clinical, a careful symptom assessment is mandatory, and it is particularly important to plan the appropriate treatment. Furthermore, it is important to quantify the degree of leakage before and after therapy to evaluate the impact of the disease on quality of life, and to identify patients with

complicated incontinence that need to be referred for specialised management (92). To achieve these objectives there are several tools including history and clinical assessment together with validated questionnaires, voiding diaries and pad tests. Many validated questionnaires have been developed to assist in the evaluation of urinary symptoms and to help in diagnosing the type of urinary incontinence (94-98). They may be used in combination with history and clinical examination. The International Consultation on Incontinence (ICI) has developed an ICI questionnaire (ICIQ) to assess pelvic floor function in both clinical practice and research settings (120,121). It includes many modules about both female and male urinary symptoms or pelvic dysfunctions in particular urinary incontinence (ICIQ-UI). It has been shown that the short form (ICIQ-SF) correlates well with the 1-hour and 24-hour pad test for evaluation of the severity of SUI (122). The severity of SUI seems to be correlated with Intrinsic sphincter deficiency, although the diagnosis is possible only by urodynamic study (Urodynamic Valsalva leak point pressure (VLPP) < 60 cm water is believed to be diagnostic) (123).

The Modified Gaudenz-Incontinence questionnaire increases the likelihood of accurately diagnosing both stress and urgency incontinence, while the Bladder Instability Discrimination Index (96) and Versi's questionnaire (124), although useful to diagnose urgency and stress incontinence, are both complex and sometimes not easily used in the practical clinical setting. The patient-completed Questionnaire for Urinary Incontinence Diagnosis contains 6 questions, of which 3 are intended to predict stress incontinence and 3 are intended to predict urgency incontinence (125). It appears to increase the likelihood of correctly diagnosing urgency incontinence (positive LR, 3.7; 95% CI, 1.6-9.0; negative LR, 0.27; 95% CI, 0.17-0.42), but is not as helpful in the diagnosis of stress incontinence (positive LR, 2.8; 95% CI, 1.6-4.9; negative LR, 0.21; 95% CI, 0.12-0.37) (18). The Urogenital Distress Inventory, that is a widely used symptom tool, is a questionnaire helpful to assess LUTS bother, including incontinence, in women (126). The Questionnaire for Urinary Incontinence Diagnosis is a reliable 6-item questionnaire able to diagnose stress urinary incontinence and urgency urinary incontinence in a referral urogynaecology patient population with accuracy (98). Overactive bladder symptom scores are also very useful for women with storage symptoms including urgency incontinence (37) (39-47) (127).

4. PHYSICAL EXAMINATION (FEMALE)

The main objective of physical examination is to detect the signs, defined as any abnormality indicative of disease or a health problem, discoverable on examination of the patient; an objective indication of disease; or a health problem. No studies were found to support evidence that clinical examination improves care for diagnosing the type of urinary incontinence (UI) in women. Nonetheless, there is a wide consensus recommending clinical examination as an important part of assessment of women with UI, including: abdominal, neurological, gynaecological and pelvic examination with the purpose of detecting associated or underlying pathology that can explain the lower urinary tract symptoms (LUTS). Height and weight should be recorded so that the body mass index can be calculated (Kg/m2) as an important risk factor for UI in women of all ages (125,128, 129,130).

a) Abdominal examination. Observation of the abdomen may yield evidence of scars from previous surgeries or abdominal stretchmark. Increased abdominal stretchmarks may be found in association with other markers of abnormal collagen metabolism and are more likely in patients with prolapse and stress incontinence (131,132).

Bladder fullness or retention may be identified by abdominal palpation or by suprapubic percussion or bimanual vaginal examination. In one study designed to look at the clinical utility of basic assessment in elderly women, palpable enlargement indicated a post-void residual volume of at least 300ml (132). Other abdominal masses or distension can be also detected by abdominal examination. Tenderness or mass palpation in the renal area must be excluded by examination.

b) Neurological examination. Neurological signs related to S2-4 can suggest a possible neurogenic lower urinary tract or pelvic floor dysfunction. Saddle anaesthesia will occur with lesions affecting S2-S4. Assessment of gait, abduction and dorsiflexion of the toes (S3) and sensory innervation to the labia minora (L1-L2), sole and lateral aspect of the foot (S1), posterior aspects of the thigh (S2), cutaneous sacral reflexes, bulbocavernosus and anal reflexes are additional features of the neurological exam that may be assessed. A rectal examination will provide a subjective assessment of resting and voluntary anal tone (S2-S4). For patients with possible neurogenic lower urinary tract dysfunction, a more extensive neurological examination is indicated. In the elderly, full cognitive and mobility assessments are also recommended. An evaluation of hand dexterity should be performed when self-catheterization is being considered as a treatment option for incontinence associated with chronic urinary retention.

c) c)Gynaecological examination (vulva and vagina). At present there are few scientific data documenting the parameters of a normal pelvic examination in women of various ages and with various obstetric histories. The components of the examination have not been universally agreed upon. Gynaecological examination should include: inspection of the vulva, perineum and vagina, as well as vaginal palpation, with the evaluation of pelvic floor muscle resting tone, muscle mass and defects, ability to contract and relax. Full list of PFM assessment has been recently published and all medical practitioners should strive to use a standard assessment (133). The location of any vaginal pain should be noted and any tenderness over the course of the pudendal nerve. Bimanual pelvic examination is also part of gynaecological examination, with the assessment of the size, location, and mobility of the uterus, the adnexal structures. Palpation of any pelvic mass or unusual tenderness is possible by vaginal examination together with suprapubic palpation.

Vulval inspection allows a description of the skin and the presence of any abnormal anatomical features (atrophic changes, scars, erythema of the vulva, lichen sclerosis, cysts, other tumours). With the inspection of the external genitalia, we can also find an urethral caruncle (a small, soft, smooth friable red outgrowth along the edge of the urethra) or urethral mucosal prolapse, a small eversion of the urethral urothelium generally involving the posterior lip.

Another important part is the observation of the perineal movements when the patient is asked to contract, cough or bear down. This is a way to evaluate the pelvic floor muscles function. We can observe a perineal elevation as the inward (cephalad) movement of the vulva, perineum, and anus (expected during voluntary PFM contraction) and a perineal descent as an outward (caudal) movement of the vulva, perineum, and anus (small descent expected during bearing down). These movements may also be palpated

during vaginal and rectal PFM assessments. During cough the perineum should show no movement, or a ventral movement may occur due of the contraction of the pelvic floor muscles; a downward movement indicates a weak pelvic floor. Decreased ability to relax the PFM may also be associated with PFM disorders and may be related to UI or pain conditions. Due to the inherent subjective nature of visual and digital assessment, many of these characteristics and properties of the PFM are more accurately assessed using investigations and referral to a pelvic floor muscle specialist would be advised.

With the vaginal examination we obtain information about of the vaginal length and mobility, presence of scarring and/or pain, and level of oestrogenisation.

Vulval and vaginal atrophy (VVA) is a common condition, resulting from the effect of oestrogen deficiency on the female genitourinary tract including vagina, labia, urethra and bladder. A consensus conference panel introduced a new terminology for vulvovaginal atrophy: Genitourinary syndrome of menopause (GSM) (134). This syndrome includes symptoms of dryness, burning, and irritation and sexual symptoms of pain and dryness. Urinary symptoms and conditions of dysuria, urgency, and recurrent urinary tract infections (UTIs) are associated with vaginal atrophy (135). Pelvic examination helps to exclude other vulvovaginal conditions that can cause similar symptoms including vulvovaginal dermatoses, infection, or cancer.

Examination of the external genitalia shows a reduced mons pubis and labia majora bulk, reduced labia minora with a narrow introitus, a pale vestibular tissue and an erythema of the urethral meatus. Urethral caruncle, a benign outgrowth of inflammatory tissue arising from the posterior urethral meatus, is common finding related to hypoestrogenism. Vaginal examination shows an atrophic epithelium, shiny and dry with a loss of rugation. With progression of GSM, severe sings of atrophy can be observed as the attenuation of the vaginal fornices and also minimal blunt trauma from the speculum may result in petechiae or bleeding due to epithelial thinning and friability. With GSM, vaginal pH is typically greater than 5.0. History and examination are essential to make a correct diagnosis of GSM and the main goal of its treatment is to alleviate symptoms. Once other causes of these symptoms have been excluded, treatment can be approached in a stepwise fashion based on symptom severity: non-hormonal in women with mild symptoms and with more severe symptomatology hormonal therapies are indicated (low-dose vaginal oestrogens, vaginal DHEA inserts, and oral ospemifene) (136).

Urethral diverticulum presenting with a palpable suburethral mass, is another pathology that can be detected on vaginal examination. The most common finding is a tender anterior vaginal wall mass and if the diverticulum communicates with the urethra, it may be possible to express a purulent exudate from the urethra. Occasionally, a stone may develop within the diverticulum. Many patients with urethral diverticula are asymptomatic and need no treatment. Symptomatic patients report swelling of the urethra, recurrent cystitis, dyspareunia, urinary incontinence, urinary dribbling after passing urine and voiding difficulties (137-139). In a large cohort of women having urethral diverticulum excision, 29% had urodynamic stress urinary incontinence (USUI)at presentation and 38% had postoperative USUI (140).

d) d)Anorectal examination. The patient can be in left lateral position with hips flexed or in dorsal lithotomy. Digital rectal examination allows assessment of resting anal sphincter (AS) tone and voluntary squeeze. Strength can be classified as good or poor, in the absence of any quantitative assessment. Ano-rectal abnormalities can be found by a combination of inspection and digital examination. Painful examination may be associated with haemorrhoids, anal fissure, infection or pilonidal abscess, rectovaginal or anocutaneous fistula or tumour; and may confirm presence or absence of faecal impaction. Anal sphincter tear may be recognized as a palpable AS gap due to a previous obstetric or surgical damage (141).

e) Specialised test for diagnosis of UI in Women

Urinary incontinence as a sign, is the observation of involuntary loss of urine on examination, this may be urethral or extra-urethral (1). Urgency urinary incontinence is the observation of involuntary leakage from the urethra synchronous with the sensation of a sudden, compelling desire to void that is difficult to defer. The observation of leakage through the vaginal it is an extra-urethral incontinence (observation of urine leakage through channels other than the urethral meatus, e.g., fistula). Stress urinary incontinence (clinical stress leakage) is the observation of involuntary leakage from the urethra synchronous with effort or physical exertion, or on sneezing or coughing (1). Stress incontinence observed only after the co-existent prolapse reduction, is a sign of occult or latent stress incontinence (2).

Three special manoeuvres can be performed during the initial assessment of women with urinary incontinence: the stress test, the Q-tip test, and the pad test.

Stress Test. In women with the symptom of stress urinary incontinence (SUI), stress test it is important as an objective measure to confirm the diagnosis, particularly when surgical treatment is planned.

The stress test involves observation for urine loss when women, with a full bladder, are coughing forcefully or during a Valsalva manoeuvre. If the patient leaks with the onset of the cough and terminates with its cessation, the test is positive and likely to be a SUI. It is an easy test to perform in a single visit and the results are immediately available. The stress test performed with coughing appears to be a reliable test, reliability data are not available for tests performed using the Valsalva manoeuvre. This procedure can be performed while the patient is in the lithotomy position, if no leakage is observed, the test should be repeated in standing position (2). A negative supine cough stress test (CST) does not exclude incontinence. Rimstad et al. found that in the supine position only 49% of the women leaked during the stress test (142). Earlier studies have also found that the supine CST test has low sensitivity (143). A stress test is helpful for diagnosing the type of urinary incontinence. When SUI is suspected by the symptoms, the CST test is the most reliable clinical assessment for confirming the diagnosis (144). When compared with multichannel urodynamic studies, the CST test demonstrates good sensitivity and specificity for SUI (145-147). A detrusor contraction may occasionally cause leakage during a CST and we cannot exclude this possibility of a detrusor overactivity (DO).

Kulseng-Hanssen et al have demonstrated that only 5 of 100 stress and mixed incontinent women had a detrusor contraction simultaneously with stress leakage, and in none was DO the sole cause of leakage (148). Lagro-Janssen et al. noted that the presence of urge incontinence in the absence of leakage with coughing (negative CST) excluded the possibility of SUI and had a high specificity for the diagnosis of DO (149). Holroyd-Leduc et al. reviewed existing

evidence on the diagnostic accuracy of the stress test for stress urinary incontinence (18). Results from the meta-analysis revealed that a positive stress test increases the likelihood of a diagnosis of SUI (summary LR, 3.1; 95% CI, 1.7-5.5), while a negative test decreases the likelihood (summary LR, 0.36; 95% CI, 0.21-0.60).

The main limitations of this test are the variability of cough intensity and bladder volume. A working group of the International Continence Society (ICS) has developed an educational module, comprising a Powerpoint™ presentation and evidence base manuscript, to instruct on the performance, interpretation, and reporting of the CST in a standardized manner: the ICS-Uniform Cough Stress Test (ICS-UCST) (150).

Pad test. A pad test it is a non-invasive diagnostic tool, it involves the continuous wearing of continence pads for a set period of time. The objective of pad testing is to quantify the volume of urine lost by weighing a perineal pad before and after some type of leakage provocation. It is as an optional test for the evaluation of urinary incontinence, to distinguishing continent, from incontinent women, but it cannot contribute to distinguish the type of urinary incontinence (151,152). Holroyd-Leduc et al. reported that a positive pad test increases the likelihood of an incontinence problem (LR, 3.3; 95% CI, 2.0-5.4), while a negative pad test makes an incontinence problem much less likely (LR, 0.11; 95% CI, 0.05-0.27). (18). Price and Noblett have demonstrated that in women with symptoms of predominant stress urinary incontinence, the CST is more reliable than the pad test (147). Pad tests can be divided into short term tests, usually performed under standardized office conditions, and long-term tests, usually performed at home for 24–48 hours. Pad tests are generally performed with a full bladder or with a fixed known volume of saline instilled into the bladder before beginning the series of exercises.

The 1-hour pad test has been standardized by the International Continence Society (ICS-pad test) (152). This short test is appropriate in routine evaluation of patients during initial evaluation. However, it can be affected by many factors, if either the patient or physician have doubts about the accuracy of the initial test, evaluation should be extended by an additional hour or repeated. A 20-min test has been described by Hahn as a short-term pad test initially was carried out with water infusion into the bladder (153). Later it was demonstrated that when performed with a bladder volume of strong-desire to void, its sensitivity is better than the 1-hour pad test for women with stress urinary incontinence (154). The 24-hours test is more reproducible than a 1-hr test, but longer testing requires more preparation and a greater commitment on the part of the patient. A pad weight gain >1 g is considered positive for a 1-hour test, and a pad weight gain >4 g is positive for a 24-hour test. These values may increase in situations of increased perspiration (155). There is wide variation in the pad weight gain in incontinent women participating in clinical trials. Although some studies have found high test-retest correlations in pad tests (156,157) other studies have reported low inter-subject and intra-subject reliability (158,159). The correlation coefficient between total leakage during two long-term tests appears to exceed of standard 1-hour tests (160-161).

A pad test is a good instrument for evaluating the severity of urinary incontinence. However, it is not a perfect “gold standard” for UI severity. Pad test should always be interpreted in conjunction with standard self-assessment questionnaires including the bother index. In the analysis of 1-hour pad test, an increase of 1–10g is classified as representing mild incontinence, 11–50g moderate and >50g severe incontinence. Good correlation has been reported by Abdel-Fattah et al between the self-assessment questionnaires and the 1-hour pad test. The King’s Health Questionnaire showed a 96% sensitivity and 93% specificity of a 1-hour pad test in identifying incontinent patients (161). The good correlation between self-assessment questionnaires and 1-hour pad test, but not the 24-hour pad test supports the value in standardization. Good correlation with the 24-hour pad test and the International Consultation on Incontinence Questionnaire—Short Form (ICIQ-SF) has been documented (162). The values for 24-hour pad test are classified as follows: Mild (4–20g/24hour), moderate (21–74g/24h.), and severe (>75g/24hr) incontinence ([163). However, these values have to be considered with caution as they may change depending on the sample characteristics (age, proportion of women with more severe incontinence, etc). In another study comparing pad-weighing test with severity index (ISI), the mean pad-weighing (grams per 24 hours, 95% confidence intervals) , were : 7 for slight, 39 (26-51) for moderate, 102 (75-128) for severe, and 200 (131-268) for very severe UI. Spearman’s correlation coefficient for pad weighing results and severity index was 0.58 ($p < 0.01$), and bother increased significantly with increasing severity (164). A recently published study aimed to assess the correlation of a 20-min pad test, with the subjective urine leakage amount perceived by the patient and a moderate positive correlation was demonstrated (165). The main limitation of the pad test, as a diagnostic tool for UI, is the value for the cut off of a positive test and the inability to distinguish between types of incontinence. This limitation is especially important when this test is used as an outcome measure, when surgical treatment of stress urinary incontinence is evaluated, as these women can suffer “de novo” urgency urinary incontinence.

Q-tip test. Stress urinary incontinence (SUI) is classified based on urethral mobility. Urethral hypermobility is associated with greater surgical success after suburethral sling placement. Assessment of urethral mobility is an essential part of pelvic examination in women with symptoms of SUI, especially when surgery is the elected treatment. The Q-tip test has traditionally been used to assess mobility of the urethro-vesical junction. The test involves placement of a lubricated cotton swab or Q-tip in the urethra to the level of the bladder neck while the woman is in the lithotomy position. The degree of rotation of the free end of the swab is then measured while the woman performs a Valsalva manoeuvre. The free end should remain horizontal if no anatomical defect is present. If the free end moves above the horizontal, urethral hypermobility is suspected, this can occur in patients with stress urinary incontinence. A straining angle of 30º or greater relative to the horizontal during Valsalva or cough has been considered clinically relevant and defined as hypermobility (166,167). In a meta-analysis by Holroyd-Leduc et al. that examined the accuracy of the Q-tip test for diagnosing stress urinary incontinence, only two relevant studies met the inclusion criteria (18). Results of the analysis suggested that a positive Q-tip test does not accurately predict the diagnosis of stress urinary incontinence in women. Although the Q-tip test is a useful tool, it may be uncomfortable for many women due to the insertion of a rigid cotton tipped swab into the urethra. The identification of a visual examination tool to determine urethral hypermobility would help to eliminate this uncomfortable test. A study compared the diagnostic accuracy of Q-tip test with visual urethral mobility examination (VUME) and concludes that, VUME is a diagnostic alternative to Q-tip test for the initial assessment of urethral hypermobility when performed by an experienced provider and is preferred by women (168). With the intention of avoiding the insertion of the swab into the urethra, a study compared a vaginal swab test with the urethral Q-tip test for and demonstrated that a vaginal swab test with a cotton-tipped swab placed in the vagina 3 cm proximal to the external meatus in the midline at rest, is equivalent to the standard Q-tip

test in measuring urethral mobility with less discomfort for patients (169).

Another non-invasive method to identify women with urethral hypermobility is transperineal ultrasound with an excellent inter-rater reliability (170,171). This more specialised testing with pelvic floor ultrasound and other imaging techniques appears to be gradually replacing the Q-tip test for a more advanced assessment of bladder neck and urethral hypermobility, however they are limited by their cost, availability and requirement of special training.

5. PELVIC ASSESSMENT: PELVIC FLOOR STRENGTH AND PELVIC ORGAN PROLAPSE

5.1. Assessment of pelvic floor muscle strength

Pelvic floor muscles (PFM) play an important role in the continence and support of the pelvic organs. The tone, the strength with a voluntary contraction and their relaxation, should be evaluated during the initial pelvic examination of women with urinary incontinence and other pelvic floor dysfunctions. When assessing PFM strength, we ask the patient for voluntarily squeezing of the pelvic floor, while pulling upward and inward, consequently a maximum isometric voluntary contraction is generated. The IUGA/ICS Joint Report of Terminology for Female Pelvic Floor Dysfunction identifies visual inspection, digital palpation, EMG, dynamometry, and ultrasound as acceptable techniques for assessing PFM contraction and relaxation, although does not designate any method as a “gold standard” for quantifying PFM strength (172). The different PFM strength measures used clinically are moderately correlated (173).

Due to the location of the PFM inside the pelvis, the evaluation of the PFM function is limited when only observation is used. Vaginal palpation is accepted as subjective method to evaluate muscle function and is perhaps the most accessible and valid measure for PFM tone and strength (174,175). There is a number of published scales to assess PFM contractility measured although by digital vaginal palpation (176). Common scales include the ICS scale: absent, weak, normal, moderate, strong (177), modified Oxford grading scale 0-5(178) and the Brink scale which includes 3 components of pressure, displacement and time (179). There is no one best scale and assessors are encouraged to understand the limitation of each test.

Other PFM factors to assess include voluntary muscle relaxation (absent, partial, delayed, complete), sustained contraction endurance (the number of seconds the patient can sustain maximal or near maximal contraction), repeatability (the number of times a contraction to maximal or near maximal force can be repeated), coordination, and co-contraction. Resting tone is also important to assess using the scale increased tone, normal tone or decreased tone (without further gradations). The terms hypertonic and hypotonic are reserved for patients with neurological conditions. If possible, it is desirable to document findings for each side of the pelvic floor separately to allow for any unilateral defects and asymmetry (11).

The ICS report into the standardization of terminology of pelvic floor muscle function and dysfunction outlines 5 categories of PFM diagnosis:

a) Disorder of increased tone: PFM tension myalgia - a condition of pain and increased PFM tone

b) Disorder of PFM pain: PFM myalgia - a condition of PFM pain

c) Disorder of decreased tone - due to a decrease in either contractile tone (decrease in any contractile functions) or non-contractile tone (decrease in support of connective tissue)

d) Disorder of coordination: PFM dyssynergia - paradoxical PFM contractions during functional activities when relaxation is required for example vaginismus and obstructed defaecation syndrome.

e) Pudendal neuralgia: neuropathic pain syndrome caused by mechanical or non- mechanical injury of the pudendal nerve (11).

The morphology and integrity of the pelvic floor muscles may be also assessed by palpating its insertion on the inferior aspect of the pubic rami.

A discontinuity of the levator muscle at its attachment to the inferior pubic ramus is defined as levator injury / avulsion. This finding is more reliably assessed using 3D ultrasound imaging. Levator injury has been found to be associated with pelvic organ prolapse (180).

5.2. Assessment of Pelvic Organ Prolapse

Urinary incontinence and pelvic organ prolapse are separate clinical entities that often coexist. It is important to assess pelvic organ prolapse in a woman with symptoms of urinary incontinence, considering that the variants of the normal statics of the pelvic organs are not well established. Additionally, we must take into account that descent of a specific vaginal compartment, identified on pelvic examination, does not correlate well with the expected corresponding urinary symptoms (181). Assessment of pelvic organ prolapse described in this section is in accordance with the joint guidelines produced by IUGA/ICS in 2016 (182, 183). Pelvic organ prolapse (POP), as a sign, is the descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix) or the apex of the vagina (vaginal vault or cuff scar after hysterectomy). The term stress incontinence on prolapse reduction (occult or latent stress incontinence) describes the development of stress urinary incontinence after the reduction of co-existent prolapse by surgical repair or pessary insertion (182,183). The presence of any sign of POP should be correlated with relevant POP symptoms, commonly this correlation would occur when the prolapsed organ reaches at the level of the hymen or beyond (184,185). All examinations for pelvic organ prolapse should be performed with the woman with an empty bladder and preferably an empty rectum. An increasing bladder volume has been shown to restrict the degree of descent of the prolapse (186). The choice of the woman’s position during examination, e.g. left lateral (Sims), supine, standing or lithotomy is that which can best demonstrate POP in that patient and which the woman can confirm as the maximal extent she has perceived e.g. by use of a mirror or digital palpation (187). When there is a discordance between symptoms and examination, we have to consider that the degree of prolapse may be worse after a lengthy time in the upright position as, in standing position, women with POP have more often symptoms and more severe discomfort. (188,189).

Pelvic organ prolapse staging. Each aspect of POP, uterine (cervical) prolapse, anterior vaginal wall (compartment), posterior vaginal wall (compartment), vaginal vault (cuff scar) prolapse can and should be subject to a clinical staging. The hymen always remains the fixed point of reference for prolapse description. To stage POP means identifying the lowest extent of any part of the vaginal wall

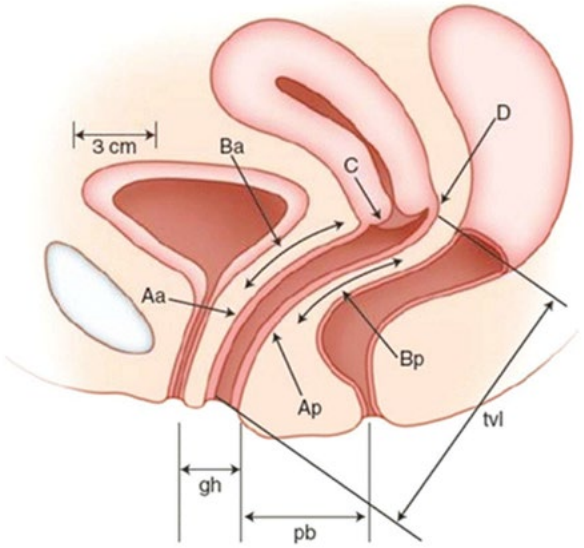

Figure 1: The six sites (Aa, Ba, C, D, Bp and Bp), the genital hiatus (gh), perineal body (pb) and total vaginal length (tvl) used cm above or proximal to the hymen (negative number) or cm below or distal to the hymen (positive number) with the plane of the hymen being defined as zero (0). Alternatively, a three by three grid can be used to organize concisely the measurements as noted in Fig. 2.

Anterior wall Aa	Anterior wall Ba	Cervix or Cuff C
Genital hiatus gH	Perineal Body pB	Total Vaginal Length TVL
Posterior wall Ap	Posterior wall Bp	Posterior Fornix D

Figure 2: Grid presentation of POP-Q measurements.

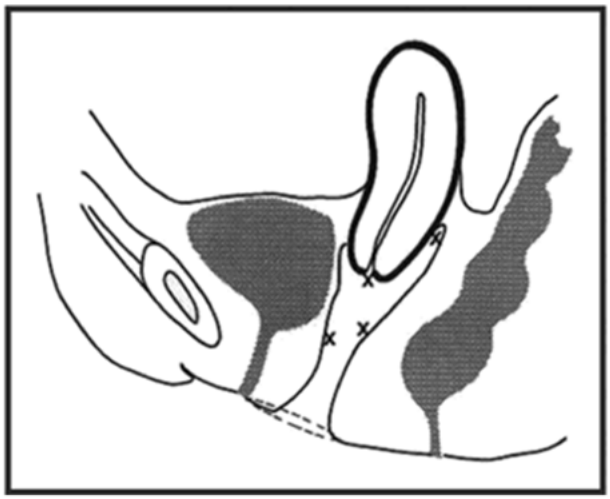

Figure 3: Simplified POP-Q.

or uterus. When this reaches close to the hymenal ring (at least stage 2), the prolapse is usually symptomatic. According with the IUGA/ICS guidelines for POP in 2016 (182,183), the following stages are considered:

Stage 0: No prolapse is demonstrated.

Stage I: Most distal portion of the prolapse is more than1 cm above the level of the hymen.

Stage II: Most distal portion of the prolapse is situated between 1 cm above the hymen and 1cm. below the hymen.

Stage III: The most distal portion of the prolapse is more than 1 cm below the plane of the hymen but everted at least 2 cm less than the total length.

Stage IV: Complete eversion or eversion at least within 2 cm of the total length of the lower genital tract is demonstrate.

Uterine/ cervical prolapse: Observation of descent of the uterus or uterine cervix.

Anterior vaginal wall (compartment) prolapse: Observation of descent of the anterior vaginal wall (compartment). Most commonly this might represent bladder prolapse (cystocele). Higher stage anterior vaginal wall prolapse will generally involve descent of uterus or vaginal vault (if uterus is absent). Occasionally, there might be an anterior enterocele (hernia of peritoneum and possibly abdominal contents), most commonly after prior reconstructive surgery.

Posterior vaginal wall (compartment) prolapse: Observation of descent of the posterior vaginal wall. Commonly, this would represent rectal protrusion into the vagina (rectocele). Higher stage posterior vaginal wall prolapse after prior hysterectomy will generally involve some vaginal vault (cuff scar) descent and possible enterocele formation. Enterocele formation can also occur in the presence of an intact uterus.

Vaginal vault (cuff scar) prolapse: Observation of descent of the vaginal vault (cuff scar after hysterectomy

Pelvic organ prolapse quantification (POP-Q). The need for an objective, site-specific method of quantifying and staging POP led to the design and validation of the POP-Q system. The original description of the POP-Q was by Bump et al in 1996 and is shown in figures 1 and 2 (190). This standard system, which represents a reliable and internationally accepted tool for describing the anatomical position of the pelvic organs, has been validated in the dorsal lithotomy, standing, upright and lateral position (191,192, 193).

The POP-Q records defects relative to the hymeneal remnants in centimetre gradients. These measurements are further staged according to the distal-most defect. The POP-Q system for POP considers the anatomical position of six defined points (two on the

anterior vaginal wall, two in the superior vagina, and two on the posterior vaginal wall) measurements are in centimetres (cm) above or proximal to the hymen (negative number) or cm below or distal to the hymen (positive number), with the plane of the hymen being defined as zero (O). For example, a cervix that protruded 3 cm distal to the hymen would be + 3 cm. All points are measured on maximal straining (except total vaginal length). The POP-Q as a system for quantitative prolapse description defines other landmarks and measurements: The genital hiatus (GH) is measured from the middle of the external urethral meatus to the posterior margin of the hymen. The total vaginal length (TVL) is the length of the vagina (cm) from posterior fornix to hymen when Point C or D is reduced to its full normal position. The perineal body (PB) is measured from the posterior margin of the hymen to the mid-anal opening.

Anterior vaginal wall prolapse is defined as descent of the anterior vagina so that the urethro-vesical junction (a point 3cm proximal to the external urinary meatus) or any anterior point proximal to this is less than 3cm above the plane of the hymen. On vaginal examination, we can observe a loss of the transverse crease between the lower and middle thirds of the anterior vaginal wall and descent of the anterior vaginal wall. Anterolateral protrusion into the vaginal canal may represent unilateral or bilateral detachment of the pubocervical fascia along the anterolateral vaginal sulcus from its attachment to the arcus tendinous fascia pelvis (white line). Central protrusions of the anterior vaginal wall may represent defects in the pubocervical fascia below the trigone and base of the bladder. Advanced prolapse of the upper anterior vaginal wall may obstruct a well-supported bladder neck. The two anterior vaginal wall points are as follows:

Point Aa located in the midline of the anterior vaginal wall three (3) cm proximal to the external urethral meatus. By definition, the range of position of Point Aa relative to the hymen is 3 to +3 cm.

A good correlation has been demonstrated between Point Aa and the straining Q-tip angle and suggested that Point Aa of the POP-Q system could be used to predict an abnormal straining urethral angle in women with Stage I anterior vaginal wall prolapse or greater. Point Aa of the POP-Q system could be a clinical tool that reflects urethral hypermobility in women with stress urinary incontinence in the initial evaluation of a patient and also before and after surgical treatment (194).

Point Ba that represents the most distal (i.e., most dependent) position of any part of the upper anterior vaginal wall from the vaginal cuff or anterior vaginal fornix to Point Aa. By definition, Point Ba is at 3 cm in the absence of prolapse and would have a positive value equal to the position of the cuff (Point C) in women with total uterine prolapse or post-hysterectomy vaginal eversion.

Prolapse of the apical segment of the vagina is defined as any descent of the vaginal cuff scar (after hysterectomy) or cervix, below a point that is 2cm less than the total vaginal length above the plane of the hymen. In some women, the intravaginal portion of the cervix may become elongated and cause the cervix to

extend into the lower vaginal canal, simulating prolapse, although the fundus may have good support. In other women, the uterus may prolapse fully outside the hymen as uterine procidentia. Following hysterectomy, the vaginal cuff may be well supported or may prolapse fully outside the hymen, along with other vaginal segments.

The two superior vaginal points are as follows:

Point C that represents either the most distal (i.e., most dependent) edge of the cervix or the leading edge of the vaginal cuff (hysterectomy scar) after total hysterectomy.

Point D that represents the location of the posterior fornix in a woman who still has a cervix. It is included as a point of measurement to differentiate suspensory failure of the uterosacral-cardinal ligament “complex” from cervical elongation. When the location of Point C is significantly more positive than the location of Point D, this is indicative of cervical elongation which may be symmetrical or asymmetrical. Point D is omitted in the absence of the cervix.

Posterior vaginal wall prolapse is defined as any descent of the posterior vaginal wall so that a midline point on the posterior vaginal wall 3cm above the level of the hymen or any posterior point proximal to this, less than 3cm above the plane of the hymen. Posterior protrusions into the vaginal canal are most commonly caused by defects in the recto-vaginal fascia allowing protrusions of the small bowel (enterocele) and/or rectum (rectocele). Normally, the anterior vaginal wall lies upon the posterior vaginal wall. Therefore, protrusions of the posterior vaginal wall can affect the function of the urethra and bladder that lie upon the anterior vaginal wall. For example, distal loss of support in the posterior segment may result in a bulge that compresses the urethra and affects voiding. The two posterior vaginal wall points are as follows:

Point Ap is located in the midline of the posterior vaginal wall three (3) cm proximal to the hymen. By definition, the range of position of Point Ap relative to the hymen is -3 to +3 cm.

Point Bp that represents the most distal (i.e., most dependent) position of any part of the upper posterior vaginal wall from the vaginal cuff or posterior vaginal fornix to Point Ap. By definition, Point Bp is at 3 cm in the absence of prolapse and would have a positive value equal to the position of the cuff in a women with total post-hysterectomy vaginal eversion.

The POP-Q system has not been widely adopted in clinical practice particularly by non-urogynaecologists; owing somewhat to difficulty in learning the assessment (195,196). Reasons for not using POP-Q include lack of training, the method is time consuming and the lack of an inexpensive and easily available ruler for the measurement. A study has demonstrated that digital assessment of POP-Q (DPOP-Q) is as accurate as measurement by a ruler type POPstix and additionally is better tolerated, faster, less expensive and can be conducted with the patient standing (197,198). A simplified version of the POP-Q was published by Swift in 2002, whereby the ordinal staging system of the original scale was retained (199). This is based on the POP-Q with similar ordinal staging but with only four points measured instead of nine. There is no Stage 0; it is combined with Stage 1. It is undertaken in the dorsal lithotomy position with the patient forcefully bearing down, performing Valsalva or coughing. Four points used: Point Ba in the anterior vaginal segment (estimated around 3 cm proximal to hymenal remnants). Point Bp in the posterior vaginal segment (estimated around 3 cm proximal to hymenal remnants). Point C (cervix). The apex / posterior fornix is Point D in non-hysterectomised women and point C in hysterectomized. (Fig.3). The inter-observer correlation of the simplified POP-Q was investigated in a secondary analysis of data from a large multicentre study. Weighted kappa statistics for the four POP-Q sites ranged from 0.53 (indicating poor agreement) to 1.0 (denoting excellent agreement) (200,201).

Despite the difficulties highlighted with the adoption of the POP-Q, reproducibility and reliability of the assessment system have been

demonstrated (202,203). Hall et al demonstrated that the examination could be completed within four minutes by new learners and two minutes by clinicians experienced with the assessment (197). With experienced practitioners, POP-Q staging performed using the measurement technique and estimation based on clinical examination are not significantly different (204). Parnell et al have described a POP-Q model in order to teach the POP-Q examination (205).

The relationship between anatomical defects measured by the Pelvic Organ Prolapse Quantification system (POP-Q) and lower urinary tract symptoms or other pelvic floor symptoms in women with pelvic floor disorders has been investigated and the symptom feeling of a bulge in the vagina is the only symptom that correlated with POP-Q in all vaginal compartments (206,207, 208,209). A study demonstrates that the sensitivity and specificity of this symptom were 60% and 83% when point Ba was 1 cm below the hymen. Whereas they were 55% and 83% when point C was 3 cm above the hymen (210).

The correlation between posterior compartment prolapse measured by POPQ and obstructed defaecation symptoms has been also investigated, the best-designed studies utilizing validated measures show a significant association between presence of posterior compartment prolapse and specific obstructed defecation symptoms, most significantly splinting, straining, and incomplete emptying (211,212). A retrospective study by Collins et al showed that a point Bp value of >-5 on the POP-Q, was found to be strongly correlated with defecatory dysfunction with symptoms of stool trapping and incomplete evacuation according with the CRADI-8 score (213).

The POP-Q has been used for the linguistic validation of condition specific health related quality of life questionnaires such as Prolapse Quality of life (P-QOL) (214,215), Pelvic Floor Distress Inventory (PFDI), (216,217), International Consultation on Incontinence Questionnaire Vaginal Symptoms (ICIQ-VS), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ12) (218) and Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR) (219-226).

The quantification of POP using the POP-Q was compared with dynamic MRI, the results showed that correlations of the anterior compartment were good to moderate, compared with central and posterior compartment that were poor to moderate. Correlations were independent of the POP-Q staging measurements. The agreement of MRI-based POP staging with the POP-Q is excellent, but the added clinical value is questionable due to poor association with clinical findings and pelvic floor symptoms (227-229). The relationship between clinical assessment of female pelvic organ prolapse using the POP-Q and dynamic 2D transperineal ultrasound (TPUS) has been also investigated and the accuracy of pelvic floor US staging was limited and that clinical assessment remains the gold standard (230). An observational study using POP-Q and pelvic ultrasound for the assessment of the type of cystocele, analyse the agreement between physical POP-Q and the Green radiological classification of cystocele. Kappa co-efficients ranged between 0.56-0.54 and 0.32-0.79 for clinical and ultrasound diagnosis respectively. The clinical utility of these findings has not been established (231). When clinical examination and imaging findings are compared, especially regarding cut-offs for the distinction between normal pelvic organ support and prolapse, conclusion is that the proposed cut-offs for 'significant prolapse' on ultrasound and POP-Q (Ba≥-0.5 and cystocele≥?10mm below the symphysis pubis, C≥-5 and uterine position of 15mm above the symphysis pubis, Bp≥-0.5 and rectocele≥15mm below the symphysis pubis) are plausible and mutually consistent. (232-235). According with the results of a recent systematic review about the value of the pelvic floor ultrasound for the evaluation of POP , it cannot replace the pelvic examination. However US, provides additional information that helps in treatment decisions (235).

An important advantage of the widespread adoption of the POP-Q system is the ability to compare surgical outcomes of different studies. The lack of standardised method to measure anatomical changes pre and postoperatively , has been one of the main difficulties in analying how different surgical procedures can correct anatomical defects in a different manner and their impact on function of the organs of the pelvic floor. The POP-Q has been used to define improvement in POP after surgical interventions in a number of studies; including native tissue repair (236-249), vaginal mesh (250-252) or abdominal mesh (253-257).

General recommendations in the female patient

A global evaluation for women is essential for effective treatment and prevention of relapse of UI, especially in patients with other comorbidities. Identifying and treating those symptoms are directly related of treatment success and resolution of symptoms, as well as their recurrence (Level 4, Grade A).

Pain and urgency must be carefully assessed, as they may indicate that incontinence can be secondary to a neurologic or other functional conditions (Level 3, Grade A).

Standardized PFM assessment can direct effective conservative management (Level 4, Grade A).

Urethral mobility can be assessed using the Q-Tip test weak evidence and predict success/failure of TOT(Level 4, Grade C).

Simulated operations, ring pessary test, VLPP and MUCP have been advocated to elucidate pelvic support-related incontinence/ symptoms and predict the outcome of a surgical procedure, but their predictive values still need to be demonstrated.

Future research is needed to establish the most reliable and valid techniques and tools to assess PFM function.

A careful assessment of associated pelvic support defects is essential for surgical planning and opportunistic resolution of all support-related symptoms in the same surgical procedure.

VI. SPECIFIC POPULATION: EVALUATION OF THE MALE PATIENT

1. CHARACTERISTICS OF MALE LUTS

In the male population, Lower Urinary Tract symptoms (LUTS) may present with dysfunction of the storage and emptying phase as well as with post micturition signs or symptoms. These symptoms can be non-specific in presentation and are multifactorial in origin. LUTS are progressive and age related but not sex or organ-specific. They cause significant bother and impair quality of life (258, 259). Traditionally LUTS were thought to be secondary to bladder outlet obstruction due to prostatic enlargement; however, recent scientific

evidence failed to show this relationship (259). Often, LUTS are unrelated to changes in prostatic size. Current research is aimed at understanding the impact of the bladder itself in LUTS. Bladder dysfunctions, such as Detrusor Underactivity, Detrusor Overactivity and other functional abnormalities can contribute significantly to LUTS (260).

In vitro as well as in vivo animal studies show a correlation between oxidative stress and ischemia with changes in bladder contractility in animals (261, 262).

LUTS are strongly associated with ageing and represent a major health burden for the patient and the society. Several epidemiological reports have demonstrated that storage symptoms (including urinary urgency and urgency urinary incontinence) defined as overactive bladder syndrome also increases with age in men. LUTS are often under-diagnosed and undertreated and still unfortunately often accepted as a normal part of ageing. Regarding urinary incontinence, epidemiological studies have shown that obesity is an independent risk factor for incontinence. Studies have shown that obesity is associated not only with a higher prevalence of incontinence (263) but also that obesity is a risk factor for postprostatectomy incontinence (264). There is a gender disparity as the correlation between obesity and urinary incontinence is higher in women, with 60 to 70% incidence of urinary incontinence among morbidly obese women. Although the incidence appears lower in men, is still quite relevant, as 24% of morbidly obese men have urinary incontinence (265). Obesity is a potentially modifiable condition. A recent meta-analysis confirmed that weight loss is associated with a reduction in incidence and severity of urinary incontinence among women and men. Specifically, in the male population, obesity appears to be more frequently associated with urgency incontinence (265).

Chronic prostatic pain syndromes (e.g. non-bacterial chronic prostatitis) and other pelvic floor dysfunctions can also present with a component of symptoms compatible with storage symptoms. In younger men, primary bladder neck dysfunction is a common cause of LUTS, with or without pelvic pain. Functional abnormalities of striated sphincter relaxation may also occur in young men. The complexity of the presenting symptoms and the various differential diagnoses mandate a thorough basic assessment of the lower urinary tract in men to plan optimal therapeutic intervention.

Epidemiological studies and meta-analyses confirm a high prevalence of LUTS in the community. There is an increased prevalence of LUTS with ageing (266). The incidence appears to be of 3.5% in men in the fourth decade of life, while in men over age of 85 the incidence is higher than 30%. These epidemiological data are confirmed by the finding that in the time period from 1992 to 2001 there was an increase of medical treatment for male LUTS from less than 2% to more than 10%. In the same time frame, there was also an increase in the time between the first diagnosis of LUTS and the time to surgery. The Multinational Survey of the Aging Male (MSAM-7) surveyed over 12 000 men age 50 to 80 in major countries of Western Europe and USA (266). Across all countries, prevalence increased from 22% in men aged 50–59 years to 45% in men aged 70–80 years. 31% of men reported moderate-to-severe LUTS (34% in the USA and 29% in Europe). Interestingly, despite the fact that 19% of men with LUTS present with complaints, only 10% received and appropriate medical treatment (267).

Based on the Integrated Health Care Information Solutions (IHCIS) database, LUTS are among the most frequent reasons for medical consultation among the male population older than 50. The fourth most common diagnosis in this population is BPH, after coronary artery disease, hyperlipidaemia, hypertension and diabetes mellitus (268).

LUTS have a significant impact on quality of life but also on potentially life-treating conditions such as falls in elderly population. As reported by Parsons et al. moderate and severe LUTS independently increase the 1-year risk of falls, particularly recurrent falls, in community-dwelling older men (269). In their study of 5,872 participants in the Osteoporotic Fractures in Men study were assessed for LUTS, using the AUA symptom score. Patients with moderate LUTS were found to have 11% higher risk of at least one fall, while the risk of fall increased to 33% in subjects with severe LUTS (269). Falls in the elderly population might have serious consequences and screening elderly patients for LUTS by primary care providers should be assessed routinely.

2. MALE INCONTINENCE

Improvement in early detection of prostate cancer has led to an increase of men treated for this condition. The rate of post-prostatectomy incontinence (PPI) is difficult to determine because of the varying definitions of incontinence, but approximately one in five men require the use of pads in the long term after radical prostatectomy (RP) (270). Incontinence has a significant negative impact on quality of life. This potential complication is also patients' greatest fear, especially in the youngest subset of patients (65 years or younger), requiring RP (271). Robot-assisted laparoscopic prostatectomy (RALP) was introduced with the aim of improving surgical outcomes, but controlled or randomized studies on the long-term effects are few and present knowledge of effectiveness is based mainly on case series or registry data (272).

The Swedish LAP PRO trial brings some very useful insights into answering the question of true incidence of PPI and whether there are any differences between techniques. In summary, this trial focused on the primary end point of urinary incontinence 12 months after RALP, as reported by the patients (to reduce the potential bias of Surgeon-Patient relationship) (273). Notably, this study recruited only patients of high volume surgeons, those with more than 100 procedures carried out to avoid the bias of the single surgeons learning curve. The study recruited 4000 patients and the final analysis included 2625 patients. 778 patients underwent an open retropubic radical prostatectomy (RRP) and 1847 underwent RALP. The study showed that patients classified as having urinary incontinence ranged from 20% to 56% after RRP and from 21% to 57% after RALP. The percentage of incontinence was even higher if a definition of dryness was combined with no use of pads and zero leaks (273).

Catalona et al. showed that incontinence after prostate surgery was primarily dependent on the age of patients (274). The older the patient, the more likely he is to be incontinent and to never regain urinary control. For 40-49 year olds only 3% (12/358) had long term incontinence but that increased to 8% (48/632) in 50-69 year olds 8% (48/632) and 13% (38/282) in men over age 70; for an overall prevalence of 7.7% (274).

Special consideration is needed for irradiated patients as the success rate and incidence of post prostatectomy incontinence surgery differ significantly from non-irradiated patients. The revision rate of Artificial Urinary Sphincter (AUS) surgery, a procedure done for PPI, was significantly higher in irradiated versus non irradiated men (mean 37.3 versus 19.8%; $p < 0.007$) after a mean follow-up of

38.4 months (275). Revision is typically performed for infection, erosion or urethral atrophy. Persistent urinary incontinence was also more than twice as likely in irradiated versus non-irradiated men (29.5 versus 12.1%; P = 0.003) with an odds ratio of 2.08 (275). Radiation induced changes involving the bladder neck and urethral tissue, such as fibrosis, are considered to be the primary aetiology for the development of incontinence. Surprisingly, the timing of radiation therapy does not seem to have any influence on the incidence of urinary incontinence. Similar rates of incontinence are reported in early and late radiation therapy after radical prostatectomy. Sowerby and colleagues reported the incidence of urinary incontinence to be 24.5% in men who underwent radiation less than 6 months from surgery and 23.3% in men with radiation greater than 6 months after prostatectomy (275).

Urgency incontinence is a failure of bladder storage usually due to the underlying pathology of detrusor overactivity (DO). Urgency incontinence commonly presents as part of the overactive bladder (OAB) syndrome. OAB is described as urinary urgency, with or without urgency incontinence, usually with frequency and nocturia, in the absence of infection or other obvious pathology (1). In men, OAB symptoms often coexist with emptying phase LUTS. Men with emptying phase LUTS such as poor flow and hesitancy are often assumed to have benign prostatic obstruction, although research has shown they may not.

3. SYMPTOM ASSESSMENT

Symptom assessment in men with incontinence should identify and exclude patients with complicated incontinence, who need to be referred for specialised management. Complicated incontinence comprises patients with recurrent incontinence after failed previous surgery, with total urinary incontinence, and/or with associated symptoms such as pain, haematuria, recurrent urinary tract infection, voiding symptoms, and/or a history of previous pelvic radiotherapy or radical pelvic surgery (276).

Because the occurrence of LUTS in men does not necessarily indicate concomitant prostate enlargement and/or obstruction, specific modalities should be used to ascertain the potential for the aetiological role of these entities. Underactive bladder (UAB) is the symptom-based correlate of detrusor underactivity (DU), as is the case with OAB and detrusor overactivity (DO).(277) The International Continence Society (ICS) consensus group has recently proposed a working definition of UAB as a symptom syndrome suggestive of DU (278). The definition is “Underactive bladder is a symptom syndrome suggestive of DU and characterized by a slow urinary stream, hesitancy and straining to void, with or without a feeling of incomplete bladder emptying and dribbling, often with storage symptoms.” Although patients with DU can present a variety of storage, voiding, and post-micturition symptoms, the voiding symptoms often predominate. However, a symptom complex of UAB is shared by LUTS attributable to bladder outlet obstruction (BOO) (277,278). Increased residual urine may cause the overflow incontinence.

A variety of symptom scores have been described to assess male patients with LUTS. It is important that symptom scores have a wide applicability across a number of different cultures and languages. Ideally, symptom scores should also help to determine the underlying aetiology of LUTS (for example, BOO, DO, impaired detrusor contractility); however, this is made difficult by the fact that different conditions can produce similar or even identical symptoms. Each symptom score has advantages and disadvantages, but it is clear that the worldwide use of such scores has helped in evaluating symptoms, treating patients, and communicating findings globally. Symptom scores have been used in male LUTS for a variety of purpose. 1) to assess symptom severity, 2) to examine the relationships between clinical measure/ test results and scores from symptom and quality of life (QOL) questionnaires, 3) to predict to treatment, 4) to assess the outcome of treatment.

The following symptom scores for male LUTS have been evaluated.

The IPSS: symptoms and QOL impact of LUTS
The International Consultation on Incontinence Modular Questionnaire-Male-LUTS (ICIQ-MLUTS): symptoms of LUTS and urinary incontinence
The Danish Prostatic Symptom Score (DAN-PSS): symptoms of LUTS and urinary incontinence
The OAB Symptom Score (OABSS)
The core LUTS Score (CLSS): symptoms of LUTS
The Urgency and Nocturia Scoring TOOL (UWIN): symptoms of LUTS

Three questionnaires with a high level of psychometric validity and reliability are the IPSS, the ICS’s ICS-male questionnaire (now known as the ICIQ-MLUTS), and the DAN-PSS. Although each was designed with the same purpose, only six symptoms are common to all three, including incomplete emptying, urgency, decreased stream, frequency and nocturia.

In men, the American Urological Association symptom score for BPH (AUA-7) is most commonly used in North America for assessment of subjective symptoms. However, equally reproducible data can be obtained from the International Prostate Symptom Score (IPSS)(279), the ICS male questionnaire (now renamed the ICIQM-LUTS, long and short forms, as part of the ICIQ modular questionnaire: www.iciq.net).

The IPSS has been the most widely used (in many countries and languages), but one of the major critiques of this questionnaire, is the fact that it is not disease or condition specific. In addition, it neglects the symptom of urgency incontinence, a symptom that produces significant bother. Urgency incontinence is an important symptom, particularly regarding the therapeutic outcome in BPO patients. The prevalence of this symptom was also reported as common by the ICS-“BPH” study group and was higher in men with BOO than in those without (280).

ICIQMLUTS (ICSmale-SF) is slightly longer but takes into account the symptom of urgency incontinence, and in fact may be divided into voiding (ICS-male-VS) and incontinence (ICS-male-IS) (281). As the concept of OAB has become widespread, as simple symptom questionnaire to quantitatively assess OAB symptoms, the OABSS, was developed and psychometrically validated. overactive bladder symptoms scores are also very useful for male patients with storage symptoms including urgency incontinence (282, 283). Other new symptom questionnaires to assess male-LUTS include UWIN and the CLSS.

Ten LUTS (increased daytime frequency, nocturia, urgency, urgency incontinence, stress incontinence, slow urinary stream, straining, a feeling of incomplete emptying, bladder pain, and urethral pain) were selected as core symptoms from 25 LUTS defined by the ICS committee, and symptom questionnaire to assess the core symptoms we developed as the CLSS (284). Symptoms were scored

according to their frequency and severity. The CLSS questionnaire was confirmed to show good test-retest reliability. The CLSS was compared with IPSS in men with LUTS, and the CLSS was shown to be more comprehensive than IPSS for symptom assessment of men various diseases and conditions (284). The CLSS provides overall assessment of relevant symptoms and may be useful for new patients, patients with multiple diseases, and patients without a definite diagnosis, as well as before and after intervention that may cause other symptoms. The CLSS was utilized for evaluation of longitudinal change of comprehensive LUTS and various types of urinary incontinence during robot-assisted radical prostatectomy (285)

Among LUTS, urgency, nocturia, and hesitancy are most bothersome, whereas weak stream, urgency, and frequency are the most prevalent in pooled populations being evaluated for BPH (286). Postmicturition dribble (PMD) is a term used to describe the involuntary loss of urine immediately after an individual finishes passing urine, usually after leaving the toilet in men or after rising from the toilet in women (1). PMD is classified as a postmicturition symptom according to the standardization of terminology. Although the exact pathophysiological mechanism of PMD has not been clarified to date, earlier studies suggest that PMD is secondary to a small amount of residual urine in either the bulbar or prostatic urethra that is normally “milked back” into the bladder at the end of micturition (287,288).

PMD is often provoked by an obstructing disease such as BPH or urethral stricture but can also be a symptom of a urethral diverticulum. As yet there is no validated symptom questionnaire that assesses post-micturition symptoms (post-micturition dribble and post-micturition incontinence).

PMD is one of the most prevalent LUTS (289-294) and is known to be one of the most common causes of bother (258,289,290). Jeong et al. (295) developed and validated the “Hallym Post Micturition Dribble Questionnaire” (HPMDQ) to assess PMD, which consists of 5 questions (frequency, severity, bother, quality of life and response to treatment for PMD) (295).

The International Consultation on Incontinence Questionnaire-underactive bladder (ICIQ-UAB) was developed as the first patient reported outcome measure for the assessment of the symptoms and impact on the health-related quality of life of UAB. (296)

To determine the cause of post-prostatectomy incontinence, many studies have stressed the lack of reliability of symptoms and emphasized the important role of urodynamic testing (297, 299). Recently, non-invasive standing cough test was utilized for evaluation of post-prostatectomy incontinence. (299,300) Nevertheless, valuable information can be gained from a careful history with regard to incontinence, especially when related to sphincter dysfunction. The symptom of stress incontinence is highly predictive of the presence of sphincter dysfunction. Chao and Mayo found that 67 of 71 men with post-prostatectomy incontinence secondary to sphincter dysfunction complained of the symptom of stress incontinence (301). Similarly, Ficazzola and Nitti found 95% positive predictive value and a 100 % negative predictive value for symptom of stress incontinence (302). Urgency incontinence as a predictor of bladder dysfunction does not seem to be as valuable, and the presence of bladder dysfunction cannot be determined accurately without urodynamic testing (301, 302).

An important aspect of the assessment of male incontinence should be a description of the type and severity of incontinence and precipitating events, Severity may be determined by the number of episodes per day, the need for protection (e.g., pads, penile clamp, external catheter), and the impact of incontinence on activities of daily living. Bladder diaries and pad tests can quantify severity. A bladder diary (or frequency volume chart) kept for 3 to 5 days may be useful in almost all male patients, especially in those with OAB. The time and voided volume are recorded for each micturition during several 24-hour periods.

Bladder diary completion by the patient provides useful evidence about the nor-mal urinary habits of the patient, including giving some estimate of bladder capacity and diurnal and nocturnal frequency, urgency and stress incontinence. It also helps to identify patients with nocturnal polyuria or excessive fluid intake which are common in the aging male. The data obtained from a frequency-volume chart provide a strong correlation with cystometric capacities and are reasonably immune to the effect of detrusor overactivity in men with LUTS (303).

The 24 hour pad test is an excellent test to quantify the amount of urine leakage in men. Since most patients use different size and type of pads, it is difficult to compare the number of pad/day per patient. Furthermore, some patients are very disturbed by any leakage at all and change the pad very frequently before they are saturated. The other distinction to be made is between a safety pad and true urinary incontinence. In general, the each 1g weight equals 1 ml urine loss. It is proposed to use a cut-off value of 250 g of urine to categorize minor from more troublesome or severe leakage (304). Recently, Machold et al. suggested that the technical feasibility of the 20-min pad test to evaluate post-prostatectomy incontinence was excellent. The results correlated significantly with both the self-assessment via questionnaire ($r = 0.63$; $p < 0.001$) and the 1-hour pad test (ICS; $r = 0.66$; $p < 0.001$). Moreover, it was highly reliable ($r = 0.74$; $p < 0.0005$) with excellent patient acceptance (305).

4. PHYSICAL EXAMINATION

The assessments focus on general physical examination, digital rectal examination (DRE) and neurological testing of the perineum and lower extremities.

In a general physical examination, specific attention should be placed on the evaluation of surgical scars, the presence or absence of a distended bladder and excoriation of the genitals, secondary to urinary incontinence. Abdominal palpation should be performed to evaluate bladder distension, especially in elderly incontinent men, who may have overflow leakage due to obstruction. In patients suspected of urinary retention, post-void residual volume should be measured. The examination should also include external genitalia, location of the urethral meatus, retractability of the foreskin and evidence of congenital malformation. The evidence of urethral discharge after abdominal straining (a Valsalva manoeuvre) or coughing in either the supine or upright position should be evaluated so that the presence of stress incontinence can be ascertained.

A focused neurological examination is also highly recommended. In a patient suspected of neurogenic bladder, evaluation of perineal sensation and lower extremity neuromuscular function, and anal sphincter tone, which is often decreased in neurogenic patients is important (306). A focused neurogenic examination should also assess the patient’s general mental status and ambulatory status.

DRE should include palpation of the prostate to assess size, symmetry and consistency of the gland and its relation to the pelvic

sidewall and the rectum. Enlarged, indurated and painful prostate may imply BPH, prostate cancer and prostatitis, respectively. The locally advanced prostatic cancer can also produce OAB-like symptoms including incontinence. DRE may exclude prostatic cancer, although its specificity and sensitivity is low (307). The DRE is 53% sensitive and 85% specific for identifying underlying prostate cancer when abnormalities (i.e. induration or nodule) are present (308). Furthermore, abnormal rectal tone can raise suspicion of an occult neurogenic disorder that may be contributing a patient`s symptoms. DRE tends to underestimate the true prostatic size: if the prostate feels large by DRE, it usually also is found to be enlarged by ultrasound or other measurement technique (309, 310). Prostate volume has been associated with the risk of BPH progression (311) and response to treatment (312). It has been reported that men with BPH with idiopathic detrusor overactivity showed a significantly higher incidence (54%) of intravesical protrusion of the prostate (313). This finding suggests that intravesical protrusion may in some way increase afferent impulses from the prostate and alter the stability status of the bladder. Occasionally tumours of the anal canal can be diagnosed while performing DRE of the prostate.

Assessment of the male PFM function should proceed using the same tests and diagnosis as the female including external observation, digital rectal palpation, EMG, and transperineal imaging ultrasound. External observation of correct male PFM contraction would result in closure and elevation of the anus, cephalad testicular lift and penile retraction. Anterior contraction of the male PFM (penile retraction) has been shown to be important in recovery of post prostatectomy UI (314). Although anterior PFM contractions may be visible externally, the best assessment is with imaging ultrasound. Skilled assessment and treatment of male PFM disorders is a valuable addition to the care of these patients

4.1. Urinalysis and Urine Cytology

All patients undergoing an evaluation for LUTS should have a urinalysis performed to evaluate for UTIs or other uropathology. The most significant findings would include evidence for pyuria, bacteriuria, and/or haematuria. Bladder cancer, carcinoma in situ of the bladder, urinary tract infections, urethral strictures, and bladder stones can cause OAB-like symptoms including incontinence in elderly men. Although haematuria or pyuria is not universally present in those conditions, urinalysis is important to rule out these conditions. Urinalysis is not a single test; complete urinalysis includes physical, chemical, and microscopic examinations. Dipstick urinalysis is certainly convenient but false-positive and false negative results may occur. It is considered an inexpensive diagnostic test able to identify patients with urinary tract infection as indicated by the presence of leucocyte esterase and nitrites. A substantial proportion of older patients with chronic OAB-like symptoms have significant bacteriuria, sometimes accompanied by pyuria. In men, recent urinary tract infections were associated with OAB without urgency incontinence (prevalence ration=2.9; 95% CI: 1.6-5.0) (315). However, infection may exist in the absence of pyuria and, in the elderly population, pyuria may develop in the absence of urinary tract infection.

Microscopic haematuria can be easily identified by dip sticks because of the presence of haemoglobin. The detection of haematuria is important because the condition is associated with a 4-5% risk of diagnosing urological disorder or malignancy within 3 years.

A systemic review and economic evaluation of diagnostic tests and algorithms used to investigate haematuria concluded that the evidence based on which to determine the ideal means of investigating haematuria was insufficient (316). However, because of the high prevalence of urinary tract infection and the increase of LUTS in the presence of urinary tract infection, various guidelines on the management of patients with LUTS suggestive of BPO, and urinary incontinence, endorse the use of urinalysis in primary care management (317,318).

Urine cytology is also recommended in male patients with haematuria and a predominance of storage symptoms, especially with a history of smoking or other factors, to aid in the diagnosis of bladder carcinoma in situ and bladder cancer.

4.2. Measurement of the Serum Creatinine

Epidemiological studies in community dwelling men have shown the absence of any association between BPO/BPE/BPO and chronic kidney disease (317, 319) suggesting that screening for renal function is not justified in male patients. Diabetes and arterial hypertension appear to be the most important causes of elevated serum creatinine in men with BPH and renal failure (315). Data from the MTOPS study showed that the risk of developing de novo renal failure in men with LUTS is low (less than 1 %) suggesting that is not necessary to monitor renal function in patients with LUTS / BPO (311). However, a study examining the association between LUTS and glomerular filtration rate (GFR) in men concluded that in older men without obvious enlargement of the prostate, as LUTS became more severe, GFR fell (320). In case of overflow incontinence accompanied with BOO, measurement of the serum creatinine might be necessary, because a significant residual urine may cause the bilateral hydronephrosis resulting in the renal dysfunction.

5. MEASUREMENT OF THE SERUM PROSTATE SPECIFIC ANTIGEN (PSA)

In most patients, a normal DRE may be sufficient to exclude locally advanced cancer as a cause of LUTS or OAB. There is no consensus as to the measurement of prostate specific antigen (PSA) in patients with LUTS. The rationale for measuring PSA is twofold: to screen for prostate cancer and to measure a parameter with prognostic value for the progression of BPH and the response to treatment. Because prostatic cancer is one of the potential causes of LUTS or OAB in men, PSA (together with DRE) is a relatively sensitive way to exclude prostatic cancer as a diagnosis (321,322). PSA measurement is recommended in men with LUTS and a life expectancy of over 10 years in whom the diagnosis of prostate cancer would change the management of patient's symptoms. Given the uncertainties surrounding prostate cancer detection physicians must use clinical judgment in determining which patients should or should not undergo transrectal ultrasonography and prostate biopsy in response to a particular PSA (323).

However, it is important to understand that about 25% of men with BPH have a serum PSA greater than 4 ng/ml. Because of the overlap between serum PSA values in men with BPH and those with clinically localised prostate cancer, other parameters (PSA velocity, free/total PSA ratio, complexed PSA and PSA density) will assist diagnostic specificity (324, 325). It has been suggested that a relationship between initial PSA level and subsequent prostate cancer detection with a stepwise increase in cancer detection rate (from <1% to 58%) in patients with <1.0 ng/ml, 1.1-2.5, 2.6-4.0, 4-1-10.0 and >10 ng/ml PSA value in over 26.000 patients enrolled in a screening program (326, 327). In addition, Thompson reported data on prostate cancer prevalence from the prostate cancer prevention trial (327) confirming a stepwise increase in the risk of having

a prostate cancer in patients with serum PSA from 0.5 to 4.0 ng/ml but showing the limitation of the current threshold of 4.0 ng/ml. Change of PSA threshold from 4.0 to 2.0 ng/ml has been proposed but currently no consensus exists (328).

In addition, serum PSA is a reasonable predictor of prostate volume in men with LUTS and can be used in this capacity in clinical decision making (323). It has been reported that the role of IPSS score in the assessment of BOO is questionable, and that the grade of obstruction is more related to prostate volume, PVR, and Qmax (329). It has been demonstrated that moderate-to-severe LUTS in men can result in urinary retention. The incidence of retention in men with untreated LUTS in community-based trials is 6.8 per 1000 during longitudinal follow-up of 4 years (330). If only patients with moderate-to-severe symptoms are considered, the rate of retention increases to 25 per 1000 (331). In a meta-analysis of predictors of retention in pooled groups of placebo patients from clinical trials of men with LUTS undergoing active interventions (4300 patients), Roehrborn et al. found PSA and prostate volume to be strong independent predictors of urinary retention and the need for surgery in men with LUTS followed up longitudinally in clinical trials (310, 332).

Laniado et al have also tested the hypothesis that PSA level could be used to predict the presence or absence of BOO, evaluated by pressure flow studies. In patients with LUTS, those with a PSA more than 4 ng/ml are significantly more likely to have some degree of BOO. Conversely patients with PSA less than 2 ng/ml have a 33% risk of BOO (333).

Recommendations

A variety of symptom scores have been described to assess patients with Male-LUTS. The IPSS, ICIQ-MLUTS, and DAN-PPS have been the most tested and were found to reproducible, valid, and sensitive for initial assessment. (Level 3, Grade A). However, the IPSS neglects of symptom of incontinence.

Urinalysis is recommended in patients with male-LUTS. There is currently insufficient evidence to recommend routine measurement of serum creatinine and post-void residual urine in male patients with incontinence (Level 3, Grade A).

In addition to DRE, PSA measurement is recommended in selected male patients with OAB (Level 3, Grade A).

Skilled assessment of the anterior PFM should be included in the assessment of patients with post prostatectomy UI.

Future research

1. Improve the understanding of the underlying pathophysiology and contributory clinical factors involved in the development and treatment of detrusor overactivity in the male patient, especially in differentiating the condition from female patients.
2. Development of simple, non-invasive, cost-effective methods to determine the contribution of bladder storage and bladder emptying abnormalities in male patients.

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COMMITTEE 4B

PATIENT-REPORTED OUTCOME ASSESSMENT

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I. INTRODUCTION

This chapter updates the previous literature reviews of Patient Reported Outcomes (PROs), for lower urinary tract symptoms (LUTS), bowel incontinence, and sexual dysfunction outcome measures providing recommendations for questionnaire selection for use in clinical practice and research. This summary will review the purpose and content of the ICI questionnaire (ICIQ) modules. In addition this chapter reviews Patient Reported Outcome Measure (PROM) development and translation into different languages and cultures. There is also an expanded review of electronic Patient Reported Outcomes (ePRO) and questionnaire bias.

A PROs is defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else". A PROM is the tool or questionnaire used to collect the data. PROs measure different aspects of disease and therapeutic impact such as: symptom frequency or symptom bother, health-related quality of life (HRQoL), treatment satisfaction, adverse events, or work productivity measures (**Figure 1**). An essential component of selecting a PRO is to ensure that the selected PRO is consistent with the objective of the study or clinical purpose. For example, if the goal is to assess treatment satisfaction, then a treatment satisfaction measure should be incorporated into the study design or as a clinical outcome. Matching of appropriate PROs with desired outcomes is critical to success when assessing PROs and will be reviewed further in this chapter.

Ultimately, the last decade has been one of tremendous growth in the area of PROs with influences from scientific and regulatory communities. As such, the ICI will endeavour to continually update the recommendations it offers on the basis of emerging data and published evidence based on the recommendations of the prior reviews.

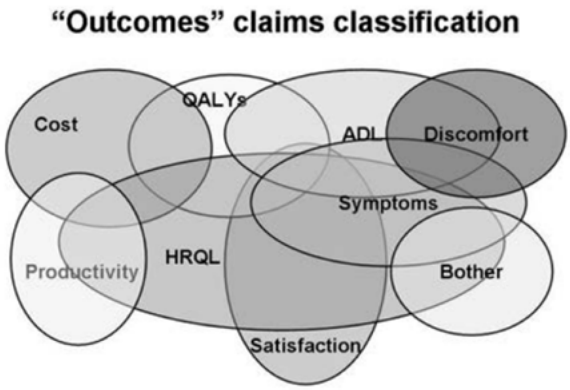

Figure 1: Patient Reported Outcome Assessment Areas

1. TERMINOLOGY AND DEFINITIONS

Symptom impact and treatment benefit can be assessed in several ways. The first line method is taking a detailed clinical history. In addition, PROMs are important and have proved their reliability in symptom and outcome assessment such as voiding diaries and validated questionnaires. They build the basis of the patient-centred healthcare system and represent the most important clinical review of symptom impact and treatment benefit from a patient perspective

. Patient reports are the best method for quantifying unobservable events such as pain and depression. Even when an event is observable, such as voiding or fluid intake, the patient is in the best position to report events over a period of time. PROMs provide a method for the standardised collection of data, or an objective assessment of subjective phenomena, from patients relating to the condition or treatment of incontinence, other LUTS, sexual function, and bowel problems. Clinicians' assessments of patients' outcomes have often been shown to underestimate the degree of bother perceived by patients, and to focus on issues of lesser importance to patients. Thus making PROMs more reliable and valid than Observer Reported Outcomes (ORO).

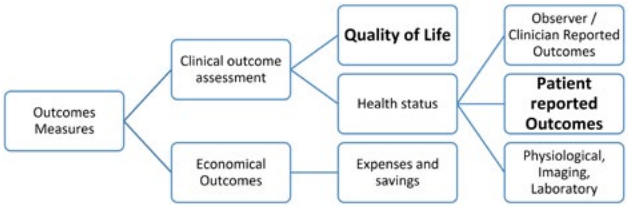

Figure 2: Types of outcomes measures

Outcome measures are categorized in 2 groups: clinical and economical (**Figure 2**). Economical outcomes report on cost of disease and treatment through expenses and saving. Clinical outcome assessment (COA) measures Health status and Quality of life. They can be further sub-classified into Observer / Clinician reported outcomes, Patient reported Outcomes and Physiological, Imaging, and Laboratory tests. If the patient is observed for the outcomes by a caregiver then the outcomes are termed observer reported outcomes (OROs). This chapter will focus on Patient Reported Outcomes (PROs) and Health Related Quality of Life Measures (HRQoL). **Table 1** provides further definitions of terms related to PROs.

Health related quality of life (HRQoL) measures are similar to PROs in that they are patient reported without interpretation by a clinician. However they differ from PROs in that they are a multidimensional measure which is indirectly related to a disease. Whereas a PRO symptom is a one-dimensional property directly related to disease and treatment effect. Thus, PROs concepts are simple whereas the concepts are complex in HRQoL.

2. TYPES OF PRO MEASURES

There are two types of PRO measures: generic and condition-specific. Generic measures are designed to assess outcomes in a broad range of populations (e.g., both healthy as well as ill individuals). These instruments are generally multidimensional, and assess at least the physical, social and emotional dimensions of life. An example of this type of instrument is the Medical Outcomes Study SF-36 Health Status Profile.

A second type of measure is condition-specific (e.g. instruments designed to assess the impact of specific diseases, conditions, age groups, or ethnic groups). Condition-specific measures can be similar to generic instruments in that they assess multiple outcome dimensions, but condition-specific measures also include items more specific to the particular condition or population being studied. Examples of condition specific instruments in urology and urogynae-

Table 1: Terminology of PRO

Clinical Outcome Assessment (COA)	A report of patient's health status. COAs can measure treatment benefit directly or indirectly. COAs include patient-reported, clinician-reported, and observer-reported outcome measures and are typically instruments that include a scale or score.
Patient Reported Outcome (PRO)	Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.
Patient Reported Outcome Measure (PROM)	The instrument or tool used to gather health status information directly from the patient, without amendment or interpretation by a clinician or anyone else.
Observer Reported Outcome (ORO)	A report of patient behaviour and symptoms given by an observer. An ORO measure does not include medical judgment or interpretation although it is subject to observer interpretation and is not a PRO. Generally, OROs are reported by a parent, caregiver, or someone who observes the patient in daily life. OROs are valuable in cases of cognitive limitation (ie an elderly patient with dementia or a child before the age of understanding).
Clinician Reported Outcome (CRO)	A report that comes from a trained health-care professional after observation of a patient's activities with a health condition. A CRO measure involves a clinical judgment or interpretation.
Performance Outcome Measures (PO)	A measurement based on a task(s) performed by a patient according to instructions that is administered by a health care professional. Performance outcomes require patient cooperation and motivation, e.g. measures of gait speed, memory recall, or other cognitive testing.
Health Related Quality of Life (HRQoL)	A multi-domain concept which represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life.
Electronic patient reported outcome (ePRO)	A PRO collected directly from the patient electronically without interpretation by the clinician or anyone else
Electronic patient reported outcome measure (ePROM)	The software or computer program used to collect PROs electronically
Interactive voice response system (IVRS)	Technology that uses pre-recorded voice questions and responses to complete the questionnaire usually administered over the phone
PRO domain	A sub-concept represented by a score of an instrument that measures a larger concept comprised of multiple domains. e.g. depression
PRO item	An individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept. e.g. Are you feeling depressed?
Conceptual framework	The conceptual framework explicitly defines the concepts measured by the instrument in a diagram that presents a description of the relationships between items, domain (sub-concepts) and concepts measured and the scores produced by a PROM.
Endpoint	The measurement that will be statistically compared among treatment groups to assess the effect of treatment and that corresponds with the clinical trial's objectives, design, and data analysis.
End point model	A diagram of the hierarchy of relationships among all endpoints, both PRO and non-PRO, that corresponds to the clinical trial's objectives, design, and data analysis plan.

Taken from several references including [7, 8, 9, 10]

cology include the Incontinence Impact Questionnaire, the King's Health Questionnaire, and the OAB-q.

In general, it is now common to include condition specific outcome measures in clinical trials due to their enhanced sensitivity to change and the need to minimise participant burden. Importantly, the type of instruments selected for inclusion in a research study will depend on the goals of the intervention and the specific research questions to be addressed. In practice, clinical trials that include PROs usually incorporate a combination of PRO measures most relevant to the study population and intervention, if applicable, being mindful of resource constraints and staff and participant burden.

II. SELECTING PRO MEASURES FOR RESEARCH STUDIES

a) Study Design

There are several protocol concerns that must be taken into account when using PRO measures in research studies, including the length of the study, the frequency of contact with the study participants, the timing of clinical assessments, the complexity of the study design, the number of participants enrolled, and participant and staff burden. The goal of the PRO assessment is to "fit" the PRO measures to the protocol without compromising either the study objective or design. For example, if the study design is complex with

frequent participant contacts and multiple clinical measures, it may be necessary to keep the PRO measures at a minimum or to reduce the number of times the PRO is assessed (e.g. baseline and end of study rather than during all participant contacts) to minimise participant and staff burden. At the same time, however, PROs must be viewed as an important variable in the overall trial design and should not be devalued in the data collection process. Consequently, PRO measures cannot be altered or reduced to accommodate study design as such alterations may yield less reliable measures or may seriously diminish the integrity of the overall study design and yield useless information. Having well developed research goals and questions regarding PROs will help to guide clinicians in the selection of measures for a study. The aim is to develop a conceptually adequate, yet practical PRO battery given the study population, the specific intervention, and the study design.

The frequency with which a PRO will need to be assessed in a research study will depend upon the nature of the condition or intervention being investigated and the expected effects (both positive and negative) of the treatment. At a minimum, as with all measurements collected in a research study, a baseline and end of study assessment should be completed. In addition, PRO assessments should be timed to match expected changes in functioning due to either the intervention, the condition or the disease itself. Timing follow-up assessments to coincide with typical patient follow-up visits, if appropriate, may also reduce the costs involved in the follow-up PRO assessments.

b) Study Population

It is critical to specify key population demographics that could influence the choice of instruments, the relevant dimensions of the PRO to be assessed, and the mode of administration. Thus, age, gender, educational level, language spoken, and cultural diversity should be carefully considered prior to selecting PRO measures. For example, a cohort of patients over the age of 70 may have more visual problems than middle-aged persons, making self-administered questionnaires potentially inadvisable. Ethnically diverse groups also require measures that have been validated across different cultures and/or languages.

In clinical trials, it is also important to consider how the disease or condition will progress and affect the outcomes of patients in the control group as it is to understand the effects of the study treatment. For example, in patients with incontinence assigned to a placebo-control arm of a study, one might expect a symptom to worsen and thus have an effect on daily functioning. The point is to select PRO measures that are sufficiently sensitive to detect changes in both the treatment and the control group patients. Use of the same measures for both groups will ensure an unbiased and comparable assessment.

c) Intervention

There are three major factors related to the intervention that are relevant to PRO assessment, and therefore require careful consideration: 1) the positive and adverse effects of treatment; 2) the time course of the effects; and 3) the possible synergism of the treatment with existing medications and conditions. It is crucial to understand how a proposed treatment can affect patient outcomes in both positive and negative ways. For example, some drug therapies may relieve LUTS but produce side effects like dry mouth or sexual dysfunction.

In addition, the time course of an intervention's effects on PROs is also critical both in terms of the selection of measures and the timing of when PRO measures are administered to study participants. For example, in a trial comparing coronary artery bypass graft (CABG) surgery to angioplasty, an assessment of PRO one week post-intervention might lead to an interpretation that the surgical arm had worse outcomes than angioplasty for PRO since the individuals in this arm of the trial would still be suffering the effects of the surgical procedure (for instance, sore muscles and surgical site discomfort) which could overwhelm any benefits associated with CABG. However, at six months post-intervention, the benefits of CABG surgery such as, relief from angina might be more profound than the benefits received from angioplasty. Thus the timing of when PROs are assessed could influence how one interprets the benefits (or negative effects) of the interventions.

Finally, it is important to have a clear understanding of the current medications the patient population is likely to be taking prior to randomisation to the study treatment, and how these medications might interact with the trial intervention, (either a pharmacological or behavioural intervention), to influence patient outcomes.

Quality-adjusted Life Year (QALY)

Increasingly HRQoL outcome measures are being used in the development of Quality Adjusted Life Year (QALY) measures. A QALY is a universal health outcome measure applicable to all individuals and all diseases, which combines gains or losses in both life quantity (mortality) and life quality (morbidity) and enables comparisons across diseases and programs. QALYs are widely used for cost-utility analysis. In the past decades, economic evaluation has been increasingly important for the decision maker to decide which treatment or intervention is more cost effective, in order to allocate limited healthcare resources soundly. Economic evaluation aims to compare interventions in terms of their costs and benefits, including their patient outcome impact. Health benefits can be quantified as QALYs which have become a standard measure and are now recommended in most of health economics guidelines as the method of choice. The economic chapter contains additional information regarding QALYs.

III. LITERATURE SEARCH STRATEGY

For the current version of this chapter the previous literature search was updated. A number of databases were accessed, electronically, with specific search criteria, such as validation work from the period January 2006 through August, 2021. Age and gender limits were not specified. Databases used included Pub-Med/MEDLINE, and websites accessed included oab.com, proqolid.com, ncbi.nlm.nih.gov and mapi-institute.com.

The following key words were used separately and/or in combination: "urinary incontinence", "urinary symptoms", "urgency", "overactive bladder", "stress incontinence," "incontinence," "questionnaire," "epidemiology," "prostate," "prolapse," "faecal," "bowel," "anal," "quality of life," "sexual," "geriatric," "paediatric," "satisfaction," "symptom bother," "goal attainment", "screener," and "gener-

ic." Questionnaires evaluated in this chapter were updated with any new information if new validation work was found. New questionnaires not in the previously updated resource tool were added to appropriate sections if they were validated and relevant with regard to the search terms specified above. Grades were evaluated for correctness, based on previous and new validation work, and modified if and when necessary to demonstrate any changes with respect to instrument validation.

Table 2: Ideal properties of PRO instrument (adapted from [19], [20])

Specific to the concept being measured
Based on end-point model
Good psychometric properties (reliability, validity, responsiveness, conceptual equivalence…)
As short as possible (minimum burden) but never too short
Wide use
Available in different languages and cultures
Easy scoring (the simpler the better)
Self-administered
Inexpensive

IV. PRO QUESTIONNAIRE DEVELOPMENT AND VALIDATION

PRO questionnaires can be used to record the presence and severity of urinary, bowel and sexual symptoms, as well as the impact of symptoms on everyday activities, health-related quality of life and satisfaction with treatment, etc. To ensure that the results obtained with PROs are clinically useful, data must be gathered using valid and reliable instruments. The characteristics of an ideal PRO instrument are shown in **Table 2**. Questionnaire design and development is not a simple process. Developing such instruments requires a multistep, structured process that incorporates cognitive psychology, psychometric theory, and patient and clinician input. The process begins by determining the intent and purpose of the PRO and culminates in studies that demonstrate the measure's validity, reliability, and responsiveness. The specific steps required for developing a PRO questionnaire are outlined in the following section and are shown in **Table 3**.

The development of a PRO is a rigorous, scientific process to provide confidence that the PRO is measuring what it is intended to measure, that it does this reliably, and is appropriate for use in the patient or population group under investigation. The final instrument must have demonstrated validity and reliability in the intended target population. PROs need to be developed with patient and clinician input and have the psychometric, or measurement, properties of the PRO evaluated to determine that it is a valid outcome measure. To be a useful measurement tool, a PRO instrument must also be easy to administer, reliable, and valid. Only PROs that have undergone this process and have published validation data are discussed in this chapter.

Table 3: A detailed description of PRO development phases (Adapted from ICI 2013 and Berger et al, [21])

Theorization of a conceptual framework	Outline hypothesized concepts and potential claims Determine intended population Determine intended application/characteristics (type of scores, mode and frequency of administration) Perform literature expert review Develop hypothesized conceptual framework Place PROs within preliminary endpoint model Document preliminary instrument development
Adjustment of the conceptual framework and outlining instrument	Obtain patient input Generate new Items Select recall period, response options and format Select mode/method of administration/data collection Conduct patient cognitive interviewing Pilot test draft instrument Document content validity
Authentication of the framework and evaluation of further measurement properties	Confirm conceptual framework with scoring rule Assess score reliability, construct validity, and ability to detect change Finalize instrument content, formats, scoring, procedures and training materials Document measurement development
Collect, examine and interpret data	Prepare protocol and statistical analysis plan {final endpoint model and responder model) Collect and analyze data Evaluate treatment response using cumulative distribution and responder definition Document interpretation of treatment benefit in relation to claim
Adapt the PRO instrument	Change wording of items, populations, response options, recall period, or mode/method of administration/data collection Translate and culturally adopt to other languages Evaluate modifications as appropriate Document all changes

De Vellis has proposed an eight-step process of scale development:

- "Determine clearly what it is what you want to measure": it is necessary to clarify exactly what it is that is going to be measured, including the different aspects (domains or dimensions) and what the purpose of that measurement is.
- "Generate an item pool"
- "Determine the format for measurement": Likert, pictorial, rating, anchored VAS or VAS, scales, multiple response, check lists, etc.
- "Have initial item pool reviewed by experts"
- "Consider inclusion of validation items"
- "Administer the items to a development sample": to pilot the new instrument with a small group of patients drawn from the target population.
- "Evaluate the items": this is the process to analyze the psychometric properties of the items of the scale.
- "Optimize scale length": it is obtained by deletion of poorly performing or redundant items.

1. DETERMINING QUESTIONNAIRE INTENT AND PURPOSE

The first task in developing a PRO measure is to determine why the instrument is needed. Given the current number of disease-specific questionnaires available in the field of incontinence and related pelvic disorders, a new PRO measure must fill a need that has not already been met by an existing instrument. Once the need for the measure is recognized, its purpose and clinical usefulness need to be considered because the purpose dictates the validation design process. For example, a symptom and a treatment satisfaction measure would be developed and validated differently because the outcome is different.

The development stage would focus on the outcome of interest (e.g., symptoms patients experience and the significance of each symptom, or what issues patients consider when determining how satisfied they are with treatment) with the items derived from the patient perspective and relating to the outcome of interest. Validation efforts would include designing a study focused on the outcome of interest, with the appropriate patient inclusion/exclusion criteria to enhance generalizability, while maintaining internal consistency and providing opportunities to test—at a minimum—reliability and validity.

2. DEVELOPING THE ITEMS

Designing a clinically useful PROM involves more than just developing a series of questions. In addition to clinician input and literature review, questionnaire items must be generated from a patient perspective and include patient views. The type of population can help to generate item wording, evaluate the completeness of item coverage, and perform initial assessment of clarity and readability. This is obtained through focus groups or one-to-one interviews to provide qualitative data on issues pertinent to patients and to identify the words patients use to describe their symptoms or disease impact. Focus groups and one-to-one interviews should be carefully planned to address the goals of the questionnaire being developed. For example, if a measure is intended to assess symptom bother, interview questions should pertain to the patient's symptom experience. Importantly, rather than using clinical terminology which patients may not comprehend, the words used during the focus groups or interviews should be common to patients. The results of the qualitative patient interviews lead to item generation. The process is done until saturation. Saturation is reached at the point when no new relevant or important information emerges and collecting additional data will not likely add to the understanding of how patients perceive the concept of interest and the items in the questionnaire. After items are generated, the newly drafted questionnaire should be reviewed by other patients and experts to ensure its readability and content validity.

An alternative approach is to adapt an existing measure to meet the needs of a new patient population or a different condition. The adapted questionnaire must be newly validated in the target population as the validity of the original questionnaire does not apply to an adapted measure.

For newly developed and adapted questionnaires, think out loud interviews or cognitive interviews can be used to ascertain the correctness and validity of the revised questionnaire. In the first approach, patients think out loud about what the question means to them and how they think through their response. For a cognitive interview approach, patients review and respond to the questionnaire items, and then they are interviewed about what each item meant to them as they completed the questionnaire. Both approaches provide information about what patients are considering when answering each question.

3. HEALTHCARE LITERACY

Healthcare literacy is defined by the CDC as "the degree to which an individual has the capacity to obtain, communicate, process, and understand basic health information and services to make appropriate health decisions". It is generally recommended that healthcare information (including PROMs) should be written in language no higher than a sixth to eight grade reading level. Avoiding clinical terminology and making words easy to understand provides the best opportunity for PROMs to be answered accurately even by those with lower healthcare literacy.

4. DETERMINING THE MODE OF ADMINISTRATION OF A QUESTIONNAIRE

When generating the PRO items, the mode of administration must be considered. Will the measure be completed by the patient (i.e., self-administered) or administered by an interviewer (i.e., interviewer-administered)? How the questionnaire will be completed needs to be determined before the validation stage because mode of administration can affect patient responses. For highly personal or intimate questions, a self-administered questionnaire is recommended to avoid response bias. Questionnaires that are self-administered are preferable to interviewer-administered questionnaires because the data collection burden is reduced and patients are more likely to provide unbiased information on self-administered questionnaires. Importantly, if a questionnaire has been validated for a particular mode of administration (self-administered pen and paper), this does not make the questionnaire valid for all modes of administration (e.g. electronic administration via web or hand held device). Should the mode of administration change from the original validation, processes must be undertaken to ensure no change in meaning or content have occurred with the format change. Recommendations

for this type of adaptation (from PRO to ePRO) are clearly outlined by Coons et al.

5. QUESTIONNAIRES' PSYCHOMETRIC PROPERTIES

All PROMs must demonstrate reliability, validity, and responsiveness, which are described in detail below. This can be accomplished in several ways:

- Perform a stand-alone cross-sectional study to validate the questionnaire in the patient population for which it was designed;
- Administer the untested questionnaire in a clinical study and use the baseline data to perform psychometric validation (the end-of-study data can also be used to evaluate responsiveness); or
- Perform a stand-alone longitudinal study with an intervention to determine the instrument's psychometric performance and responsiveness in a non-clinical trial setting.

The following psychometric properties must be tested for and demonstrated in a validated questionnaire.

Reliability refers to the ability of a measure to produce similar results when assessments are repeated (i.e., is the measure reproducible?). Reliability is critical to ensure that change detected by the measure is due to the treatment or intervention and not due to measurement error. Reliability can be predicted in three ways: 1) internal consistency 2) test-retest reliability (reproducibility), 3) inter-rater reliability. Inter-rater reliability does not apply to PROs and will not be developed in this chapter.

Internal consistency indicates how well individual items within the same domain [or subscale) correlate. Cronbach's alpha coefficient is used to assess internal consistency reliability, with higher alphas indicating greater correlation. Typically, Cronbach's alpha should be greater than 0.70 to indicate adequate internal consistency reliability [26,,]. Alpha-coefficient values >0.90 suggest possible redundancy in the questionnaire items. If the item-to-total alpha is less than 0.20, the question should be removed or rewritten. Item-total correlation is yet another test that may be considered for internal consistency. It is the measure of the association between an item and the total score from the set of the items within the scale [22]. It can be measured by using Pearson correlation coefficient. If the value of the Pearson correlation coefficient is high then there is a stronger relationship between the items.

Test-retest reliability, or **reproducibility,** indicates how well results can be reproduced with repeated testing. To assess test-retest reliability, the same patient completes the questionnaire more than once, at baseline and again after a period of time during which the impact of symptoms is unlikely to change (e.g., a few days or weeks) [26, 27]. The Spearman's correlation coefficient and intraclass correlation coefficient (ICC) are used to demonstrate reproducibility. For group data, a Spearman's correlation coefficient or an ICC of at least 0.70 demonstrate good test-retest reliability [7,26, 27].

Validity is a qualitative assessment and refers to the ability of an instrument to measure what it was intended to measure [26, 27]. A PROM should be validated for each specific condition, patient population, and language for which it will be used. For example a measure designed to assess stress incontinence would not be valid for OAB unless it were specifically validated in patients with OAB symptoms. Validity includes content, criterion, and concurrent validity.

Content validity is a qualitative assessment of whether the questionnaire captures the range of the content it is intended to measure [26, 27]. For example, does a measure of symptom severity capture all the symptoms that patients with a particular condition have, and if so, is the measure capturing the items in a manner meaningful to patients in language patients can understand? Content validity can affect all other measurement properties. Irrelevant items and missing concepts may decrease internal consistency and responsiveness. Good reliability does not guarantee that the full construct of interest is being measured or that no important concepts are missing thus risking over- or underestimating outcome results[7]. FDA guidelines recommend establishing content validity before testing other psychometrics[1]. To obtain content validity, patients review the measure and provide feedback as to whether the questions are clear, unambiguous, and comprehensive. FDA recommends to document the development process and instrument attributes to support content validity, including: item generation, data collection method, instrument administration mode, recall period, response options, instrument format, patient understanding, scoring system and respondent-administrator burden[1].

Criterion validity reflects the correlation between the new questionnaire and an accepted reference, or gold standard [26,] . One difficulty in establishing criterion validity is that a gold-standard measure might not be available [22,29]. Correlations approaching 1.0 indicate that the new questionnaire is very similar to the gold-standard measure and might be redundant[22,29]. When criterion validity can be established with an existing measure, the correlation should be 0.40 to 0.70. Criterion validation is usually divided in two types: concurrent validity and predictive validity[26].

Concurrent validity is a type of Criterion Validity. Concurrent validity measures how well a new test compares to a well-established test administered at the same time. It can also refer to the practice of concurrently testing two groups at the same time, or asking two different groups of people to take the same test.

Predictive validity: if the test accurately predicts what it is supposed to predict. It can also refer to when scores from the predictor measure are taken first and then the criterion data is collected later.

Construct validity is a quantitative assessment of whether the questionnaire measures the theoretical construct it was intended to measure [26, 27]. It encompasses convergent and discriminant validity.

Convergent validity indicates whether a questionnaire has strong relationships with similar PROM of the same concepts or variables. For example strong correlations should be seen between the new PROM and an existing tool measuring the same constructs. And weaker correlations should be seen with PROMs of unrelated constructs [26, 27, 28].

Discriminant validity indicates whether the questionnaire can differentiate between known patient groups (e.g., those with mild, moderate, or severe disease) [26, 27]. Generally, measures that are highly discriminative are also highly responsive.

Responsiveness indicates whether the measure can detect change (for better or worse) in a patient's condition. An aspect of responsiveness is determining not only whether the measure detects change but whether the change is meaningful to the patient. This can be done by determining the minimal clinically important difference (MCID) of the measure.

Minimal clinically important difference (MCID) is the smallest change in a PROM score that would be considered meaningful or important to a patient. A second component of MCID is the smallest change which would be related to a change in patient management. A treatment that is statistically significantly better than another may not necessarily have made a meaningful difference to the patient; the MCID indicates whether the treatment made such a difference from a patient perspective.

Unfortunately, there is no scientific test for MCID as it is an iterative process that involves two methodologies to determine the MCID of a questionnaire: an anchor-based approach or a distribution-based approach. With the anchor-based approach, the MCID is determined by comparing the measure to other measures (or "anchors") that have clinical relevance [33]. With the distribution-based approach, the MCID can be determined by the statistical distributions of the data [33], using analyses such as effect size, one-half standard deviation, and standard error of measurement [33,34].

Another methodology to evaluate treatment benefit is to examine the cumulative distribution function (CDF) of responses between treatment groups. The CDF provides plots to examine the treatment effect and mean improvements by treatment group to see if the mean improvement varies by patient subsets [1, 35].

6. LINGUISTIC AND CULTURAL VALIDATION

Cross-cultural research has specific methodological problems, most related to translation quality and comparability of results in different cultural and ethnic groups. Increasingly, PROMs are required to be used in a number of different populations and settings, however, questionnaires and their psychometric properties are not necessarily transferable. It is not enough to translate a questionnaire literally. The challenge is to adapt it in a comprehensible and cultural form, maintaining the meaning and intention of the original questions. A measure that is valid and reliable for a particular language and culture may not prove to be so after translation. As most of the questionnaires have been developed and validated in English, there is a potential risk of cultural bias. Linguistic and cultural adaptation of a questionnaire can occur during the development phase before validation, or it can be done after the questionnaire is validated in the language in which it was initially developed, with the latter being the more common approach. Ensuring the linguistic and cultural validity of a questionnaire is especially important for measures used in multinational clinical trials [36,37]. Cultural validation is needed if the questionnaire is available in the target population language, but it was developed in a different cultural and social context (for example Spanish from Spain and Spanish from South America). Both linguistical and cultural validations are necessary if the language is not the same.

There are different approaches to the translation process. The simplest and most common (but less reliable) is the direct translation (made often by unqualified translators) to the new language without further validation measures. The second is the translation committee: 2 or more translators work together or separately to produce a consensus questionnaire. The third is the back translation method: one translates into the new language and a second independent translator comes back to the original language; then two versions are compared.

Producing high-quality translation is labour-intensive and time-consuming. Many different translation methods exist, and there is no scientific evidence than one is superior to another. Although, there is the lack of scientific evidence in favour of one specific method of translation, it is strongly recommendable to adopt a multistep approach to ensure quality[37].

The ISPOR (International Society for Pharmacoeconomics and Outcomes Research) Task Force for Translation and Cultural Adaptation recommends some principles of good practice for the translation and cultural adaptation process for PROMs, which can be summarized in 10 steps:

1. Preparation: obtain permission to use the instrument, recruit key researchers to the project, invite instrument developer to be involved, etc.
2. Forward translation: there is a general agreement that more than one forward translation is needed, and all forward translators should be native speakers of the target language with previous experience in the translation of PROMs.
3. Reconciliation: resolves discrepancies between translations, should be carried out by researches and translators.
4. Back translation: of the reconciled translated version into the original language. Back translators should be native speakers of the original language.
5. Back translation review: comparing with original version to ensure conceptual equivalence of the translation. Some methods using Likert scales for assessing comparability of the language (refers to the formal similarity of the words, phrases and sentences) and similarity of the interpretability (refers to the degree to which the two versions engender the same response even if the wording is not the same) have been developed[38].
6. Harmonization: of the new translations through panel expert meeting
7. Cognitive debriefing: the new translated questionnaire is tested in a focus group of patients[5,6,7,8] native speakers of the target language, assessing the level of comprehensibility and cognitive equivalence with original tool.
8. Review of cognitive debriefing results and finalization
9. Proofreading: it is a final control quality step to fix minor errors previously undetected,
10. Final report

Some check lists to ensure the translation process quality have been proposed[34]. (and to encourage investigators to publish detailed steps. Design: From a synthesis of existing guidelines, we propose important considerations for getting started, followed by six early steps: (1. However, if a backward translation of the measure does not produce a semantically equivalent instrument, then the instrument may need to be developed in the target language, rather than just translated [36]. Equivalence between original and target PRO versions need to be achieved at many levels (**Table 4**).

After cultural and linguistic validation, PROMs should also be psychometrically validated within the target language. Thus, reliability, validity, and responsiveness need to be assessed with each language translation to confirm the same measurement properties are present in the translated language(s) and to ensure psychometric equivalence. If psychometric equivalence is not present (e.g., not achieving similar or better results in new language translation), the cultural and linguistic translations need to be re-evaluated and perhaps a new instrument may need to be developed.

The ICIQ questionnaires and many of the other questionnaires discussed in this chapter have multiple linguistically validated versions making them useful for International implementation. It is also

Table 4: Terminology in linguistic and cultural validation [36]

Conceptual equivalence	It is the equivalence in relevance and meaning of the concepts and domains of health an QoL being measured in different languages and /or cultures.
Item equivalence	It exists when items estimate the same characteristics and they are equally relevant and equivalent in both languages and cultures
Semantic equivalence	The meaning and the level of the language have to obtain the same psychological and understanding effects on both populations
Operational equivalence	It refers to the possibility of using a similar PROM format, instructions, mode of administration and measurement method in both populations
Measurement equivalence	The comparability of the conceptual and psychometric properties of the data obtained in different languages or cultural versions It applies for data obtained from PRO via two administration modes[25]
Functional equivalence	It is defined as the extent to which an instrument does what is supposed to do equally well in two or more cultures (or modes of administration)

important to note that the step after linguistic validation, demonstrating psychometric equivalence, should also be demonstrated to ensure that the PROM performs equivalently in different languages and cultures.

7. BIASES IN RESPONDING TO QUESTIONNAIRES AND SCALES

We generally assume that patients will respond honestly to questionnaires, but this is not a reflection of the reality. A number of factors may influence the response. Many different biases have been identified and should be minimized as much as possible.

Cognitive requirements[26] Answering questions is a complex cognitive task that usually has 4 steps (each of them with potentially bias risk):

1. Understanding: it is important to avoid ambiguous items, to use simple language and to avoid the "time-frame" effect. If you give a patient a long time-frame ("over the last year"), they will be more likely to remember the one worst event over that time frame. This is less with a shorter time frame ("over the last week").
2. Recalling the relevant behavior, attitude or symptom: patients need to recall specific events to answer questions, and it is very common to forget them. Patient memories for events that occur over a period of one year are extremely poor. Patients with chronic conditions have difficulties recalling specific events. It may be even more difficult if the disorder shows fluctuating symptoms over time. Patients with pain disorders tend to recall the last and most painful event suffered just prior to completing the questionnaire.
3. Inference and estimation: patients tend to overestimate infrequent events and underestimate frequent ones. Very often numerical responses are given in multiples of 5 or 10.
4. Mapping the answer onto response alternatives: the patient's response has to adapt to the questionnaire format, and in the "translation" process some information may be lost.

Questionnaires (especially those with many items) require a cognitive effort, and patients tend to minimize it. This is called the "satisfying" strategy, and results when a patient accepts the available option as satisfactory. However, that option may not be truly representative of their symptoms.

The strategy has 6 forms:

1. Selecting the first option that seems reasonable: in written forms, patients tend to choose the first item on the list, and in verbal forms they more easily remember the most recent option.
2. Simply agreeing with every statement, or answering "true" or "false" to all items.
3. Endorsing the social "status quo"
4. Selecting one answer to the first question and using it for all the rest. This is a typical problem of Likert and analog scales.
5. Answering "I don't know" or a neutral position in Likert scales.
6. Choosing the options randomly.

Minimizing this "satisficing" bias requires the tool to be as simple as possible (few items, one thing per item, short recall period, few options but including all the possibilities and be appropriate). Motivating the patient is crucial for avoiding satisficing bias.

Social desirability This bias appears when patients want to give a socially desirable answer. When the patient is not aware of it, is also called *self-deception*. When the patient is aware of it and is intentionally attempting to give a positive impression, it is also called *faking good*. Many factors can influence social desirability bias (individual, gender, cultural background, etc.).

Deviance (faking bad) This is the opposite to social desirability, a tendency to respond with deviant responses, occurring specially in the context of personality assessment.

The hello-goodbye effect. This is a well-known phenomenon that occurs typically in interventional clinical studies. At the beginning the patient presents himself as bad as possible for ensuring the staff include him in the study, and at the end, he may want to thank the investigators showing an improvement better than the real one, minimizing the actual problem.

Acquiescence Also called *yes-saying* bias, is a tendency to give positive responses. There is an equivalent bias for *no-saying* responders.

End-aversion Also called *central tendency bias*, when patients avoid systematically extreme options in a scale. The effect of this bias is to reduce the range of possible responses (losing reliability and sensitivity). This bias is highly influenced by social and cultural factors (e.g. some Asian cultures are considered more collectivistic, and individuals do not like to be considered different from the group).

Positive skew The responses are clustered in a positive trend. The result is a ceiling effect, and as most of the responses are in one extreme, then it may be very difficult to detect improvements after any intervention.

Framing. The manner in which a question is posed affects the results obtained. For example, it is not the same to ask about preferences of taking a drug giving the information of 1% of morbidity, or 99% of no adverse events.

Biases related to measurement change. The *response shift phenomenon*: self-judgment of health or QoL may remain stable despite large objective changes or the reverse, may change without objective variations. This is due to tree cognitive process: recalibration, reconceptualization and reprioritization. The description of this process is out of the goals of this document.

An alternative point is that patients do not remember the previous state. They are only conscious of the actual state, and try to infer what the initial state must have been. This is the *implicit theory of change.*

Hawthorne effect. Patients enrolled in clinical studies tend to pay more attention to questionnaire items than they would do in daily clinical practice, because they think clinicians may require them some explanation for their answers.

8. REGULATORY OVERSIGHT

As clinicians and scientists have begun to appreciate and accept PROs as appropriate outcome measures, regulatory authorities have issued guidance documents on current best practices in the development and implementation of PROMs in the approval process of medical devices[1, ,]. For PROs to be acceptable outcome measures for regulatory authorities, documentation of measurement properties must be present as well as evidence of inclusion of the patient perspective and understanding of the PRO and a cohesive conceptual framework that stipulates how the PRO is related to the intervention. While PROs within this document may have a "recommended" status, they may not meet all of the required regulatory guidelines and may require additional validation work either from a qualitative or quantitative perspective. Researchers seeking approval for medical devices should contact regulatory authorities early in the process of selecting a PROM for clinical trials to ensure regulatory acceptance of the PROM. The FDA's Medical Device Development Tools (MDDT) program qualifies tools that can be used during the medical devise approval process[10]. This process includes many measurement tools including PROMs. Qualification of a PROM means that the FDA has evaluated the supporting evidence for the tool and found it to have good qualities. The Center for Devices and Radiological Health PRO document gives a few examples of qualified PROMs including the International Prostate Symptom Score (I-PSS).

9. ELECTRONIC PATIENT REPORTED OUTCOMES

The use of electronic PROs (ePROs) and studies comparing transfer from paper to electronic format date back to the late 1990s[4]. Today the use of ePROMs is well established in research and is increasingly seen in clinical practice. These tools can vary from simple pre and post treatment data collection to complex, multisystem programs which track patient information regularly (usually weekly) and send alerts to medical professionals when responses are out of range. Easy to use ePROMs have been shown to result in increased compliance and patient satisfaction[8]. Some medical professionals have expressed concern that only collecting patient symptoms on ePROMs may miss important symptoms. In the clinic, all PROMs should be reviewed with the patient during a one-on-one interview to ensure that all symptoms and concerns have been addressed. The majority of research in comprehensive ePROMs is in the treatment of cancer and has shown improvements in patient care and HRQoL,,. Electronic data collection (ie ePROMs) allows clinicians to longitudinally monitor response to therapy and advancement of disease without increased clinical time investment[49]. Standardized routine symptoms and QoL assessment is a key component of quality patient centered care. Privacy of ePROs must be secured and considered in creation, maintaining, archiving, retrieving, and transmitting clinical data[1].

There are benefits and negatives to the use of ePROs in research and clinical practice (**Table 5**). Overall the benefits far outweigh the negatives in research. It has been shown that electronic data collection yields more reliable and accurate data, allowing a stronger test of the study objectives and a better picture of the patient's experience (16). Studies show no significant variation of scores from paper to electronic tool in older patients or those with low computer literacy [4,8]. An area where ePROs can have a positive influence is in patient reported adverse events. Research shows adverse event symptoms are often under-reported by clinical researchers. The field of cancer treatment has led this research with large data bases

Table 5. Benefits and drawbacks of ePRO (taken from multiple sources including Brancato G et al 2006)[50]

Benefits of ePRO	Drawbacks of ePRO
• Reduce missing data by requiring an answer before advancing • Can include complex skip patterns • Easily captured in the electronic medical record reducing data entry error by medical professionals • Real time ePRO reduce recall-bias (avoid retrospective data entry by the patient) • Automatic scoring • Increased patient compliance • No out of range data • More accurate in recording sensitive topics such as sexual function, drug use, or adverse events • Multiple formats available (personal computer, tablet, smartphone) • Convenience for massive interviews (web based questionnaires)	• An electronic device is needed • Difficulties of some patients in interacting with computers (computer anxiety or computer illiteracy) • Space limitations requiring splitting of questions (questions and responses must be short) • Referring back to response of a previous question is more difficult (flow and navigation must be easy for patients) • Should be completed in less than 30 minutes • Inability of the patient to add information about symptoms or concerns not included in the tool

of ePROMs on adverse events in chemotherapy and other cancer related treatments[49] .

Measurement equivalence studies investigate the comparability of the conceptual and psychometric properties of the data obtained via two administration modes such as paper versus electronic questionnaires[25]. These studies have also looked at the comparability between ePROM types such as handheld device versus desk top or web based versus interactive voice response system (IVRS). Several large studies and meta-analysis have shown good measurement equivalence between paper and electronic PROMs [4,8,25,,]biological agents, and devices was underscored by the release of the US Food and Drug Administration's draft guidance for industry titled \"Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.\" The intent of the guidance was to describe how the FDA will evaluate the appropriateness and adequacy of PRO measures used as effectiveness end points in clinical trials. In response to the expressed need of ISPOR members for further clarification of several aspects of the draft guidance, ISPOR's Health Science Policy Council created three task forces, one of which was charged with addressing the implications of the draft guidance for the collection of PRO data using electronic data capture modes of administration (ePRO. A recent meta-analysis shows ePROMs are quantitatively comparable to paper with a difference in absolute scores of less than 2% and a pooled correlation coefficient of 0.88 (95 % CI 0.87 to 0.88)[8]. This paper reviewed ePROMs used in 23 different patient populations including cancer, depression, orthopedic, pulmonary, neurological conditions, and more[8]. Types of ePROM, in order of their uses, include: desk top computers, handheld devices such as smart phones, tablet / touch screen devices, and interactive voice response system (IVRS). Studies comparing paper to tablet conversion show the greatest level of agreement. Studies comparing paper versus IVRS had the lowest level of agreement although it is still good (true agreement 0.82)[8].

Coons et al defined levels of changes in migrating PROMs from paper to electronic format as follows[25]. Minor changes are described as transferring a paper questionnaire into a text screen format without significantly altering item content, recall period or response options. Minor changes also include going from multiple items per page to one item per screen. Meta-analysis of measurement equivalence studies shows there is no need to perform quantitative migration studies for minor changes from paper to electronic format [4,8] evaluating 278 scales, provided sufficient detail to allow quantitative analysis. RESULTS Among 233 direct comparisons, the average mean difference between modes averaged 0.2% of the scale range (e.g., 0.02 points on a 10-point scale However there is a need to standardize migration practices.

Moderate changes include changing the order of the questions, requiring a scroll bar to view the full question or all the responses, or splitting an item into multiple screens (e.g., having a question and its responses on different screens). Moderate changes to a questionnaire would require formal measurement equivalency testing. This testing would be required to ensure comparability between scores in different formats but also to ensure usability of the electronic format. Transfer to IVRS is the most common moderate change as it requires the transfer from visual to auditory testing. Significant changes and substantial modifications to a tool (including changes in wording or options) can fundamentally change the properties of an instrument and thus require a new full psychometric testing.

10. EPRO RELATED TO PFM DYSFUNCTION

In general, electronic versions of sexual, prolapse and digestive PROMs show good correlations with paper versions, and a high proportion of patients prefer ePROMs because they are easier to use[,,].

Some studies have not found differences in pain description between electronic a paper PROM versions,. Interestingly, Marceau et al[57] found that patients prefer electronic diaries and consider them easier to use; moreover, patients reported that the diary enabled them and their doctor to make care adjustments according to changes in pain status.

11. QUESTIONNAIRE DEVELOPMENT CONCLUSION

PROs are the most suitable method for assessing the patient's perspective of their lower urinary tract, sexual and bowel symptoms[34]. Questionnaires may be long and detailed for use in research, but need to be short and easy to use to be relevant for clinical practice. In addition to being valid and reliable, they need to be easy to complete and score, and, if they are being used to measure outcome, sensitive to change. Developing a new questionnaire and testing it thoroughly takes a great deal of time and is only necessary if there is not an existing instrument available.

There are many questionnaires currently available for use and these have been reviewed and described with recommendations from the Committee for their use in the last six ICI reports.

The major purpose of the ICI has been to provide a definitive international review and consultative opinion regarding the recommended measures to assess patient reported outcomes within the area of urinary incontinence and LUTS. To this end since the First Consultation, the ICI has worked to develop a modular format for the various patient reported outcomes allowing clinicians and researchers to select internationally recommended questionnaires for the assessment of their patients in both clinical practice and clinical trials. In this seventh ICI review, the ICIQ modular questionnaires (supported by the International Consultation) are presented in detail and their use evaluated. Whilst some of the modular questionnaires are still currently under full evaluation their content and format are presented within this chapter.

12. RECOMMENDED PRO QUESTIONNAIRES

Grades of Recommendation for Questionnaires 2021
As with previous Consultations, the Committee continues to use three grades of recommendation. However, we have added a + sign to indicate when published content validity is available for an instrument:

- Questionnaires were 'highly recommended' and given a **Grade A** if the Committee found "Published data indicating that the questionnaire is valid, reliable and responsive to change following standard psychometric testing. Evidence must be published on all three aspects and questionnaires must be relevant for use with

persons with incontinence. **Grade A + indicates there is additional evidence of *published* content validity."**

- Questionnaires were "recommended" and given a **Grade B** if the Committee found "Published data indicating that the questionnaire is valid and reliable following standard psychometric testing. Evidence must be published on two of the three main aspects (usually validity and reliability). **Grade B + indicates there is additional evidence of *published* content validity."**
- Questionnaires were considered to have "potential" and given **Grade C** if the Committee found "Published data (including abstracts) indicating that the questionnaire is valid or reliable or responsive to change following standard psychometric testing. **Grade C + indicates there is additional evidence of *published* content validity."**

The Committee decided that evidence published in abstracts or posters could be used to indicate a developing questionnaire's potential, but was not sufficiently peer-reviewed to provide the basis for a stronger recommendation.

As decided in the Fourth Consultation the recommendation will be to preferably utilize questionnaires from the ICIQ modules described in detail below. Many, but not all, of these questionnaires are Grade A or A+ questionnaires by previously stipulated criteria. Within the description of the ICIQ modules below the grade assigned to each module is indicated.

Should none of the modular questionnaires be deemed appropriate for specific research or clinical purposes, ICI's recommendation is to use a Grade A+ or A questionnaire as previously recommended. When no suitable instrument exists a Grade B or C questionnaire, performing additional validation as indicated prior to use if feasible, should be used.

For UI and UI/LUTS, the Committee examined the quality of the psychometric evidence. Only where published data were scientifically sound was the label 'with rigor' allowed. Where the Committee had concerns about the quality of evidence, this is noted in the descriptions of the questionnaires below. The Committee considered that the number of high quality questionnaires means that there are now sufficient questionnaires for most purposes and it is not necessary to encourage the development of new questionnaires, except for particular patient groups.

V. INTERNATIONAL CONSULTATION ON INCONTINENCE MODULAR QUESTIONNAIRE (ICIQ): WHAT IS THE ICIQ?

The ICI Questionnaire project was started in 1998, to meet the need for universally applicable questionnaires for use in clinical practice and research[1]. It was recognised that there was a proliferation of validated questionnaires each developed for a specific purpose and each subtly different. Although developers of the questionnaires were familiar with their content and use, the increasing number of questionnaires made appropriate selection difficult and limited the ability to compare similar clinical and research data due to different data collection methods.

The decision to develop standard questionnaire modules was taken by the Committee after the first ICI meeting in 1998, and resulted in the development of the ICIQ core questionnaires discussed in this section. The first questionnaire as a result of this initiative was the ICIQ-Urinary Incontinence Short form (ICIQ-UI-SF) for the assessment of urinary incontinence and its impact on quality of life. This remains the most widely used and requested questionnaire and has now been translated into over sixty languages.

An international advisory board was established to continue the development of the modular ICI questionnaire and to expand the scope of the modules to evaluate symptoms and impact of dysfunction of the lower urinary tract, lower bowel and pelvic organ prolapse. The advisory board consisted of clinicians and researchers with experience in the design and use of questionnaires representing the major societies involved in the assessment and research of lower genital tract, lower urinary tract and bowel function. The ICIQ recognised that many high quality published questionnaires already existed and, with permission from the authors, those instruments were adopted into the modular project. It was not possible to adopt all available questionnaires and where more than one option existed, the most appropriate questionnaire for the purpose was included. Where high quality questionnaires were not available, the need to develop a new questionnaire was acknowledged Researchers who have developed questionnaires that they would like to be reviewed by the advisory board for inclusion are encouraged to contact the ICIQ group through the website www.iciq.net. The ICIQ research group is based in the Bristol Urological Institute, at Southmead Hospital, Bristol, in the United Kingdom.

1. AIMS AND OBJECTIVES

The ICIQ's objective is to provide international consensus on the use of patient completed questionnaires for the assessment of lower pelvic symptoms and their impact on patient's lives. Four aims underpin the ICIQ in order to achieve clarity over questionnaire use:

1. To develop psychometrically validated questionnaires to evaluate symptoms and impact of dysfunction of the lower urinary tract, lower bowel and pelvic organ prolapse.
2. The adoption of existing questionnaires, that are psychometrically valid and complement the existing ICIQ questionnaires
3. To increase the use of patient reported questionnaires to standardise the assessment of lower urinary tract, lower bowel and pelvic organ prolapse and their impact on patients' lives.
4. To use the questionnaires to facilitate communication in different patient settings and different patient groups both in clinical practice and wider clinical research

The ICIQ Questionnaires are developed according to rigorous methodology which complies with industry-standard guidance for PRO development[1]. The ICIQ continues to update its methodology to maintain pace with the current advances in PROM development. Questionnaires that are newly developed and adopted as part of the ICIQ modules must meet current regulatory guidance and standards of documentation. As part of this, the development should include patients at each stage, and be published in scientific journals, to allow the quality of development to be publically available for the assessment of quality. The ICIQ's international nature requires that linguistically validated translations are available. More than 300 language versions of various modules have been validated to date and conducted according to an established protocol[62].

Table 6. The ICIQ Modular Structure

CONDITION	RECOMMENDED MODULES	OPTIONAL MODULES	RECOMMENDED ADD-ON MODULES		
	A) Core modules		**QoL**	**Sexual Matters**	**Post-Treatment**
Urinary Symptoms	Males: ICIQ-MLUTS Females: ICIQ-FLUTS	Males: ICIQ-MLUTS LF Females: ICIQ-FLUTS LF	ICIQ-LUTSqol	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	ICIQ-S* (satisfaction)
	ICIQ-Bladder diary				
Vaginal Symptoms	ICIQ-VS		ICIQ-VSqol*		
Bowel Symptoms	ICIQ-B	ICIQ-IBD			
Urinary Incontinence	ICIQ-UI SF	ICIQ-UI LF*	ICIQ-LUTSqol	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	
CONDITION	B) Specific Patient Groups		QoL	Sexual Matters	
Nocturia	ICIQ-N		ICIQ-Nqol	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	
Overactive Bladder	ICIQ-OAB		ICIQ-OABqol	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	
Underactive Bladder	ICIQ-UAB/UAB PRO*				
Neurogenic	ICIQ-Neuro Bowel		ICIQ-Neuro bowel*		
Long term catheter	ICIQ-LTCqol				
Children	ICIQ-CLUTS*		ICIQ-CLUTSqol*		
Absorbent pads			ICIQ-Padprom*		
Cognitively impaired elderly	ICIQ-Qoldem*				
Inflammatory bowel disease incontinence	ICIQ-IBD				

2. ICIQ MODULES

In this chapter, questionnaires forming part of the ICIQ modular format are referred to as those **recommended** for use. Although many of the modules are Grade A or A+ questionnaires, others are still under various phases of development and are graded appropriately. Questionnaires that are in early stages of development are described as “in development”.

Nineteen ICIQ modules/questionnaires are currently available for use, with further modules in development (discussed in detail below). Clinicians or researchers can select module(s) to meet the requirements of their study or clinical practice. To simplify this selection process, modules have been categorised as shown in **Table 6**.

2.1. Core Modules

Questionnaires recommended to assess the core symptoms and impact on health related quality of life (HRQL) of lower pelvic dysfunction are contained in this section, in addition to impact on sexual matters. Core modules (**Table 6**) provide evaluation of:

- Lower urinary tract symptoms (Male and Female separately)
- Urinary incontinence
- Vaginal symptoms
- Bowel symptoms

Each symptom module is intended for the comprehensive yet succinct measurement of symptoms and associated ‘bother’. The bother item attached to symptom items, where applicable, enables the individual to indicate areas that cause the greatest negative impact on HRQL as perceived by them. This can be a more sensitive indicator of treatment goals than frequency of symptoms alone. The associated HRQL questionnaires cover specific issues that are a consequence of symptoms, such as life limitations and emotional impact. Sexual matters modules specifically evaluate the impact of lower urinary tract symptoms on this aspect from the male and female perspective.

A further core module has been added that moves away from the retrospective questionnaire format in the form of a bladder diary. This is a fully validated prospective tool for the measurement of bladder events as they occur.

2.1.1. Specific Patient Group Modules

Questionnaires to assess specific conditions or symptom complexes such as nocturia, overactive bladder and underactive bladder, in addition to management strategies such as long term catheter and pad usage are contained in this section along with HRQL modules for these specific symptom complexes where available. This category also includes specific patient groups, for example, children. These instruments contain only question items characteristic of the symptom complex or have been developed specifically for use in a diverse group This defines their context of use making the items/questionnaire only utilisable in this population.

- Nocturia
- Overactive bladder
- Underactive bladder
- Inflammatory bowel disease
- Lower urinary tract symptoms in children
- Individuals using long term catheters
- Individuals using absorbent pads

2.2. Optional Modules

This category lies within the core symptoms and includes lengthier questionnaires for more in- depth evaluation of lower pelvic dysfunction. There is the long form for the assessment of LUTS in men (ICIQ-MLUTS LF) and the long form for the assessment of LUTS in women (ICIQ-FLUTS LF). Whilst these questionnaires are suitable for use in clinical practice, they have not been shortened for clinical efficiency and are therefore more widely used in research studies where exploration of broader associated symptoms may be desired.

2.3. Post-treatment Module

The ICIQ-S assesses patient satisfaction experience, expectations and outcomes after urological surgery. The ICIQ-S is intended to be applicable to other urological patient populations after any urological or gynaecological procedure. A further questionnaire to assess patient satisfaction after urodynamic investigation is also under development.

3. GUIDANCE FOR USE OF THE ICIQ

The ICIQ recommends the use of a symptom and HRQL module that match the intended purpose of a study in order to provide a comprehensive evaluation of these two perspectives. The extent of burden placed on the respondent and the study or clinical outcomes must be considered however and ultimately guide questionnaire selection. The updated website, launched in 2019 www.iciq.net has the information required for permission for use, including licensing requirements if necessary. More information about the modules can be found here, including scoring instructions, sample copies and information on the associated validation publications. After registration through the website, access is given to the online library of the modules and translations where they may be downloaded freely. Additional information on any modules that are under development are also detailed here, and any announcements or developments are updated regularly through the ICIQ twitter account: @ICIQ_PROMs.

4. ICIQ QUESTIONNAIRE IMPLEMENTATION

The ICIQ modular questionnaire has attracted considerable attention from both clinicians and researchers worldwide since its structure was finalised in 2004. As of October 2019 there have been over 3700 publications that mention the 'ICIQ' or the modules[62]. The ICIQ is widely applied to clinical and general practice settings, alongside its considerable uptake for research purposes. The ICIQ has also been adopted in national guidelines for the management of urinary incontinence

The ICIQ is widely applied to clinical and general practice settings, alongside it's considerable uptake for research purposes. The ICIQ has also been adopted in national guidelines for the management of urinary incontinence in:

- women (NICE clinical guideline 171)
- primary care (SIGN 79)(www.sign.ac.uk/pdf/ sign79.pdf)

Table 7. The ICIQ modular structure (adapted from (Uren et al., 2020a)). The following modules were adopted as ICIQ modules with author's permission: ICIQ-Nqol, ICIQ-OABqol, ICIQ-LUTSqol. *These questionnaires are currently in development.

Condition	Core questionnaires				Post-Treatment
	Symptoms	**Optional**	**HRQoL**	**Sexual Matters**	
Urinary Symptoms	Males: ICIQ-MLUTS[53] Females: ICIQ-FLUTS[54]	Males: ICIQ-MLUTS Long Form Females: ICIQ-FLUTS Long Form	ICIQ-LUTSqol [13]	Males: ICIQ-MLUTSsex Female: ICIQ-FLUTSsex	ICIQ-Satisfaction[55]
Vaginal Symptoms	ICIQ-VS[56]		ICIQ-VS	ICIQ-VS	
Bowel Symptoms	ICIQ-B[57],[58]		ICIQ-B	ICIQ-B	
Urinary Incontinence	ICIQ-UI Short Form[61]		ICIQ-LUTSqol ICIQ-UI SF	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	
Prospective bladder events	ICIQ-Bladder diary[59]				
Condition	**Specific patient groups**				
	Symptoms		**HRQoL**	**Sexual Matters**	
Nocturia	ICIQ-N		ICIQ-Nqol[70]	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	
Overactive Bladder	ICIQ-OAB		ICIQ-OABqol[71]	Males: ICIQ-MLUTSsex Females: ICIQ-FLUTSsex	
Underactive Bladder	ICIQ-UAB*[72], [73]				
Long Term Catheter			ICIQ-LTCqol[74]		
Children	ICIQ-CLUTS[75]				
Absorbent Pads			ICIQ-PadPROM[76]		
Inflammatory Bowel Disease	ICIQ-IBD				
Cognitively Impaired Adults	ICIQ-Cog*[75]				

- included in a primary care resource pack by the British Society of Urogynaecology.

There is an ongoing demand for innovative digital solutions that facilitate the administration of the ICIQ modules in electronic format, for both research and clinical practice. The advantages are automatic collection of PROM data, reducing the need for costly paper administration and data analysis. Evaluations of electronic ICIQ modules have been completed, indicating equivalence of their measurement properties and acceptability to the target audiences. In addition, the ICIQ has partnered with an existing eHealth platform provider to pilot test an electronic option for the routine clinical and research administration of the ICIQ questionnaires.

5. CONCLUSION

The ICIQ modular questionnaire project (www.iciq.net) provides a growing series of standardised questionnaires for the patient reported assessment of lower pelvic dysfunction symptoms and their impact on patients' lives. The ICIQ provides clarity over the selection of questionnaires by recommending only those with evidence of high quality and robust psychometric validation including validity, reliability and sensitivity to change. Increasing awareness of the ICIQ aims to promote increased use of standardised questionnaires and further evaluation of existing modules in order to advance the evidence base supporting use of these tools. These efforts aim to increase communication between clinicians and researchers and enable more wide- spread comparisons between different treatments and patient groups worldwide. The ICIQ continues to have international usage, and facilitates dissemination through its website, online library and a social media presence. In future, it is anticipated there will be a greater demand for their use in electronic format for both research and clinical practice.

VI. PATIENT-REPORTED OUTCOME (PRO) QUESTIONNAIRES TO ASSESS THE IMPACT OF URINARY INCONTINENCE, OAB AND LOWER

1. URINARY TRACT SYMPTOMS

There are a variety of PRO measures available for use in clinical practice and research that assess a range of concepts (e.g. HRQL, patient satisfaction, symptom bother, etc). Encouragingly, PROs awarded the highest ICI grade are being used widely in studies, with short forms that are easily accessible being preferred. This section provides an overview and assessment of these measures. Importantly, clinical practitioners and researchers need to clearly determine their clinical and research objectives before selecting a PRO as it is these objectives and the target patient population that will help determine which validated PRO is appropriate to use. **Tables 8 to 12** provide a brief overview of all current PRO measures for urinary incontinence and LUTS, their purpose, psychometric properties, translation availability, and recommended ICI grade.

Please note, as instrument development and validation is an ongoing process, the tables below contain publications through to November 2020. As additional work may have been performed on an instrument, it is always prudent to conduct a further literature search and/or contact the instrument developer prior to selecting an outcome measure for your clinical practice or study. This is particularly relevant for translation availability, which we have not included here due to the dynamic nature of translation production. Further study-specific testing should also be considered to ensure a tool's appropriateness for the intended purpose.

When using a questionnaire in a patient group other than the group for which it was initially developed, cognitive interviews with the new patient population should be held to review the applicability of the questionnaire to the new patient group. Several of the main questionnaires to be discussed below have now had modified versions published in the literature. The Committee's view is that although it may be appropriate to modify established questionnaires for use with some populations, it is advisable to keep such modifications to a minimum, and to use the original versions whenever possible. Any modifications of established questionnaires may result in changes (sometimes substantial) in the psychometric performance of the instrument, and thus all modified instruments should be subjected to the same psychometric testing as that employed in developing a completely new instrument. Specifically, modified instruments should report information regarding the instrument's construct validity, reliability, and test- retest reliability, at a minimum, and sensitivity to change, in intervention studies.

2. HEALTH-RELATED QUALITY OF LIFE MEASURES

Health-related quality of life (HRQL) measures help to assess the impact of disease and treatment on those aspects of quality of life related to health. UI is a symptomatic condition that has been shown to affect many aspects of a patient's life - physical, emotional, and social relations and cause concern and burden. As such, it is important to assess HRQL in clinical research and practice as this can aid identification of the most troubling aspect of the symptom experience and guide individualised management planning. **Table 6** provides a quick overview of the variety of HRQoL measures available and their validity and characteristics to determine which mea- sure is suitable for your objectives.

3. PATIENT SATISFACTION AND GOAL ATTAINMENT SCALING

Patient satisfaction and Goal Attainment Scaling are two important but separate types of PROs that allow for individualised assessment of disease impact and treatment. Patient satisfaction is the subjective, individual evaluation of treatment and includes a complex consideration of multiple components including treatment effectiveness, side effects, and/or the accessibility and quality of service provided by the healthcare system. Goal attainment scaling (GAS) is a method developed to ascertain individual patient treatment goals and using those to facilitate patient-provider interaction and tailor the treatment plan based on those individual's goals .

Measures of patient satisfaction can include evaluation of care provision, availability of resources, continuity of care, efficacy, finances, humaneness, information gathering and giving processes, pleasantness of surroundings and perceived quality/competence of health care personnel. At its most basic level, satisfaction is a comprehensive evaluation of several dimensions of health care based

on patient expectations and provider and treatment performance. As an outcomes measure, patient satisfaction allows health care providers to assess the appropriateness of treatment ac-cording to patient expectations. In chronic diseases, where patients must live with treatment, patient satisfaction may be the distinguishing out-come among treatments with comparable efficacy.

Table 7 presents a summary of satisfaction instruments identified in UI, OAB and other LUTS.

GAS has been used to measure clinically important change in several therapeutic areas. Although it was originally developed to assess health outcomes in mental health settings, it has recently been expanded to include evaluations in urogynaecology[79]. GAS has been linked to several possible benefits compared with traditional outcome measures, such as improved clarity concerning treatment objectives for both the healthcare provider and the patient, active involvement of the patient in problem-solving efforts, establishment of realistic patient and healthcare provider expectations of treatment, and increased motivation of patients toward improving their health condition[80]. The end result of GAS is to clarify patients' expectations for their treatment, document goal achievement, and eventually increase patient satisfaction and improve therapeutic outcomes. The overwhelming distinction between GAS and other PROMs is the individualised nature of expectations are accounted for and the opportunity to address unrealistic goals can be actively managed.

One GAS instrument for lower urinary tract symptoms has been well developed, the Self-Assessment Goal Attainment (SAGA) questionnaire. Numerous linguistically validated translations are available at: http://www.pfizerpatientreportedoutcomes.com .

4. SCREENING TOOLS

In order to improve the detection of incontinence, OAB and other LUTS, several screening tools have been developed (**Table 8**). These tools help patients self-describe symptoms and facilitate diagnosis of LUTS by the clinician. Only the B-SAQ has been designed to screen for general lower urinary tract symptoms (LUTS) rather than solely symptoms of one condition. The majority of patients with LUTS have mixed urinary symptoms, and therefore a questionnaire which can detect more than one symptom complex may be more functional as a screening tool in clinical practice than a highly specific questionnaire. The Leicester Impact Scale (LIS), OAB-V8, OAB-SS and QUID are all Grade A, short, simple to understand and complete, and easy to interpret. However the LIS is interviewer, not patient administered. Importantly, with screeners, responsiveness is not assessed, however the sensitivity and specificity of each tool is critical.

5. ASSESSING SYMPTOM BOTHER AND OVERALL BOTHER

Measures to assess this are included in **Table 9**. The Patient Perception of Bladder Condition (PPBC) [65][65] and the Urogenital Distress Inventory are the only Grade A recommend instruments. However, there are several Grade B and C measures which assess bother for incontinence and LUTS.

Symptom bother questionnaires provide insights into the experience of urinary incontinence symptoms by comparison with presence or absence. Measures to assess this are included in **Table 9**. It is highlighted that a number of symptom scores include bother ratings and therefore important to review all potentially relevant assessment tools when selecting the instrument of choice. The Patient Perception of Bladder Condition and the Urogenital Distress Inventory are the only Grade A recommend instruments. However, there are several Grade B and C measures which assess bother for incontinence and LUTS.

6. ASSESSING THE IMPACT OF URGENCY

Several instruments have been developed specifically to assess urinary urgency, which is defined by the International Continence Society as "the complaint of a sudden compelling desire to pass urine which is difficult to defer". Urgency is the driving symptom of OAB, thus assessing the effect of treatment on this symptom and its impact on HRQL is important. With any measure designed to evaluate urgency, patients must be able to distinguish between the normal desire to urinate (urge) and the difficult-to-postpone need to urinate (urgency),. Wording thus becomes critical in the development of urgency assessment measures. Chapple and Wein make a case for describing urgency as a "compelling desire to void in which patients fear leakage of urine" as a means of distinguishing this abnormal sensation from the normal need to void. However, some patients may have a sensation of urgency without fear of leakage, further complicating attempts to define urgency. Importantly, with some of these scales, patients have the option of indicating that they experienced UUI (an event) rather than the strongest feeling of urgency (a sensation) itself. Several instruments have been developed to assess urinary urgency these are summarised in **Table 10**.

VII. QUESTIONNAIRES FOR SPECIFIC PATIENT GROUPS

Most studies and questionnaires have been developed for use with members of the general population or urology/gynaecology patients with incontinence or POP. However, some specific patient groups may experience particular problems with incontinence (for example, children, frail elderly or those who are severely disabled), which may require independent investigation and potentially the development of more specific measures or the addition of a new subset of items on already developed instruments. This is an important consideration during questionnaire selection as determining the context of use for the tool and its appropriateness to the population in question is essential. The Committee advises that researchers should use existing highly recommended or recommended questionnaires if possible as this aids comparison and to reduce the increasing proliferation of questionnaires. Many of the questionnaires developed below for particular conditions (e.g. prostate cancer) pre-dated the development of highly recommended questionnaires, and highly recommended questionnaires should be used preferentially.

1. OLDER PEOPLE

Urinary incontinence symptoms play an influential role on the overall HRQL in older people (>65) and causes a significant decrease in HRQL, as severe as that of many chronic disease states. Since

the elderly commonly have a number of associated co-morbid conditions, it may be difficult to measure the impact of urinary incontinence with generic HRQL measures. The use of incontinence specific tools to measure patient-reported outcomes in the elderly, therefore, is of considerable importance. Validated incontinence-specific PRO questionnaires, such as IIQ, I-QOL or KHQ, are used for clinical trials or research on urinary incontinence including elderly people, but their validity has not been specifically assessed in this age group. Okamura assessed symptoms and HRQL in older people (men and women) with lower urinary tract symptoms including incontinence, using the KHQ and IPSS. They demonstrated that symptoms and HRQL in the elderly with LUTS could be assessed by IPSS and KHQ and that urinary incontinence appeared to be more associated with a decreased HRQL in elderly women.

On the other hand, there are a variety of factors affecting older people, including physical, social, mental, economic or environmental conditions, which are different from those of the young. In frail elderly people with dementia or physical impairment, it may be difficult to assess the impact of urinary incontinence alone. Questionnaires specifically developed for the elderly may be of great importance in this respect. However, there is little relating to the development or validation of particular questionnaires for older people with urinary incontinence and this has not progressed since the previous update. Three questionnaires dealing with older people were found and are described below. No questionnaires dealing with patient outcomes specifically for frail older incontinent people were found.

1.1. The Urge Impact Scale (URIS) [Grade B]

The Urge Impact Scale (URIS) was designed and tested specifically for older persons with urgency incontinence. The URIS was developed and validated by DuBeau et al. [72] and included 32 items, reduced to 24 items (URIS-24). The URIS-24 was psychometrically assessed for validity and reliability in community-dwelling older (>65y) men and women with urgency incontinence. Cronbach's alpha was 0.84 for the URIS-32 and 0.94 for the URIS-24. In assessment of test-retest reliability, interclass co- efficient (ICC) was 0.88. The URIS-24 had modest but nearly significant correlation with the number of urgency incontinence episodes (rho=-0.39, p=0.05). Factor analysis revealed 3 component structures corresponding to physiological burden, perception of personal control and self-concept. There was no analysis for responsiveness. They showed that the URIS-24 is an internally consistent, highly reproducible tool for the assessment of the QOL impact of urgency incontinence on older persons.

1.2. Geriatric Self-Efficacy Index for Urinary Incontinence (GSE-UI) [Grade A]

The GSE-UI was developed to provide measurement of a person's confidence in their ability to prevent urine loss and whether this is an important aspect contributing to improvements in UI. The questionnaire was developed by Tannenbaum et al and is intended for use in community dwelling adults aged 65 years and older. The developmental version of the questionnaire included 38 items, which was reduced to 20 following psychometric testing. This has since been further reduced to 12 items. Question items focus on confidence of the respondent to prevent urine loss in varied situations and produce a score where a higher score is indicative of a higher level of self-efficacy related to UI. During original testing, item responses were normally distributed with no ceiling effects. Positive correlations were observed with quality of life scores (r=0.7, P<.001), while negative correlations were evidenced for symptom severity (r=−0.4, P<.001). Initial test-retest reliability of the reduced 20 items using intraclass correlation coefficients, ranged from 0.50 to 0.86. Later evaluation of the reduced 12 item GSE-UI demonstrated responsiveness of the instrument and found it to be clinically useful.

1.3. Caregivers

The Overactive Bladder Family Impact (OAB-FIM) scale was developed to assess the impact of OAB on family members of patients with OAB. This 19-item tool consists of 6 subscales. Four subscales (Irritation, Activities, Travel, Concern) could be used for all family members; however 2 additional subscales (Sleep, Sex) should only be administered to spouses/ significant others. The OAB-FIM was highly discriminating between OAB and control family members, with all OAB family members indicating significant impact (all $p<0.0001$). Internal consistency reliability (Cronbach's alpha >0.71) and 2-week test-retest reliability (intra-class correlation coefficients >0.73) were high for all subscales. Concurrent validity of the OAB-FIM was demonstrated through statistically significant ($p < 0.001$) Spearman correlations with the OAB-q (coefficients ranging from 0.35 to 0.58) and the PPBC (0.31 to 0.56). No differences were noted on the OAB-FIM by patient incontinence status (none, urge vs. mixed). OAB-FIM scores also discriminated by family member perceptions of OAB severity, particularly among the Irritation, Activities and Travel subscales. Correlational analyses among the OAB-FIM and relationship quality measures suggest that greater OAB symptom impact on the family member was associated with increased problems in the patient–family member relationship. The responsiveness of the OAB-FIM is yet to be assessed. This measure can be found at www. pfizerpatientreportedoutcomes.com.

2. CHILDREN

Some questionnaires have been developed specifically to assess issues for children and can include parent and child versions of the questionnaire. Enuresis is a particular focus in addition to specific disorders such as Spina Bifida (ISI-P). A recent contribution in this area is a new Pictorial Urgency Scale for Children. Published evidence demonstrates robust correlations between standard verbal descriptors, bladder volumes and PUS images. This is an example of population-specific advances to improve communication of urgency sensation, which can be difficult to articulate for younger children. More comprehensive details of questionnaires for children are included in Chapter 9 (Children) and the section on the ICIQ modular questionnaire.

3. SPINAL CORD INJURED/ NEUROLOGICAL IMPAIRMENT

Individuals who have a spinal cord injury or are neurologically damaged can experience particular difficulties with incontinence and the use of various devices. It would be useful to investigate whether Grade A questionnaires, developed for people without neurological damage, can be used in this group, or whether additional modules or instruments are required. New instruments available in this area are detailed below.

3.1. ISI-P: Incontinence Symptom Index – Pediatric

The ISI-P was evaluated among a population 11-17 year olds with spina bifida to test its reliability and validity. The ISI-P is an 11 item, self-reported questionnaire and provides assessment of symptom severity and impairment. The response rate of 42.3% indicates ac-

ceptable validity although the sample size was small (n=33). Cronbach's alpha demonstrated internal consistency for both factors (0.936 and 0.792 respectively) with the two factor solution of 'symptom severity' and 'bother from incontinence' providing the best fit. The questionnaire would benefit from further testing but provides a brief, focused and clinically relevant tool for adolescents with Spina Bifida.

3.2. QUALAS-A: Quality of life assessment in Spina Bifida for Adults

The QUALAS-A was developed to evaluate quality of life associated with bladder and bowel disorders in adults with Spina Bifida. Items were generated through interviews and a focus group and refined to develop the 53 item pilot instrument. International recruitment achieved a sample of 532 participants to evaluate validity and reliability to assist item reduction. The resulting 15 item questionnaire provides a comprehensive assessment organized within three domains: Health and relationships, Esteem and sexuality, and bladder and bowel.

3.3. IUI: Incontinence Utility Index

The IUI is a condition-specific preference-based measure for urinary symptoms related to neurogenic detrusor overactivity that provides population based utility scores to value health states. The instrument was developed from the I-QoL and neurogenic module by applying Rasch modeling. 442 participants were interviewed to estimate social preferences and explanatory models identified that demonstrated adequate predictive validity.

3.4. Qualiveen: Quality of Life Related to Urinary Problems in Spinal Cord Injury [Grade A]

The Qualiveen was developed to evaluate the specific impact of urinary dysfunction on the quality of life of spinal cord injury patients in France. The initial items were developed following patient interviews, and were then assessed for validity and reliability in 281 spinal cord injury patients with urinary difficulties. The Qualiveen contains 30 items and has demonstrated good reliability and validity. Further validation of the Qualiveen has been performed in multiple sclerosis patients and it has been translated and validated into English, German, and Portuguese. The Qualiveen has demonstrated responsiveness in multiple sclerosis patients and has a suggested MID of 0.5.

4. PROSTATE/BLADDER CANCER

Many PRO questionnaires are available for assessment in this area: Post-radical prostatectomy questionnaire, Cancer Rehabilitation Evaluation System - Short Form (CARES-SF), Prostate Cancer Treatment Outcome Questionnaire (PCTO-Q),PROSQOLI, Modified South-west Oncology Group (SWOG), Functional Assessment of Cancer Therapy - (FACT-G), Bladder form (FACT-B) and Prostate form (FACT-P), Functional Assessment of Cancer Therapy Vanderviet Cystectomy Index (FACT-VCI), EORTC metastatic prostate cancer, Changes in Urinary Function, Prostate-targeted Health Related Quality of Life. More recently the C-PAT has been published for the assessment of the quality of care within the cystectomy pathway, providing insights to inform improved care across cancer centres. While it is beyond the scope of this chapter to review and recommend PROs in this area, the principles and guidelines discussed herein apply to selecting a PRO related to prostate and bladder cancer.

5. LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATE DISEASE

Many questionnaires have been developed to assess LUTS and benign prostate disease; however, most do not contain a full evaluation of UI. Perhaps the most widely known urology PROS are the AUA Symptom Index and the I-PSS (International Prostate Symptom Score). The IPSS has been utilitised internationally to assess symptoms of prostate disease with documented reliability, validity and responsiveness. More recently a Visual Prostate Symptom Score has been developed and an app version of the IPSS has been evaluated, providing alternative approaches to the assessment of symptoms associated with prostate disease. Additional PRO measures for BPH are as follows: Patient-completed modification of the Boyarsky, BPH Impact Index and BPH Health-related QoL survey.

6. PERINATAL WOMEN

Pregnancy and childbirth are associated with the onset, and aggravation of interrelated pelvic floor disorders (PFDs), such as urinary incontinence, faecal incontinence, pelvic organ prolapse and sexual dysfunction. Although many questionnaires have been developed to assess these disorders such as the ICIQ-UI SF for incontinence[61], ICIQ-B for anal incontinence[68], Accidental Bowel Leakage Evaluation (ABLE) questionnaire for bowel symptoms, the ICIQ-VS for vaginal symptoms[66], and the Pelvic organ prolapse-urinary Incontinence Sexual function Questionnaire-IUGA revised (PISQ-IR) for sexual symptoms, few have been validated specifically for use with women in the pre-natal or post-partum period (Madsen et al., 2021; Zuchelo et al., 2018)1,2 Italla Maria Pinheiro Bezerra,1,3 Adna Thaysa Marcial Da Silva,1,4 Jéssica Menezes Gomes,1,4 José Maria Soares Júnior,4 Edmund Chada Baracat,4 Luiz Carlos de Abreu,1,3 Isabel Cristina Esposito Sorpreso1,4 1Study Design and Scientific Writing Laboratory at ABC Medical School, Santo André, Brazil; 2Research Laboratory of Uninorte (Barão do Rio Branco Faculty. There are no tools specifically designed for screening of PFDs in pregnant women, however the Bulge, Bladder, Bowel questionnaire has been recommended as an initial screening tool before further in detail assessment of symptoms. Gray et al 2019 has recently reviewed in detail the PROMs for use in urogynaecology and female pelvic floor medicine. Although the list is likely to be comprehensive, the evaluative standards of assessing the psychometric robustness were not clear. Nevertheless, the ePAQ-Pelvic Floor and the Australian Pelvic Floor Questionnaire (APFQ) were recommended as the most comprehensive in scope and with sufficient evidence of validity. No questionnaire comes highly recommended by the ICI for the complete assessment of these issues in a complete and integrated way. The only questionnaire identified that has been developed specifically for women post-partum is the German pelvic floor questionnaire. This was derived from the German version of the APFQ and is yet to be available in other languages so its universal accessibility is yet to be determined in clinical practice.

Table 8: Health-related Quality of Life measures for Lower Urinary Tract Symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
ICIQ-FLUTS (ICIQ-Female Lower Urinary Tract Symptoms Formerly known as BFLUTS-SF (Bristol Female Lower Urinary Tract Symptoms Short Form) Grade A[64]	12-question tool used to assess female LUTS, particularly urinary incontinence, measure impact on quality of life and evaluate treatment outcome	Women incontinence	√	√	√		√		None
Contilife® (Quality of Life Assessment Questionnaire Concerning Urinary Inconti- nence); Grade B[139]	28-intem tool used to assess the impact of urinary incontinence on HRQL. Originally developed in French and designed for women with UI (urge, stress and mixed UI)	Women, SUI	√	√ (ICC = 0.96)			√		√
DAN-PSS-1(Danish Prostatic Symptom Score); Grade A [140]	15-item tool used to evaluate males with LUTS suggestive of uncomplicated BPH	Men, BPH	√	√	√		√		
EPIQ (Epidemiology of Prolapse and Incontinence Questionnaire); Grade B [141]	49-item tool developed and validated in English and Spanish to assess the presence or absence of AI, OAB, SUI, and pelvic organ prolapse in female population	women, PFD	√	√	√	√	√	√	
ICIQ-UI Short Form (International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI Short Form); Grade A [61]	4-item tool used to assess the symptoms and impact of urinary incontinence in clinical practice and research	men and women, Urinary symptoms	√	√	√		√	√	√ (8 weeks)
ICIQ-MLUTS ICIQ-Male Lower Urinary Tract Symptoms SF Grade A[142]	13-item tool used to provide an evaluation of the occurrence and bothersomeness of lower urinary tract symptoms and their impact on the lives of men with LUTS	men with LUTS	√	√	√		√		

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
IIQ (Incontinence Impact Questionnaire); Grade A[143]	30-item tool developed to describe the severity of incontinence in a population. It was validated in a group of women aged 45 and over attending two continence clinics for SUI primarily. Used to assess the impact of urinary incontinence on HRQL.	Women, UI		√	√		√		√ (12Weeks)
IIQ-7 (Incontinence Impact Questionnaire); Grade A[144]	7-item tool used to assess the impact of urinary incontinence on HRQL	*validationstudy on men after radical prostatec-tomy whohad UI	√ (Cronbach's Alpha = 0.93)	√ (Spearman's Rho = 0.99; ICC = 0.75)	√	√	√	√	
IOQ (Incontinence Outcome Questionnaire); Grade B [145]	27 question tool developed for assessing quality of life after surgery for stress urinary incontinence	Women SUI	√ (Cronbach's Alpha = 0.83)		√	√			√
I-QOL (Urinary Incontinence- Specific Quality of Life Instrument); Grade A [146],[147]	22-item tool used to assess quality of life of women with UI	women, UI	√	√	√			√	√
ISI (Incontinence Severity Index); Grade C [109], [148]	2-item severity measure recommended by the World Health Organization for studying the epidemiology of incontinence and other LUTS; Developed in an epidemiologic study of 28,000 women in Norway.	Women, SUI				√	√		
ISQ (Incontinence Stress Index: ISQ-P [Patient]; ISQ-SOPS [Staff Observation of Patient Stress]; ISQ-SR [Staff Reaction to UI]); Grade C [110, 149]	40-item tool (20-items in short form) used to assess psychological stress associated with urinary incontinence	Women	√	√					

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
ISS (Incontinence Symptom Severity Index); Grade A [111], [150]	8-item instrument used for the self-assessment of severity of female urinary storage and voiding symptoms, rather than symptom bother or effects of on quality of life	Females		√ (ICC = 0.62 - 0.91)			√		√ (Duration not specified)
KHQ (ICIQ-LUTSqol) (King's Health Questionnaire); Grade A+[13]	21-item tool used to assess the symptoms impact of LUTS including urinary incontinence on HRQL. Developed in a clinical perspective to evaluate incontinence in women.	UI, OAB, men and women	√ (all domains except severity measure (Cronbach's Alpha = 0.60) demonstrated excellent IC)	√	√	√	√	√	√ (12Weeks)
LIS (The Leicester Impact Scale); Grade A[151]	21-item tool used as a quality of life measure for males and females with urinary storage symptoms of urgency, frequency, nocturia and incontinence.	men and women, LUTS	√	√	√		√		√
LUTSS (Lower Urinary Tract Symptom Score) Grade A1[52]	14-item tool used as a symptom evaluation for urinary storage symptoms (9 items), voiding symptoms (4 items) and associated bother (1 item).	Men and women, LUTS	√	√		√		√	√
M-ISI (Michigan Incontinence Symptom Index)[153] Grade B	10-item tool used to measure urinary incontinence and its bother, including three sub-domains: stress and urge urinary incontinence, and pad use	Women, aged 35-64 UI	√		√		√	√	

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
MUDI (Male Urogenital Distress Inventory); Grade B+[154, 155]	27-item tool used to address the dimension of physical health, focusing on bother from multiple symptoms associated with UI in men. Created by eliminating four gender specific items from UDI and IIQ.	Men with LUTS following a radical prostatec- tomy for prostate cancer	√		√		√		
MUSIQ (Male Urinary Symptom Impact Question- naire); Grade B+ [156, 157]	32-item tool used to capture mental/psychological health, social health, and global perceptions of function and well-being in men with urinary incontinence. Created by eliminating four gender specific items from UDI and IIQ.	Men, UI	√		√		√		
Nocturia Impact Diary[158]	12-item, 3 day diary to evaluate the impact burden associated with nocturia and its treatment. To be completed in conjunction with a voiding diary.	Men and women with nocturia	√	√	√			√	√
ICIQ N-Qol (Nocturia Quality of Life Questionnaire) GradeA+[70]	13-item tool used to assess the impact of nocturia on the quality of life of patients	men and women	√	√	√		√	√	√
OAB – q SF (OAB-q Short Form) Grade A[159]	19-item tool (shortened version of the OAB-q) used to evaluate both continent and incontinent symptoms of OAB and their impact on HRQL	OAB, men and women	√	√	√		√	√	√ (12 Weeks)
OAB-q (ICIQ-OABqol) (Overactive Bladder Questionnaire); Grade A [160]	33-item tool used to evaluate both continent and incontinent symptoms of OAB and their impact on HRQL. Developed from focus groups of men and women, clinician opinion, and a literature review	Continent and incontinent OAB	√	√ (ICC = 0.93 for 4-week recall period)	√	√	√	√	√ (12 Weeks)
OABSS (Overactive Bladder Symptom Score) Grade B[161]	4 item tool to evaluate key symptoms of OAB	OAB Men Women		√		√			

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
PFDI (Pelvic Floor Distress Inventory); Grade A[162]	46-items to assess presence of symptoms and HRQL in women with POP; 3 Scales (Urinary-28; Colorectal-17 Prolapse-16)	Females with symptomatic POP, UI	√ (Cronbach' s Alpha = 0.88)	√ (ICC = 0.87)	√			√	√
PFDI-20 (Pelvic Floor Distress Inventory Short Form); Grade A[162]	20-item short form of the PFDI (Urinary-6; Colorectal-8; Prolapse-6)	Females with symptomatic POP, UI		√ (ICC = 0.93)	√			√	√
PFIQ (Pelvic Floor Impact Question- naire); Grade A [162]	93-item functional status tool used to assess presence of symptoms and HRQL in women with POP; 3 Scales (Urinary-31, Colorectal-31, Prolapse-31)	Females with symptomatic POP, UI	√ (Cronbach' s Alpha = 0.98)	√ (ICC = 0.86)	√			√	√
PFIQ-7 (Pelvic Floor Impact Questionnaire Short Form); Grade A [162]	21-item short form of the PFIQ used to assess presence of symptoms and QOL in women with POP; 3 Scales (Urinary-7, Colorectal-7, Prolapse-7)	Females with symptomatic POP, UI		√ (ICC = 0.77)	√			√	√
PRAFAB (Protection, Amount, Frequency, Adjustment, Body image); Grade A[163]	5 item questionnaire widely used in the Netherlands by physiotherapists and researchers used to evaluate treatment effects for UI in women	women with UI	√	√	√		√	√	√
UIHI (Urinary Incontinence Handicap Inventory); Grade C [164]	17-item tool used to identifydifficulties patients may be experiencing because of their incontinence	Elderlywomen, UI due to detrusor instability	√(Cronbach's Alpha = 0.87)	√				√	
UISS (Urinary Incontinence Severity Score); Grade A[165]	10-item tool to assess symptom severity and impact of urinary incontinence	Women, UI		√	√	√	√		√
Urolife (BPHQoL9) (Benign Prostatic Hypertrophy Health-Related Quality of Life Questionnaire);Grade A[166]	9-item tool used to assess the impact of BPH and its treatment on the quality of life of patients	Men, BPH	√	√	√		√		√
YIPS (York Incontinence Perceptions Scale); Grade B [167]	8-item tool used to measure the psychosocial aspects of urinary incontinence and its management	Women, UI	√	√	√		√		√

Table 9: Patient Satisfaction Measures for Lower Urinary Tract Symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
BSW (Benefit, Satisfaction with treatment, and Willingness); Grade B[168]	3 single-item tool used to capture patients' perceived benefit, satisfaction with treatment, and the willingness to continue treatment	Men and women, OAB					√	√	√
GPI (Global Patient Satisfaction and Perception of Improvement); Grade C[169]	Single-item tool used to assess patient's improvement	Women, UI, SUI, MUI						√	
OAB-S (Overactive Bladder Satisfac- tion measure); Grade B[170]	51-items to assess following domains: expectations, control impact on daily living, medication tolerability, satisfaction and 5 overall assessments	Men and women, OAB	√	√	√		√	√	
OAB-SAT-q OAB Satisfaction questionnaire; Grade B[171]	21 or 40 -item tool used to assess patients' satisfaction with overactive bladder treatment including medication or non-pharmaceutical options such as physical therapy or biofeedback. The pre-medication module is designed assess the patient's expectations with medication and impact on OAB on patient's day to day life	Men and women, OAB	√	√	√		√	√	
PSTB (Patient Satisfaction with Treatment Benefit Questionnaire (Grade B)[172]	24 item tool to a patient satisfaction with OAB treatment	Men and Women OAB	√		√		√		
PSQ (Patient Satisf- action Question- naire); Grade C[169]	Single-item tool used to measure how satisfied a subject was with a program	Women, UI, SUI, MUI						√	
SAGA (Self- Assessment Goal Achievement Questionnaire); GAS; Grade C[173]	9-item tool on Goal Attainment related to lower urinary tract symptoms and the establishment of patients' goals concerning treatment for lower urinary tract symptoms (LUTS),	Men and Women aged ≥18 years with OAB			√	√	√		

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
TBS (Treatment Benefit Scale); Grade B[174]	Single-item tool used to assess the patient-reported benefits of treatment of OAB	Men and Women OAB					√	√	√

Table 10: Screening Tools for Lower Urinary Tract Symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
3IQ (Three Inconti- nence Questions Questionnaire); Grade C [175]	3-item tool used to classify urge and stress incontinence	Women, UI						√	N/A
ABSST (Actionable Bladder Symptom Screening Tool Grade B[176]		Women, OAB	√				√	√	
B-SAQ (Bladder Self-Assessment Questionnaire) or Bladder Control Self-Assessment Questionnaire (BCSQ); Grade A [177]	8-item screening tool used for the presence of bother- some LUTS in Women	Women	√	√		√	√	√	N/A
CLSS (Core Lower Urinary Tract Symptom Score) Questionnaire; Grade C[178]	10-item tool used in the overall assessment of lower urinary tract symptoms	Men & Women		√					
ISQ (Incontinence Screening Ques- tionnaire); Grade B [179]	5-item tool developed to screen for incontinence in women	Women, UI		√				√	N/A
MESA (Medical, Epidemiological, and Social Aspects of Aging Question- naire); Grade C[180]	15-item screening tool used for urinary incontinence in female pelvic medicine and reconstructive surgery patients	Women, UI		√					N/A
OAB-SS (Overactive Bladder Symptom Score); Grade A [181]	7-item tool used to measure overall symptom severity due to the four index symptoms of OAB	Men and women, LUTS with or without OAB	√	√	√			√	√

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
OAB-V8 (OAB Awareness Tool); Grade A[182]	8-item screening tool for use in a primary care setting to identify patients who may have OAB	Men and women, OAB	√		√	√	√	√	N/A
OAB - V3 (OAB short form) A[183]	3-Item awareness tool & shortened version of the OAB-q/OAB-V8	Men and women, OAB, UUI	√		√	√	√	√	n/a
PUF patient symptom scale (Pelvic Pain, Urgency, and Frequency); Grade C[184]	8-item tool used to evaluate of patients with suspected IC/PBS	Women and women, IC/PBS						√	√
QUID (Questionnaire for Urinary Incontinence Diagnosis); Grade A[185]	6-item tool used to diagnose stress and/or urge types of urinary incontinence	Women with UI and SUI	√	√	√	√		√	√
USP (Urinary Symptom Profile); Grade B[186]	13-item tool used to assess urinary symptoms in male and female with stress, urge, frequency or urinary obstructive symptoms for use in clinical practice to complement clinical measures and diagnosis	Men and women stress UI, urge UI, frequency, low stream, combined symp- toms	√	√	√		√	√	N/A

Table 11: Symptom Bother Measures for Lower Urinary Tract Symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
I-PSS (International Prostate Symptom Score); Grade B[137]	8-item tool used to capture the severity of urinary symptoms related to benign prostatic hyperplasia. Originally developed from the American Urological Association Symptom Index.	Men	√	√			√	√	√
LUSQ (Leicester Urinary Symptom Questionnaire); Grade A[188]	10-item tool used to measure the presence and severity of storage abnor- mality symptoms of incontinence, urgency, frequency and nocturia	Men and women	√	√	√	√	√		√ (12Weeks)

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
PGI-I and PGI-S (Patient Global Impression of Severity and of Improvement); Grade A[189, 190]	Two single-item global indices used to measure symptom bother related to urinary incontinence	Women with SUI	√	√			√	√	√ (12Weeks)
PMSES (Broome Pelvic Muscle Exercise Self-Efficacy Scale); Grade C [191]	23-item tool used to measure self-efficacy for the performance of pelvic muscle exercises in females and males	Men and women					√	√	
POSQ (Primary OAB Symptom Questionnaire); Grade C[192]	5-item tool used to assess which symptom of OAB is the most bothersome to patients	OAB, men and women		√	√				
PPBC (Patient Perception of Bladder Condition); Grade A[193]	Single-item tool used to assess patients' subjective impression of their current urinary problems. Developed as a global assessment of bladder condition	Men and women		√			√		√
PFBQ (Pelvic Floor Bother Questionnaire); Grade B[194]	9-item global instrument used to assess female patients over the age of 18 years with symptoms of urinary incontinence, urinary urgency, and frequency, urgency incontinence, faecal incontinence, obstructed defecation, dyspareunia and pelvic organ prolapse	Women, Urinary Inconti- nence, e UUI, SUI	√	√	√	√		√	
SPI (Symptom Problem Index); Grade B[195]	7-item tool used to measure how troublesome the patients find their urinary symptoms	Male, BPH	√	√	√				
SSI and SII (Symptom Severity Index and Symptom Impact Index for stress incontinence in women); Grade B [196]	3-item tool used to measure stress incontinence severity and impact or bothersome of symptoms. This question- naire was developed and administered to women undergoing stress inconti- nence surgery	Women, SUI		√	√		√		
UI-4 (Urinary Incontinence -4 Questionnaire); Grade C[197]	4-item tool used to assess how patients are bothered by urinary incontinence	Women, UI					√		

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
UDI (Urogenital Distress Inventory); Grade A[198]	19-item tool used to asses symptom bother related to urinary incontinence. UDI is a complement to the IIQ	Women, UI, SUI	√	√	√		√	√	
UDI-6 (Urogenital Distress Inventory -6); Grade A[199]	6-item tool used to assess LUTS, including inconti- nence, in women.	Women	√	√	√	√	√	√	√

Table 12: Urinary Urgency Measures for Lower Urinary Tract Symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
IUSS (Indevus Urgency Severity); Grade A[200]	Single-item tool used to quantify the level of urgency associated with each toilet void as measured during standard voiding diaries.	OAB with urgency inconti- nence, men and women		√		√	√	√	√ (12 Weeks)
PPIUS (Patients' Perception of Intensity of Urgency Scale); Grade B [201, 202]	Single-item tool used to assess female patient perception of urgency intensity in those women with UUI	Women, UUI		√			√	√	√
SUIQ (Stress/Urge Incontinence Questionnaire); Grade B[203]	2-item tool used to differentiate between symptoms of stress and urge urinary incontinence	Women, UI		√			√		
U-IIQ (Urge Incontinence Impact Question- naire); Grade A[204]	32-item tool used to assess the interference of urine leakage and bladder problems Developed for use in patients with all types of incontinence.	MUI, UUI	√	√			√	√	√ (12Weeks)
UPS (Urgency Perception Score); Grade B[205]	5-item OAB tool used for grading the urge to void and assessing the reason why individuals usually void	Men and women	√	√			√	√	

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
UPS (Urgency Perception Scale); Grade B[206]	Single-item tool used to assess the severity of urgency – whether or not urgency, the sudden and compelling desire to urinate should have a severity measure is debated.	OAB, men and women			√		√	√	√
UQ (Urgency Questionnaire); Grade B[207]	15-Likert Scale Item & 4-VAS tool used to assess the severity and impact of urinary urgency symptoms on HRQL. VAS scale is used to measure the impact of urinary urgency on overall HRQL, the severity, the intensity, and the discomfort of urgency.	Women, OAB	√	√	√		√	√	√ (10 Days)
URIS-24 (Urge Impact Scale); Grade B[208]	24-item tool used to assess of the impact of the most common form of UI in older persons	Older persons, UI	√	√	√		√		
USIQ-QOL (Urgency Severity & Intensity Questionnaire: Symptom Severity); Grade B[209]	To measure severity impact from urinary urgency	Females, POP, UI	√			√		√	
USIQ-S (Urgency Severity & Intensity Questionnaire: Quality of Life); Grade B[210]	To measure quality of life impact from urinary urgency	Females, POP, UI	√ Cronbach's Alpha = 0.85)			√		√	
USS (Urinary Sensation Scale); Grade B [211, 212]	5-point scale used to assess the impact of urgency with patients with OAB derivation from EMA's recommended 5-point scale	Urologists or urogynecologists, Survey respondents with OAB symptoms	r √ (Cronbach's Alpha = 0.85)		√		√	√	√
UU Scale (10-item Scale to Measure Urinary Urgency); Grade A[213]	10-item tool used to measure urinary urgency	Men and women		√			√		√

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant	
U-UDI (Urge-Urogenital distress inventory); Grade A[214]	9-item tool used to assess the extent to which the patient is bothered by the symptoms of urge urinary incontinence or mixed urinary incontinence with a primary urge component.	Men and women		√	√		√		√

Table 13: Summary of PRO Measures for Faecal incontinence and other bowel symptoms

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Psychometric Validation in Other Languages
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
Questionnaire for assessment of FI and constipation Grade A [215]	47-item general questionnaire for constipation and anal incontinence, also including abdominal and urinary symptoms and medical history	Men and women		√		√			√	√
Bowel function questionnaire [216] Ungraded	28-item bowel specific questionnaire including 10 anal incontinence-specific items	Men and women								
Faecal Inconti- nence Question- naire Grade C [217]	63-item general questionnaire for bowel habits including faecal incontinence, also urinary symptoms and medical history	Men and women		√						
BBUSQ (Birmingham Bowel and Urinary Symptom Questionnaire Grade A [218, 219]	22-item questionnaire for bowel and urinary symptoms including 4 faecal incontinence-specific items	women	√	√		√			√	

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Psychometric Validation in Other Languages
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
FICA (Faecal incontinence and constipation assessment) Grade B [220]	98-item general questionnaire for constipation and faecal incontinence, also including abdominal and urinary symptoms and medical history	women		√		√				
PFBQ (Pelvic floor bother question- naire) Grade B [221]	9-item symptom and bother questionnaire for pelvic floor disorders	women	√	√		√	√			

Table 14: Summary of PRO Measures for Faecal incontinence and HRQL associated specifically

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Psychometric Validation in Other Languages
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
ICIQ-B [67,68] Grade A+	19-item anal incontinence symptoms and HRQL questionnaire	Men and women	√	√	√	√	√		√	√
FIQL (Faecal Incontinence Quality of life Index) Grade A[222]	29-item faecal incontinence HRQL questionnaire	Men and women	√	√			√		√	√
MHQ (Manchester Health Question- naire) Grade B[223]	31-item anal incontinence HRQL questionnaire	Women	√	√			√			
Bowel control self-assessment questionnaire Grade B [224]	5-item faecal incontinence symptom and HRQL questionnaire	Men and women	√	√		√	√			

Table 15: Summary of PRO Measures for Faecal incontinence in specific patient groups

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity				Responsiveness (Treatment Duration)	Psychometric Validation in Other Languages
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant		
Postpartum flatal and faecal incontinence quality of life scale[225] Ungraded	68-item anal incontinence HRQL questionnaire (adaptation of FIQL for postpartum females)	Women			√					
Surgical outcome tool for faecal incontinence[226] Ungraded	10-item anal incontinence symptoms and HRQL questionnaire for evaluation of incontinence surgery	Women								
COREFO (Colorectal functional outcome questionnaire Grade B[227]	27-item anal incontinence symptom and HRQL questionnaire for evaluation of colorectal surgery	Men and women	√	√	√		√			
EBSQ (Elderly Bowel Symptom Questionnaire) Grade B[228]	56-item general questionnaire for gastrointestinal function including faecal incontinence, including and medical history and HRQL	Men and women		√		√				

Table 16. Sexual Health and Quality of Life Measures

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity			
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant
FSFI (Female Sexual Function Index); Grade B[229]	19-item tool used to assess the effects of incontinence on multiple dimensions of sexual function in sexually active, adult women	Women, OAB; SUI, MUI	√ (Cronbach's Alpha >/= 0.82)	√ (r = 0.79 - 0.86)				√
FSFI (Female Sexual Function Index) Grade B[230,231]	19-item tool used to assess the effects of incontinence in adult women with hypoactive sexual desire disorder	Women with hypoactive sexual desire disorder (Pre and Post menopausal)	√	√				√

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity			
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant
WSID-SF) Women's Sexual Interest Diagnostic Interview--Short Form Grade B[232]	9 items to assess sexual function in adult women with hypoactive sexual desire disorder	Women with hypoactive sexual desire disorder (Post menopausal)				√		√
(WSID-SF) Women's Sexual Interest Diagnostic Interview[232] Ungraded	39 items to assess sexual function in adult women with hypoactive sexual desire disorder	Women with hypoactive sexual desire disorder (Post menopausal)						
(DLSA) Daily Log of Sexual Activities Grade B[232]	9 items to assess sexual function in adult women with hypoactive sexual desire disorder	Women with hypoactive sexual desire disorder (Post menopausal)	√		√	√		
(MSIQ) Menopausal Sexual Interest Questionnaire Grade A[233]	10 items to assess of sexual interest in postmenopausal women	Post-menopausal women	√		√	√	√	√
(FSDS) Female Sexual Distress Scale Grade B[234]	20 items to measure sexually related personal distress in women.	Women	√		√	√		√
(FSDS) Female Sexual Distress Scale Grade B[234]	12 items to measure sexually related personal distress in women.	Women	√		√	√		√
(FSDS-R) Female Sexual Distress Revised Grade B[265]	13 items to differentiate HSDD from no FSD	Women with HSDD or FSD	√		√			√
(MSHQ) Male Sexual Health Questionnaire Grade B[236]	25 items to assesses sexual function and satisfaction in older men with urogenital	Men LUTS	√		√			√
(IIEF) International index of erectile function Grade A[237]	15 items to assess men with erectile dysfunction	Men	√		√	√	√	√
ICIQ-VS (International Consultation on Incontinence Questionnaire -Vaginal Symptoms); Grade B [66]	14-item tool used to assess effects of vaginal symptoms and associated sexual matter on sexual quality of life for sexually active females	Women	√ (Cronbach's Alpha = 0.81-0.88)	√	√			√ (all items except 'leakage during intercourse')

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity			
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant
PISQ (Pelvic Organ Prolapse/ Urinary Incontinence Sexual Question- naire); Grade B[238]	31-item tool to assess sexual function after surgery in women with Pelvic Floor Dysfunction	Females with Pelvic Floor Dysfunction	√ (Cronbach's Alpha = 0.85)	√ (k = 0.56 - 0.93)		√		√
(PISQ-IR) The Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-Revised] Grade C[239]	31-item tool to assess sexual function after surgery in women with Pelvic Floor Dysfunction	Females with Pelvic Floor Dysfunction	√					√
SFQ (Sexual Function Questionnaire); Grade C[240]	Generic Instrument used to assess the impact of OAB on sexual health/function in the male & female population	Men & women with OAB						
SQoL-F (Sexual Quality of Life–Female); Grade B[241]	To assess the impact of female sexual dysfunction on quality of life	Women	√	√			√	√
SSS-W (Sexual Satisfaction Scale for Women) Grade B[242]	22 items to measure of sexual satisfaction and sexual distress	Women	√		√		√	√
(BISF-W) Index of Sexual Functioning for women Grade B[243]	22 items to evaluate female sexual function and quantifies the nature and degree of impaired sexual function in surgically menopausal women.	Women	√		√			√
CSFQ- Change in Sexual Functioning Questionnaire Grade A[244]	36 items to measure illness- and medication-related changes in sexual functioning	Community Sample	√				√	√
CSFQ- Change in Sexual Functioning Questionnaire Grade B[245]	14 items to measure illness- and medication-related changes in sexual functioning	Women Depressed non depressed	√		√			
(DISFI) Derogatis Sexual Functioning Inventory Grade A[246]	26 items to measure the quality of the current sexual functioning of an individual	Community Sample	√			√	√	√
SIDI-F) Sexual Interest and Desire Inventory Female Grade B[247]	13 items to measure hypoactive sexual desire disorder (HSDD) severity in women	Women HSSD FSAD	√					√

PRO Name/ICIQ Grade	Purpose/Description of Tool	Population Sample	Reliability		Validity			
			Internal Consistency	Test-retest	Content (Item Generation)	Criterion	Concurrent	Discriminant
(SHOW-Q) Sexual Health Outcomes in Women Questionnaire Grade C[248]	12 items to assess the impact of pelvic problems on sexual desire, frequency, satisfaction, orgasm, and discomfort.	Women Functional/dysfunctional women in same sex relationship	√					

VIII. QUESTIONNAIRES TO ASSESS SYMPTOMS AND HRQOL IMPACT OF PELVIC ORGAN PROLAPSE

Women complaining of lower urinary tract symptoms often also complain of concomitant symptoms associated with urogenital prolapse and there are now a number of validated questionnaires available to use in the subjective assessment of women with prolapse symptoms. These questionnaires should be used in conjunction with the clinical assessment and standardised measurement of urogenital prolapse which is reported elsewhere in this section. In addition, given the number of conservative and surgical management options available for women with symptomatic prolapse standardisation of subjective outcome measurement is increasingly important.

This section will review the standardised symptom assessment tools for pelvic organ prolapse and, whilst the questionnaires described do not allow the clinical staging or planning of prolapse treatment they should be used alongside more objective tools to measure the subjective outcome of treatment. Evidence from previously reported studies has shown the importance or patient reported outcome measures and subjective assessment may provide a more meaningful assessment tool when compared to more traditional objective measurements. The use of these subjective outcomes has been shown to be robust and correlated with objective assessments during long term follow up.

Although the number of HRQoL questionnaires available to assess impact of urogenital prolapse is not as great as those associated with lower urinary tract dysfunction there are now a number of recommended and validated questionnaires available. However, it is important to consider that where specific problems associated with urogenital prolapse need to be considered, such as lower urinary tract symptoms or sexual function, then it may be preferable to consider the use of one of the questionnaires designed specifically for that purpose. In addition, as prolapse is often multidimensional, selecting questionnaires in the modular format of the ICIQ may be more useful in clinical practice.

For this current report the previous literature search was updated using the Pubmed/Medline databases from August 2016 – December 2020. The following key words were used either separately or in combination; ‘questionnaire’, ‘prolapse’ and ‘quality of life’. The grading of questionnaires was also reviewed and updated if new information had become available.

1. HRQOL QUESTIONNAIRES: PELVIC ORGAN PROLAPSE

There are now a number of HRQoL questionnaires that have been validated for the assessment of pelvic organ prolapse and have been reported by the International Consultation on Incontinence **(Table 17)**.

Although HRQoL questionnaires remain the most commonly used form of patient related outcome measure that are used in patients with pelvic floor dysfunction other measures of outcome have also been developed and reported. The Patient Global Impression of Improvement (PGI-I) was initially developed for lower urinary tract symptoms and has more recently been validated for use in patients with urogenital prolapse. The use of a simple one-answer patient reported outcome measure has also been used in studies using composite endpoints (Subjective and Objective measures) with the validated HRQoL questionnaires.

Table 17: Recommended questionnaires for the evaluation of symptoms and HRQoL impact of Pelvic Organ Prolapse

Grade A (recommended)
Pelvic Floor Distress Inventory (PFDI)[253]
Pelvic Floor Impact Questionnaire (PFIQ) [15]
Prolapse Quality of Life Questionnaire (P-QoL) [254]
Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire (PISQ) [255],(PISQ 12) [256]
Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire – IUGA Revised (PISQ-IR) [257]
ICIQ vaginal symptoms questionnaire (ICIQ-VS) [258]
The Australian Pelvic Floor Questionnaire (AFPQ) [259]
Grade B
Pelvic Organ Prolapse Symptom Score (POP-SS) [260]
Pelvic Floor Symptom Bother Questionnaire (PFBQ) [261]
Electronic Personal Assessment Questionnaire-Pelvic Floor (ePAQ-PF) [262]
Grade C (with potential)
Pelvic Floor Dysfunction Questionnaire [263]
Danish Prolapse Questionnaire [264]

2. PROLAPSE QUALITY OF LIFE QUESTIONNAIRE (PQOL)

The Prolapse Quality of Life questionnaire (P-QoL)[254] is a validated questionnaire which has been shown to be reliable and responsive. HRQoL scores have been shown to strongly correlate with objective assessment of prolapse using the Pelvic Organ Prolapse Quantification Questionnaire (POPQ) and women with symptomatic prolapse had a significantly higher score in each domain.

Since the original validation PQoL has now been validated in a number of new linguistic validations including Spanish, French Persian, Polish and Mandarin although a recent systematic review of the psychometric properties and cross –cultural adaptations and translations has suggested that there is limited evidence to support the robustness of the original validations of the translated versions.

3. PELVIC FLOOR DISTRESS INVENTORY (PFDI) AND PELVIC FLOOR IMPACT QUESTIONNAIRE (PFIQ)

The PFDI and PFIQ are based on the structure and content of the Urinary Distress Inventory (UDI) and the Incontinence Impact Questionnaire (IIQ) and also include specific domains covering pelvic organ prolapse and colorectal dysfunction.

The PFDI assesses symptom distress in women with pelvic floor dysfunction and includes the Urinary Distress Inventory (UDI), Colorectal-anal Distress Inventory and Pelvic Organ Prolapse Distress Inventory.

The PFIQ assess HRQoL impact and includes the Incontinence Impact Questionnaire (IIQ), Colorectal-anal impact questionnaire and the Pelvic Organ Prolapse impact questionnaire.

The questionnaires have been shown to be internally consistent and reproducible. Both the UDI and IIQ were shown to correlate with the number of urinary incontinence episodes per week and pad usage. In addition the Pelvic Organ Prolapse distress inventory and Pelvic Organ Prolapse impact questionnaire correlated with POPQ objective prolapse assessment whilst the Colorectal-anal Distress Inventory and Colorectal-anal impact questionnaire significantly correlated with episodes of faecal incontinence and defaecatory dysfunction.

The Pelvic Floor Impact Questionnaire (PFIQ-7) [15] and Pelvic Floor Distress Inventory (PFDI-20)[15] have recently been validated in Brazilian Portuguese, Swedish Danish, Polish, Chinese, Trigrigna, Finnish and Norwegian

4. THE AUSTRALIAN PELVIC FLOOR QUESTIONNAIRE (AFPQ)

The Australian Pelvic Floor Questionnaire (AFPQ) is a validated interviewer administered questionnaire with four domains assessing bladder, bowel, prolapse and sexual function in women complaining of pelvic floor dysfunction [259]. The AFPQ has been demonstrated to be valid, reliable, and responsive to change. More recently the Minimally Reported Difference (MID) has been reported and the questionnaire has also been validated in patients folllowing surgery for colorectal cancer.

5. PELVIC ORGAN PROLAPSE SYMPTOM SCORE (POP-SS)

The POP-SS consists of seven items each with a 5-point Likert response and has been shown to have good construct validity, internal consistency and to be sensitive to change. It has been validated using data from three large studies of women with urogenital prolapse and has now been translated into Turkish and Amharic.

Women having surgery were found to have higher POP-SS scores compared to those managed with conservative measures and these women, in turn, had higher scores than those who were asymptomatic. In addition significant differences in POP-SS were detected following surgery and PFMT.

6. HRQOL QUESTIONNAIRES; PELVIC ORGAN PROLAPSE AND SEXUAL DYSFUNCTION

6.1. Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire (PISQ)

Both urinary incontinence and pelvic organ prolapse are known to have an important impact on HRQoL although until relatively recently there was no disease specific questionnaire available.

The Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire (PISQ)[238] has now been validated in women who complain of symptomatic prolapse in addition to asymtomatic controls. Those women who complained of prolapse were noted to have a greater impact on HRQoL related to sexual function when compared to asymptomatic women and the instrument was found to correlate well with the Incontinence Impact Questionnaire-7 (IIQ-7) and the Sexual History Form-12 (SHF-12).

Subsequently PISQ has been validated as a short form (PISQ-12) and has been validated in Turkish , French, Chinese, Swedish, Portuguese, Iranian and Dutch.

6.2. Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire – IUGA Revised (PISQ-IR)

One of the difficulties with PISQ was that it was only applicable to women who were sexually active. More recently an International Urogynaecology Association (IUGA) revised version (PISQ-IR) [239], for both sexually active and inactive women, has been validated using the Incontinence Severity Index (ISI), Pelvic Floor Distress Inventory -20 (PFDI-20), Epidemiology of Prolapse and Incontinence Questionnaire (EPIQ) and the Female Sexual Function Index (FSFI). Urogenital prolapse was assessed objectively using the POPQ system. Overall both sexually active women and non-sexually active women with symptomatic prolapse were found to have greater bother and there was good correlation with other, previously validated questionnaires.

The PISQ-IR has now been validated in French,Japanese, Arabic, Mandarin Chinese, Hungarian, German, Polish, Czech and Spanish. In addition a single summary score, based on the ten individual subscale scores has now also been validated which may be easier to use in clinical practice and cutoff scores for sexual dysfunction have recently been reported.

IX. QUESTIONNAIRES TO ASSESS SYMPTOMS AND HRQL IMPACT OF FAECAL INCONTINENCE

There are now a number of patient reported outcome measures which have been developed for the assessment of patients with Anal Incontinence (AI) and Faecal Incontinence (FI). Due to the considerable overlap between faecal incontinence and other forms of pelvic floor dysfunction questionnaires used for urinary and prolapse symptoms may also contain domains for anal and faecal incontinence. Likewise, items relating to faecal incontinence may also be included in questionnaires used to evaluate colorectal disease. In addition, due to the wide variation in normal bowel function within, and between individuals, some of these questionnaires may lack sensitivity and specificity for more specific bowel disorders such as Irritable Bowel Syndrome (IBS), Irritable Bowel Disease (IBD) evacuation disorder and constipation.

Since anal incontinence, faecal incontinence and bowel evacuation are closely related to pelvic floor function it may be inappropriate to consider bowel function simply in terms of continence and constipation. Constipation and evacuation disorders may result from a number of different pathologies such as outlet obstruction and slow transit in addition to other mechanical, pharmacological, metabolic and neurogenic causes.

Anal incontinence is known to occur in both men and women with the prevalence depending on age and the symptom is known to be important in terms of the underlying pathophysiology. Faecal urgency and faecal urgency incontinence are thought to be associated

with the loss of voluntary control due to impaired external sphincter function whereas passive faecal incontinence is thought to be associated with impairment of the smooth muscle of the internal anal sphincter .

For this current report the previous literature search was updated using the Pubmed/Medline databases from August 2016 – December 2020. The following key words were used either separately or in combination; 'questionnaire', 'faecal', 'anal', 'bowel' and 'quality of life'. The grading of questionnaires was also reviewed and updated if new information had become available.

The updated search found one new validated HRQoL instrument for the assessment of anal or faecal incontinence although there were no further validation studies reported on those questionnaires which were ungraded. Consequently the recommendations of this report have been revised appropriately.

The grades of recommendation are as outlined in previous sections. **Table 18** summarises the questionnaires reviewed and grades of recommendation.

1. ACCIDENTAL BOWEL LEAKAGE EVALUATION QUESTIONNAIRE

The Accidental Bowel Leakage Evaluation questionnaire [308] is a patient completed instrument which has now been fully validated and found to have good internal consistency, and test rest reliability in addition to construct validity. The questionnaire deals with patient important domains including predictability, awareness, control, emptying and discomfort. More recently the responsiveness and minimally important difference have also been reported.

Tables 13, 14 and 15 provide details of the specific psychometric properties and development of each questionnaire

Table 18: Recommended questionnaires for the evaluation of symptoms and HRQoL impact of faecal incontinence

Grade A+
ICIQ-B [67, 68]
Grade A (recommended)
Faecal Incontinence Quality of Life Index [222]
Birmingham Bowel and Urinary Symptom Questionnaire [218,219]
Questionnaire for assessment of Faecal Incontinence and Constipation[307]
Accidental Bowel Leakage Evaluation[308]
Grade B
Colorectal Functional Outcome Questionnaire [309]
Manchester Health Questionnaire [223]
Bowel Control Self Assessment Questionnaire [224]
Pelvic Floor Bother Questionnaire [310]
Elderly Bowel Symptom Questionnaire [228]
Faecal Incontinence and Constipation Assessment [220]
Grade C
Faecal Incontinence Questionnaire [311]
Ungraded
Postpartum Flatal and Faecal Incontinence Quality of Life Scale [225]
Bowel Function Questionnaire [216]
Surgical Outcome Tool for Faecal Incontinence [226]

X. QUESTIONNAIRES TO ASSESS SEXUAL FUNCTION/ SEXUAL HEALTH AND URINARY SYMPTOMS

Sexual dysfunction affects many people and may be caused by psychological, emotional or physiological factors, often with multifactorial and interrelated aetiologies. Sexual function may be regarded as a dimension or aspect of overall HRQL, for which a number of dimension-specific measures have been developed and validated. There is a wide choice of available instruments, the selection of which will depend on the clinical or research setting where the instrument is to be employed. Established and widely used measures that have been shown to be valid, reliable and responsive are clearly desirable, however the feasibility and appropriateness of using a particular instrument in a particular setting must also be considered. A large number of different instruments exist in this field, which aim to evaluate specific aspects of sexual function and sexual health.

While the importance of investigating male sexuality as part of a normal male urological assessment is established, this has not been established for female evaluation. Many physicians underestimate the prevalence of female sexual dysfunctions and do not routinely perform an assessment of sexual wellness as a part of their practice, despite evidence that many women with LUTS have sexual problems

In a comprehensive assessment of women with pelvic dysfunction sexual function should be investigated. However it is may be a difficult issue to discuss during a consultation because of discomfort or embarrassment. Female discomfort may stem from personal embarrassment, a sense that sexual dysfunction is not a medical problem and this may be compounded by a lack of time during health care visits.

In addition many physicians report a lack of training in how to appropriately address sexual function with patients. Clinicians who treat sexual problems often prefer to use unstructured rather than structured interviews or questionnaires in clinical practice as an unstructured approach allows the tailoring of questions to suit the couple or the individual being assessed. Unstructured interviews enable the clinician to support patients who feel vulnerable and encourage discussion. In this setting, vocabulary can be modified, as can the level of assertiveness and the depth of questioning to suit the needs of the individual. This flexibility is not readily achievable with questionnaires which individuals may also find difficult to complete due their impersonal nature or because of physical or mental impairment, cultural or language differences. However, some patients find the discussion of intimate issues with clinicians very difficult and questionnaires may allow these issues to be measured in private, at ease and more effectively before subsequently exploring questionnaire responses in the clinical interview itself. Therefore there is a wide choice of available instruments, which could help the physician during history taking and the selection of an instrument will depend on the clinical or research setting where the instrument is to be employed.

Table 16 outlines sexual health measures with a Grade A, B, C rating based on the criteria provided above, and the linguistic validations of each questionnaire are also documented.

This table includes the questionnaires useful to assess female and male sexual function in patients with any pelvic dysfunction and uri-

nary symptoms. Questionnaires obtaining an A+ rating demonstrate reliability and validity and also that content was derived with patient input and responsiveness to treatment has been shown.

A Rated group: the Female Sexual Function Index (FSFI) [229], the Female Sexual Distress Scale (FSDS) [234], the International Consultation on Incontinence Questionnaire-Vaginal Symptoms (ICIQ-VS)[66] and the Derogatis Sexual Functioning Inventory (DISFI) [232]. These questionnaires assess female sexual function and measure the quality of a patients current sexual functioning. The Menopausal Sexual Interest Questionnaire (MSIQ)[233] is also included in this group but only two domains. For male patients the International Index of Erectile Function (IIEF) [237] is recommended to assess men with erectile dysfunction. Most of the identified measures are self-reported, easy and quick to administer and many have various language versions available. The majority have also been previously used in incontinence populations

***B Rated group*:** the Daily Log of Sexual Activities (DLSA)[232] the Female sexual distress scale-revised (FSDSr)[235], the Index of Sexual Functioning for women (BISF-W)[243] the Change in Sexual Functioning Questionnaire (CSFQ) [244,245],and the Sexual Interest and Desire Inventory Female (SIDI-F)[247]. They assess the sexual dysfunctions in women with sexual desire disorder and functional sexual arousal disorder. The Pelvic Organ Prolapse Urinary Incontinence Sexual Question (PISQ-12) assesses sexual function after surgery in women with Pelvic Floor Dysfunction and has been validated in women with urinary incontinence and pelvic organ prolapse. The Sexual Quality of Life–Female (SQoL-F)[241] is useful to assess the impact of female sexual dysfunction on quality of life, while the Sexual Satisfaction Scale for Women (SSS-W) [242] measures the women's sexual satisfaction and distress in patients with pelvic floor dysfunction. The Sexual Function Questionnaire (SFQ)[240] is an instrument for both partners. This questionnaire also addresses some of the consequences of female sexual dysfunction for the woman, her partner and their relationship. Both the physical and the cognitive aspects of sexual response are evaluated within the SFQ items. The Male Sexual Health Questionnaire (MSHQ) [236] assesses sexual function and satisfaction in older men with urogenital symptoms of LUTS and sexual dysfunctions.

***C Rated group*:** The Women's Sexual Interest Diagnostic Interview--Short Form (WSID-SF) is used to assess sexual function in adult women with hypoactive sexual desire disorder, The Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR) [239], and the Sexual Health Outcomes in Women Questionnaire (SHOW-Q)[248] to assess the impact of pelvic problems on sexual desire, frequency, satisfaction, orgasm, and discomfort.

The choice of which tool to use will be dependent on the type of patient, age, type of pelvic dysfunction and on research hypothesis. For instance, if you wanted to assess impact of OAB on sexual function e.g. arousal in women then the FSFI should be used rather than the SQOL-F because the FSFI has a specific arousal domain whereas the SQOL-F assesses sexual quality of life.

XI. RECOMMENDATIONS FOR RESEARCH

1. The selection of a PRO questionnaire must reflect study purpose and objectives.
2. Grade A recommended questionnaires should be used in all clinical trials evaluating treatments
3. The inclusion of the ICIQ modules is preferred in all studies in order to standardize outcome assessment
4. Continued PRO development, refinement, and usage should accurately and adequately report on the methods, samples, statistical analyses and psychometric properties of questionnaires in scientific journals. This includes documentation of validity, reliability and responsiveness and consequently the quality of each study can be assessed.
5. Researchers are encouraged to use existing questionnaires and refine for specific populations when required; such as frail elderly and children.
6. Researchers are also encouraged to participate in collaborative work with the ICIQ project allowing the development and refinement of modules and translations.
7. Further work is required to establish the validity and utility of electronic patient reported outcome measures.

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COMMITTEE 5

URODYNAMIC TESTING

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I. WHAT ARE URODYNAMIC STUDIES AND WHAT SHOULD, IN GENERAL BE THE ROLE OF URODYNAMIC STUDIES IN CLINICAL PRACTICE?

1. OVERVIEW

1.1. Introduction

Urodynamic testing (urodynamic studies - UDS) should be performed to objectively measure, document and diagnose the entirety of lower urinary tract (LUT) function and/or dysfunction. UDS should be done when it can have consequences for the patient's management, including pretreatment patient counselling(1)the role of urodynamics (UDS and/or when part of a surveillance or a research program. For this, the individual patient's symptoms, including their impact in terms of bother and degree of hindrance they cause, as well as the impact of other relevant circumstances (e.g. comorbidity and or use of other medication, or operability), should be kept in mind.

UDS can demonstrate signs not otherwise elucidated at presentation, such as an elevated postvoid residual urine (PVR) or detrusor underactivity (DU), which may be relatively unnoticed by the patient, even when neurologically intact. Upper urinary tract (UUT) signs (e.g. dilatation) can exist or develop without any symptoms, especially, but not uniquely in patients with relevant neurological abnormalities. Furthermore, the patient can present with complaints such as 'urinary frequency', 'nocturia' or 'recurrent UTIs', which are difficult or impossible to reproduce in the usual UDS laboratory. Therefore, UDS do not necessarily demonstrate or mimic the presenting symptoms of the patient but may reveal the underlying LUT dysfunction that may lead to lower urinary tract symptoms (LUTS).

Nevertheless, in the usual setting of a UDS study, a feature of LUT function or dysfunction may be observed/measured that is relevant to these unnoticed phenomena and may explain the patient's symptoms. Finally, UDS may provide a basis for the identification and prevention of conditions, signs or symptoms that may arise later and not present at the time of the testing; e.g. urinary retention or UUT dilatation or deterioration.

UDS allow direct assessment of LUT function by the measurement of relevant physiological parameters (2,3). Invasive UDS are defined as any test that involves insertion of one or more catheters or any other transducers into the bladder and/or other body cavities, or insertion of probes or needles, for example for needle EMG measurement(4)\" a new ICS Standard was developed in the period from December 2013 to December 2015. In July, a draft was posted on the ICS website for membership comments and discussed at the ICS 2015 annual meeting. The input of ICS membership was included in the final draft before ICS approval and subsequent peer review (for this journal.

The point of a clinical/biological test is that it will show a result on a continuum between what is considered normal and abnormal; UDS is no exception to this. The key to determining the cause of the signs and/or symptoms of lower urinary tract dysfunction (LUTD) will be to reproduce the function and the dysfunction of the LUT of the individual patient. In addition, concomitant UDS findings accompanying the main symptom or sign should be carefully assessed for the optimal management plan. For example, concomitant DU or detrusor overactivity (DO) or bladder outflow obstruction (BOO) in a female patient who presents with stress urinary incontinence may be important to diagnose and to optimize her treatment. The implicit consequence of this is also that ideally at least one complete filling (cystometry -storage) and pressure-flow study (PFS - voiding) cycle, that adequately represent the patient's problem (e.g. with regard to volumes) including post voiding features, (e.g. PVR or after contraction) should be tested, analysed, and documented, even if only storage or only voiding signs or symptoms have been expressed by the patient. Last but not least: when LUT sensation is altered, as it frequently is in patients with neurogenic LUTD, the symptoms are even less reliable than those of patients with intact sensation, making UDS as an objective evaluation to advise or justify a specific management even more important.

A definite indication for UDS is LUTD due to a demonstrable neurogenic deficit. Besides planning symptomatic treatment in such patients, UDS provides a risk assessment to predict UUT damage in all age groups and genders as mentioned and described by the relevant chapters in this consultation.

Thus, the role of UDS in broad clinical perspective can be:

a) To demonstrate all elements of LUT(patho)physiology of the patient presenting with signs or symptoms of dysfunction;

b) To identify all factors that contribute to the LUT dysfunction signs (e.g. urinary incontinence (UI)) and/or are the origin of the symptoms (e.g. frequent voiding) and assess their relative importance;

c) To obtain information about all other aspects of LUT function or dysfunction, whether or not expressed as a symptom or recognizable as a sign;

d) To allow a prediction of the possible consequences of LUTD for the UUT;

e) To allow a prediction of the outcome, including undesirable side effects, of a contemplated treatment, and include the possibility of additional treatment options in preoperative patient counselling (e.g. inform between-treatment options);

f) To confirm the effects of intervention or understand the mode of action of a particular type of treatment for a LUTD; especially a new and/or experimental one;

g) To understand the reasons for failure of previous treatments for UI, or for LUTD in general.

UDS is the gold standard to assess LUT function and dysfunction. Some studies have challenged the utility of UDS with a clinical diagnosis as the comparator. Specifically, the 'clinical diagnosis of SUI' was used as a predictor of outcome of suburethral tapes in a very select group of patients(5). When this clinical diagnosis (which is not standardized in general and was not for these trials) had been compared with one specific element of sometimes non-standard UDS diagnosis (and also including patients with DO(6)) neither method of diagnosis was superior for the patients recruited in this study with signs and/or symptoms of SUI. The question remains whether the overall outcome of the surgery (or alternatives for some of the patients) could have been better than the ±65% overall success rate (dry, without taking into account other symptoms e.g. frequent voiding), if a more structured clinical and UDS diagnosis

and/or analysis had been used in these studies(5,7). Furthermore, it was shown that even in the index or uncomplicated patients, preoperative UDS changed the clinical diagnosis in more than half of the patients, but this change was claimed not to affect the surgical outcome(5). However, the outcome of surgery in terms of DO and DU was not assessed in the long term. Last but not least, the definition of index or uncomplicated female patients with SUI is still not clear and they constitute only a minority of the whole patient pool(1) the role of urodynamics (UDS.

1.2. Conclusion

UDS in clinical practice evaluates a person's LUT function with at least one complete and representative filling, voiding and post-voiding cycle by testing with relevant pressures and flowmetry. UDS includes quality control, subsequent analysis, and systematic documentation.

2. UROFLOWMETRY

This is the non-invasive measurement of urine flow rate for both women and men, as well as for children. The general principles are universal, although voiding position is relevant(8), and a small series of young men voiding in the healthy range demonstrated that time after ejaculation may play a role(9). Uroflowmetry is also relevant for patients with neurological abnormalities, if they use a toilet in their daily life situation. The patient voids into a flowmeter in private, ideally with a normal to strong (but not uncomfortable) desire to empty their bladder(3,10).

Urine flow rate is continuously measured and displayed graphically. Various parameters from the trace are automatically calculated and printed out together with the trace. After adjustment for artefacts, the maximum flow rate, the volume voided and shape of the curve are usually the principal determinants of whether or not the patient is emptying their bladder in a normal way. Volume dependency on flow rate should be considered. If abnormal voiding occurs, it is good clinical practice to repeat the assessment to attempt to reproduce normal behaviour.

Several factors, such as patient apprehension, can give an abnormal recording in patients who normally have no voiding difficulty. Asking the patient about what she or he thinks about the voiding, whether the voiding was an adequate representation of their usual voiding, (if possible by comparison with the usual voiding diary volumes) must be regarded as good urodynamic practice. Repeating the assessment can remove such confounding factors. Unambiguous and careful instruction of the patient, privacy, appropriate leg/foot support and a short meatus to flowmeter distance are all inherently relevant(11).

The committee has not found any relevant technical changes or innovations to uroflowmetry equipment since 2013, but the committee notes with interest the current availability of home-based-uroflowmetry devices and recommends an evaluation of these technologies.

3. FILLING CYSTOMETRY

This is the measurement of the pressure inside the bladder to assess its storage capabilities. It is an invasive test which involves a catheter being placed into the bladder, usually transurethrally, and another catheter being placed rectally, vaginally or through an abdominal stoma to measure abdominal pressure.

Subtracting the indirectly measured abdominal pressure (p_{abd}) from the pressure measured inside the bladder (intravesical pressure, p_{ves}) gives a representation of pressure changes due to the action of the detrusor smooth muscle, the detrusor pressure, p_{det} (= p_{ves} – p_{abd}). During this assessment, the bladder is usually filled with normal saline solution, or x-ray contrast solution in the case of video UDS (VUDS), either through a separate catheter placed transurethrally or through the filling channel of a dual lumen catheter, if used.

Usually, the filling rate is much faster than physiological bladder filling (which is 1-2 mL/min) and therefore referred to as non-physiological in ICS terms. The bladder will become filled in about 10 minutes when 10% of estimated usual capacity (based on the voiding diary, taking into account the PVR whenever possible) is taken as the filling rate (mL/min)(4)\" a new ICS Standard was developed in the period from December 2013 to December 2015. In July, a draft was posted on the ICS website for membership comments and discussed at the ICS 2015 annual meeting. The input of ICS membership was included in the final draft before ICS approval and subsequent peer review (for this journal.

The intravesical, abdominal pressure and the calculated detrusor pressure are monitored as the bladder is filled and before the patient has been given 'permission to void'. The storage ability of the bladder is assessed in terms of the volumes required to elicit various sensations from the patient, its cystometric capacity, its compliance (passive muscle adaptation to volume increase and detrusor muscle relaxation), and the presence or the absence of phasic detrusor pressure rises. The filling (storage) phase of cystometry is when urodynamic SUI (USI) can be assessed by means of coughing, straining,or other provocative manuever on the request of the urodynamicist(12)four fellowship-trained urogynecologists reviewed 39 abstracted cases of urinary incontinence on two occasions: first without and subsequently with urodynamic data. Treatment recommendations were made for each case after each review. The probability of urodynamic data modifying treatment recommendations was estimated for each reader and for the population of readers using a random effects logistic regression to account for reader variability. The overall probability that urodynamic data would change treatment was 26.9% (95% confidence interval (CI. Good urodynamic practice demands that all three of abdominal, intravesical and detrusor pressures are evaluated to assess urinary bladder storage function.

The committee has not become aware of any changes since 2013 in technique of cystometry.

Pelvic muscle EMG during cystometry is not an ICS standard and not further discussed in this chapter (see chapter on imaging and neurophysiological testing for this). Alternatives for the ICS standard water (or saline) filled catheters and tubing are being evaluated and will be discussed in a separate paragraph. Specific attention to artefacts and errors merits attention and has been included in the update of the ICS Good Urodynamic Practices(13–15).

4. PRESSURE-FLOW STUDIES

Pressure-flow study (PFS) is the (ICS) term for measurement of the mechanics of micturition. When the filling phase of cystometry is complete, the patient is given 'permission to void' and asked to empty the bladder into a flowmeter whilst intravesical, abdominal and detrusor pressures are being recorded. The simultaneous measurement of flow rate and pressure enables voiding to be as-

sessed and PFS analysis can help determine whether a slow urine stream is due to BOO or to DU or to a combination of both. PFS can also assist the diagnosis of detrusor-sphincter dyssynergia (DSD) and a clearer description of dysfunctional voiding and/or quantification of outlet dynamics during voiding. Similar precautions as for uroflowmetry must be taken regarding representativeness, artefacts and patient apprehension.

Since 2013 no new studies have been published about the technique of PFS. Analysis of PFS regarding detrusor underactivity (DU) or 'poor contractility' during voiding has received increased attention and is suggested to be of future relevance(16,17).

5. URETHRAL PRESSURE PROFILOMETRY

This is a test to estimate the urethra's and the surrounding structures' ability to maintain a closed bladder outlet, allowing the body to contain urine within the bladder. A catheter is placed transurethrally into the bladder and then withdrawn along the urethra (usually by a mechanical puller at a constant rate). Catheters that use water perfusion but also catheters with microtip pressure sensors or catheters with air-filled ('charged') balloons are used to this aim. The pressure along the length of the urethra is measured and interpreted relative to the pressure inside the bladder or abdomen. The maximum pressure measured in the urethra is assumed to give an indication of the urethral closure function. The clinical relevance of the urethral pressure profile (UPP) is frequently discussed in the literature and alternative technical systems to measure urethral pressure or function have been published and will be discussed in following paragraphs.

6. ABDOMINAL LEAK POINT PRESSURE

This test estimates the urethra's ability to contain urine within the bladder when intra-abdominal pressure is increased. Intra-abdominal pressure is measured whilst the patient is asked to increase their abdominal pressure by Valsalva or by coughing. The abdominal pressure required to produce leakage from the bladder (leak point pressure or LPP) gives an indication of the closure function of the urethra and is termed the abdominal LPP. Diverse methods as well as reference pressures are used. New evidence (since ICI2013) for the relevance of LPP measurements and variants of LPP will be discussed in the specific paragraphs of this report. Detrusor leak point pressure (detrusor LPP) is conceptually very different from abdominal LPP and is discussed in detail later in this chapter.

II. TECHNOLOGICAL INNOVATIONS IN URODYNAMIC STUDIES

1. CATHETERS FOR PRESSURE MEASUREMENT

Traditionally, UDS is done with water-filled catheters and tubing and external pressure sensors. This is the ICS Standard.

Air-filled catheters have a small balloon on the tip and a lumen attached to a pressure transducer. After introduction, the balloon is 'charged' with air and measurement can take place. Air-filled catheters (T-Doc® Air charged™ catheters, Laborie, Mississauga, Canada) can be used for intravesical, intra-urethral as well as for abdominal pressure measurement in UDS and are CE (Conformité Européenne) marked and FDA (US – Food and Drug Administration) approved for their technical safety for use in humans.

1.1. Conclusions and Recommendations 2016

ICI2016 concluded that air-filled catheters may provide an acceptable alternative to other techniques for measuring the pressure closing the female urethra however normal values had not been established. Further, ICI2016 concluded that studies show that air-filled catheters record different pressure values to water-filled lines in UDS and are therefore not interchangeable(18) (19). The recommendations of the ICI2016 were that investigators planning to use air-filled catheters for intravesical and intra-abdominal pressure in UDS were advised to check for themselves that they have an equivalent performance to their current system for measuring pressure, and how their system compares to the standard reference values for clinically relevant limits of pressures obtained with the ICS standard water-filled systems.

1.2. New evidence 2021

Four further studies examining the performance of air-filled catheters have been published since ICI2016, two comparing air-filled and water-filled systems' readings during filling and voiding UDS(20) (21), one examining urethral pressure measurements(22), and one confined to usability and safety assessment(23). The first study(20) compared only intravesical pressure between the two systems, using the filling line of an air-filled catheter as a water column, and reported results in 50 women. The second(21) examined data from 25 patients (9 male, 16 female), comparing both intravesical and abdominal pressures by the same method. Significantly, though both studies report good correlation between the two methods of measurement, they also both report up to 20 cmH_2O spread in pressure differences between the two limits of agreement on Bland-Altman analysis, a result that agrees with previous studies(18) (19). Concern over this variation was raised in a subsequent letter to the editor(24), echoing concerns in a previous review(25). The reason for these differences, as well as the clinical significance is still not apparent, as these studies had all taken initial resting pressures into account, showing that some other unknown factor is causing the variations seen. Until this disparity is understood, the committee maintains the previous conclusion that the two pressure measurement systems are not interchangeable during filling and voiding cystometry. The study dealing with urethral pressure measurements(22) confirmed previous data that air-filled systems read higher urethral pressures than water-filled systems, while having a more reproducible reading. Given the small number of patients (33, all neurogenic), there is still a need for further investigation to ascertain normal values for air-filled urethral measurements. The fourth study(23) did not examine the pressure readings, but was limited to assessment of usability and safety of a new thinner catheter, which were positively reported.

1.3. Conclusions

- Air-filled catheters may provide an acceptable alternative to other techniques for measuring the pressure closing the female urethra, however reference values have not been established. (level 3)
- New studies confirm that air-filled catheters record different pressure values to water-filled lines in UDS and are therefore not interchangeable. (level 2)

- Air-filled catheters have not been widely tested in men or in children, or in patients with NLUTD.

1.4. Recommendation (Grade C)
- Investigators planning to use air-filled catheters for intravesical and intra-abdominal pressure in UDS are advised to check and reassure themselves that they have an equivalent performance to their current system for measuring pressure.
- Investigators planning to use air-filled catheters for intravesical and abdominal pressure in UDS are advised to check for themselves how the performance of their system compares to the standard reference values for clinically relevant limits (especially of resting pressures, obtained with the classical systems).
- Clinicians using UDS should be well aware of the technical demands of measuring with a water-filled system with external transducers and should be able to minimize, correct and recognize artefacts.

1.5. Topics for Research
- Studies to compare the performance of air-filled catheters with ICS standard water-filled pressure lines in the measurement of intravesical and abdominal pressure during filling and voiding cystometry in male, neurological and paediatric patients as well as analysis of test-retest reliability.
- Studies to determine the cause(s) of the observed differences in pressure readings between water-filled and air-filled systems.
- Studies to determine the clinical relevance of difference in pressure readings between water-filled and air-filled systems, including urethral pressures.
- Studies to establish standard values for urethral pressures, filling cystometry and pressure flow studies using air-filled catheters.

2. IMPLANTED TRANSDUCERS FOR PRESSURE MEASUREMENT

2.1. New evidence 2021

As an alternative to catheterised pressure measurement, interest has been shown in developing pressure sensors that can be implanted or placed within a body cavity and communicate readings wirelessly to a body-worn data receiver. Clearly better suited to long-term or post-operative monitoring, such devices would offer data sets longer than the most advanced ambulatory devices currently available and would allow monitoring without the intrusive effect of a catheter.

One such device(26), the ‘Bladder Pill’, was trialled in five Gottingen minipigs, being inserted into the bladder lumen. The pressure readings were validated by a comparison urethral pressure measurement catheter and demonstrated agreement. The same group reported data from a combined pressure and accelerometer system(27), again in pig models but within the bladder mucosa, adding another dimension to the potential for research. Another group has reported a device implanted in the mucosa first with wires connecting and then with telemetry connecting to the data receiver(28), followed by a new device ‘Uromonitor’, which was placed in the bladder lumen of human subjects(29).

Since these devices will only be monitoring one pressure, the intravesical, there may be limitations in that abdominal pressure variations will be present in this signal. However, the latter group above have also presented work that suggests that advanced signal processing can identify true bladder events from single channel data(30). Historic articles on the use of only one channel have urged caution or careful selection of patients. This work will need careful and convincing validation therefore if it is to be used in a diagnostic test.

2.2. Conclusions (Level 4) and Topics for Research
- Implanted devices hold promise for long term monitoring for research purposes or post-operative monitoring. Only animal studies have been done to date.
- Studies to investigate the use of these devices in humans will be needed before clinical applications can be targeted.
- Studies to validate and apply algorithms for event detection from single channel urodynamics are needed before use in routine clinical UDS.

3. OBJECTIVE ASSESSMENT OF BLADDER SENSATION

3.1. Conclusions and Recommendations 2016

Based on published results ICI2016 noted that there was a significant variation in clinical practice to determine bladder filling sensation landmarks and maximum cystometric capacity despite the standardisation of terms. The committee concluded that strategies to derive bladder filling sensation parameters in a more automated and objective way had been showing plausible and applicable results. ICI2016 stated that these were however not sufficiently tested with regard to reliability, relevance, investigator independency or test-retest robustness. Bladder filling sensation has received increasing attention since urinary urgency and early filling sensation remain clinically important and some treatments are believed to influence LUT sensation.(31) (32)

A patient-activated, keypad ‘urge score’ device to measure sensations during bladder filling was previously described in ICI2016 (33) (34) (35). Measuring of different bladder sensations has not been further investigated or adopted into standard practice.

In the development of the ICIQ bladder diary, the data from 264 patients’ diary recordings of urinary urgency showed weak agreement with questionnaire responses and UDS observations(36). Although cystometry is regarded as the gold standard to assess bladder filling sensation there is a paucity of evidence regarding its clinical relevance. Also, the question whether cystometry or alternative (diary–like) evaluations are more relevant remains unanswered.

Research has provided some *in vivo* evidence of the specific brain areas that are involved in LUT sensation, control and modulation, but this type of observation cannot yet be regarded as a replacement of cystometry, because up to now no brain pattern has been shown to correlate with a specific UDS abnormality.(37) (38).

Many studies consistently show that the correlation between objective and subjective features of detrusor adaptation to volume increment, bladder proprioception and the subjective interpretation of filling is weak.(39) (40) (41) (42) (43) (44) (45) In fact these observations also demonstrate that UDS is adding new and objective diagnostic information to what has been gathered with history, voiding diary and clinical investigation. Both UDS, as well as signs and symptoms, are relevant to select further treatment, for instance in the identification of DU.(46)

3.2. New evidence 2021

Two recent reviews have summarised developments to date in assessment of bladder sensation(47) (48). These again highlight the lack of consensus and the subjective nature of commonly used descriptions. One group reported(49) (21 participants) and validated(50) (10 participants) a sensation meter on a tablet computer that uses a combination of meter-style, slider bar and verbal summaries to record sensation. The meter produces a sensation–capacity curve, as used in another group's study(51), both of which demonstrated good repeatability. The filling rate and pressure on the abdomen were found to affect sensation, and further study will investigate clarifying objective description to take these factors into account.

3.3. Conclusions (Level 3-4)

- Based on published results, a significant variation exists in clinical practice to determine bladder filling sensation landmarks and maximum cystometric capacity, despite the standardisation of terms.
- Strategies to derive bladder filling sensation parameters in a more automated and objective way, have been published and show plausible and repeatable results. Assessment of confounding factors and larger studies are yet to be carried out.

3.4. Heart Rate Variability

Heart rate variability was evaluated to serve as a monitor of the autonomic nervous system as an objective measure for LUTD and/or bladder filling sensation, without arriving at a clinical application yet.(52) (53) (54). A recent study(55) in patients with myelopathy failed to show a significant rise in sympathetic or parasympathetic components of heart rate.

3.5. Conclusions (Level 3-4)

- None of the analysis or testing methods of the autonomic nervous system has, to date, shown any relevance for the objective diagnosis of LUT function.

4. NON-INVASIVE PRESSURE MEASUREMENTS

4.1. Conclusions and Recommendations 2016

Non-invasive measurements of bladder pressure during voiding in men by the penile cuff or condom catheter have been shown to correlate with traditional invasive measurement of bladder pressure. ICI2016 recommended (grade B) that non-invasive measurements of bladder or detrusor pressure can be considered in clinical experiments in order to evaluate voiding function when the male patient is not required to undergo an invasive assessment of the storage function of the LUT. The ICI2016 did not recommend condom or penile cuff pressure, nor near infrared detrusor spectroscopy, for the diagnosis of UI, nor of LUTD(56). Measurement of perineal noise during voiding as another way of non-invasively quantifying male BOO has been evaluated but has also not demonstrated relevance for the diagnosis of male UI(57). Transabdominal wall near-infrared spectroscopy (NIRS) was used to detect the haemodynamic changes that are associated with detrusor contractile activity (58) (59) (60).

4.2. New evidence 2021

Data has been published on a new version of a device (the 'urethral connector') to measure a proxy for isovolumic intravesical pressure during an interruption of voiding at the location of the fossa navicularis(61). The pressures obtained were similar to those obtained by conventional PFS and were significantly different between groups of obstructed and unobstructed men. No new data on perineal noise or NIRS have been presented.

Despite advances being made, both a systematic review(56) and a consideration of developments in 'less-invasive UDS'(62) concluded that since current technologies cannot yet replace invasive tests for pressure measurement, they are best placed for consideration as screening or triaging tools, to spare some patients from invasive UDS early in the treatment pathway.

4.3. Conclusions (Level 3)

- Non-invasive measurements of bladder pressure during voiding in men by the penile cuff, condom catheter and urethral connector have been shown to correlate with traditional invasive measurement of bladder pressure.
- Near-infrared detrusor spectroscopy has, in very selected recordings, shown a relation with detrusor activity but this could not be reproduced in an independent clinical follow up evaluation.

4.4. Recommendation (Grade B)

- The committee endorses that in clinical experiments non-invasive measurements of bladder pressure may be considered in order to evaluate voiding function, as screening tools for assessing male patients.
- The committee does not recommend condom, penile cuff or urethral connector pressure, nor near infrared detrusor spectroscopy, for the routine assessment of LUTD.

5. URETHRAL PRESSURE REFLECTOMETRY

5.1. Conclusions and Recommendations 2016

Urethral pressure reflectometry (UPR) is an alternative method of assessing urethral function that measures pressure and the cross-sectional area along the entire urethra continuously. This technology was evaluated in an *in vitro* study.(63) Subsequently UPR parameters of 30 SUI-S women and 30 volunteers (23 'continent' and 7 'nearly continent') were reported and compared with UPP(64). A feasibility study using the technique was also reported in 10 male patients(65). The committee recommended that urethral pressure reflectometry not be used in clinical practice for the diagnosis of UI

5.2. New evidence 2021

The group that developed the technique has since published several studies using UPR to monitor changes in urethral pressure in women before and after medical ((66), n=24), surgical ((67), n=28) and conservative ((68), n=31) treatment. Several of these studies showed that UPR can detect changes in urethral pressure that correspond to clinical indicators and relevant changes. Furthermore, in a study of 30 women(69), UPR was found to be highly reproducible in its measurements. These data suggest that larger studies are indicated in order to ascertain the utility of UPR within a diagnostic or prognostic framework.

5.3. Conclusion (Level 3)
- Clinical measurements of urethral pressure reflectometry opening pressure and cross-sectional area have provided some insight into urethral closure function, but, as yet have no clinical relevance in the diagnosis of UI.

5.4. Recommendation (Grade B)
- The committee recommends that urethral pressure reflectometry is not used in clinical practice for the diagnosis of UI before clinical relevance, non-inferiority and/or superiority over current UDS has been demonstrated.
- The committee considers that larger trials assessing the diagnostic and prognostic value of UPR would be justified.

6. ULTRASOUND IMAGING

6.1. Conclusions and Recommendations 2016

Imaging and ultrasound in relation to UI will be discussed in a separate chapter of this book. We will only give a short summary of ultrasound in relation to UDS observations.

The measurement of detrusor wall thickness has been used in several studies as a screening test for DO or for BOO with a variety of measurement techniques using transvaginal, transabdominal or transperineal ultrasound. Different protocols were used and measured different parts of the bladder. This has resulted in contradictory data. Some data showed a smaller cystometric capacity in patients with overactive bladder syndrome (OAB-s) or DO, and an association between increased detrusor wall thickness and DO on UDS. Also, observations of an association of ultrasound detrusor wall thickness and BOO have been reported. Most researchers conclude that overlap of the results and the relatively low predictive value should be improved before bladder wall thickness is used in clinical practice.(70) (71) Furthermore, the specificity of detrusor wall thickness for UI (or DO) has not been determined and is probably unlikely to be clinically meaningful. Studies of other specific patient groups have been reported. One, in SCI patients, concluded that detrusor wall thickness could not be used in such patients(72) and another in nocturnally enuretic children suggested that detrusor wall thickness could be applied as a screening tool to select children with DO(73).

Twenty men (mean ± SD age 66 ± 6 years) with LUTS were included in a study to evaluate radio frequency ultrasound imaging of detrusor wall strain. This bladder wall strain correlated positively with detrusor pressure in some patients with an isovolumetric and/or voiding detrusor contraction. It has however been difficult to continuously measure the bladder wall in a large proportion of the patients(74).

6.2. New evidence 2021

The latter group above have published data on the method of decorrelating sequential ultrasound images of voiding as a method of diagnosing BOO(75). Processing of transperineal ultrasound from 45 voiding male patients yielded a 95% specificity and 88% sensitivity for the diagnosis. Another group has been investigating the quantification of bladder wall biomechanics using ultrasound(76), as an adjunct to conventional UDS. The application of advanced image analysis could well offer non-invasive options for screening and potentially for diagnosis, as well as inform research into bladder physiology. This study also referred to a simpler assessment of bladder outline shape which has been explored by the group(77), and which is the subject of an ongoing research project elsewhere(78). Both groups report significant differences in measurable shape indices between patients with bladder contractions and patients with acontractile bladders, suggesting a non-invasive tool for the detection of DO.

Developments in the use of bladder wall thickness (BWT) measurements have also been reported, both in relation to the diagnosis of male BOO(79) (65% diagnostic accuracy for age>70y, n=196) and of male DU(80) (73% accuracy, n=448). Increased BWT in male patients has also been reported in patients with DO(81). Studies have also been reported in female patients(82), but a multicentre accuracy study reported that BWT is not a good replacement test for DO in women(83), where the lower urethral closure pressure in females may be a factor. The conclusion of the EAU systematic review(56) that BWT may have a multifactorial basis has been repeated in these more recent studies. Guidelines for reliable cut-offs in clinical practice for accurate diagnostics in place of invasive methods have yet to be developed, but researchers report that it may have a role in assisting patient management(79) (82).

6.3. Conclusion (Level 3)
- There is some evidence that detrusor wall thickness is related to BOO, DU and DO in men.
- There is no evidence that ultrasound detrusor wall thickness analysis can discriminate between DO (with or without UI) and BOO. Detrusor wall thickness has a relatively low predictive value to discriminate from normal LUT function.
- There is a large overlap between normal and abnormal values in detrusor wall thickness and a lack of standardisation in ultrasound detrusor wall thickness measurement.

6.4. Recommendation (Grade C)
- The committee recommends that ultrasound detrusor wall thickness not be used in routine clinical practice for the diagnosis of LUTD related to UI, but that guidelines for use in patient management be investigated.
- The committee recommends that studies into the analysis of bladder wall biomechanics and bladder shape using ultrasound be encouraged and supported.

III. URODYNAMIC STUDIES: NORMAL VALUES, RELIABILITY AND DIAGNOSTIC PERFORMANCE; REPRODUCIBILITY AND RELIABILITY OF URODYNAMIC STUDIES

1. CYSTOMETRY: NORMAL VALUES AND TEST-RETEST VARIATION

1.1. Introduction

Awareness of lower urinary tract （LUT） function and physiology is important when UDS is performed. Similarly, normal anatomy should be known when medical imaging is performed or evaluated. The function and physiology of the LUT is fairly simple by itself: the bladder should adapt to the increasing volume of urine produced by the kidneys as the bladder fills during the micturition cycle with only little or no pressure increment. The stretching bladder muscle should signal to the conscious brain to create awareness of fullness, and the necessity to empty, at adequate volumes and safe pressures. In humans the bladder should contract and empty quickly and effectively in tandem with voluntary pelvic floor striated muscle relaxation. The smooth muscle bladder outlet should be contracted during storage and relaxed and funnelled during voiding. Bladder muscle dome and base are antagonists and the pelvic floor muscle acts as the voluntary learned control, rather than these autonomic innervated smooth muscles. Any deviation from this is abnormal, may cause difficulty and may provoke the need for medical therapy. In neurologically normal persons signs and symptoms are sensitive but not specific for the dysfunctions, if measured with UDS. In neurologically affected persons, symptoms are, usually because sensation is affected, less sensitive and/or usually less specific. UDS is usually done for persons that present with symptoms and the result of the test can be used to explain all elements of function and can be used to put the presenting symptoms in the perspective of dysfunction and pathophysiology, in relation to what can be physiologically expected from the lower urinary tract. This description is qualitative, not quantitative; the ICI2021 working group and earlier ICI working groups have summarized the more quantitative evidence.

1.2. Summary of earlier conclusions and recommendations

Earlier ICI consultations(84) concluded that various studies have been helpful in giving normal values and test-retest variation of UDS parameters in healthy volunteers. But also, that there has been some evidence that evaluation of bladder filling sensation may be different between laboratories. These may be observer dependent, making data exchange as well as generalization and interpretation of published data difficult. It was advised that investigators and clinicians recognize ‘normal’ test-retest variation as well as the differences and/or variations between usual lower urinary tract behaviour and UDS, with a specific recommendation that investigators and clinicians assess the representativeness of the evaluation based on the patient’s perception as to how well the tests have reproduced their usual LUTS. UDS are showing test-retest variation of ±10-15% for various parameters (volume, pressure or flow) and observations, as well as a variation in evaluation(85–89)abstracted clinical and urodynamic information from 100 charts, selected for adequate completeness from a consecutive series of 135 women referred for urodynamic testing. For each of the 100 cases, the reviewers assigned International Continence Society filling and voiding phase diagnoses, and overall clinical diagnoses. Raw agreement proportions and weighted kappa chance-corrected agreement statistics (kappa. A test-re-test variation in clinical testing is expected and unavoidable(90) and UDS performs similarly to other clinical tests where cooperation between patient and clinician is relevant. Apart from the inherent physiological variation of UDS, clinically relevant practice variations and inter-observer interpretational variations were noted in earlier ICI reports(91,92). Further standardisation of UDS as well as education were recommended(84).

1.3. New Evidence 2021:

ICS has published a new practice standard for invasive UDS(4) that has included further standardisation of the evaluation of filling sensation. This standard has also included the recommendation of earlier ICI committees to include patient reported representativeness in the evaluation. The new standard was followed up and well explained in narrative reviews(93,94). One health care system has earlier proposed a national quality standard for UDS(95), that led to a renewed document(96). Recognition of artefacts and features, that may occur while performing or evaluating UDS, was substantiated and standardized with a manuscript as well as with an International Continence Society (ICS) teaching module(14,97) and software may become increasingly relevant in supporting measurement quality control(13). Standards of equipment performance are still valid(98). Further additional attention has been given to the reference to the surrounding atmospheric pressure(99) and the vulnerability of the ICS standard(4) water-filled system in this regard(100). The drawbacks of the traditional water-filled system were a driver for innovation(101) although sufficient evidence was deemed required in order to replace or adjoin the standard system(102,103). Comparative evidence is evolving *in vitro*(104) and in clinical measurements(105–108) and is enthusiastically discussed(109,110).

Normal LUT function is well defined and easy to understand, and two groups have found studies that represent normal lower urodynamic physiology (111–113). Some research again draws attention to continuous urethral pressure(114,115) but with unknown clinical relevance at present(116,117). Video (X-Ray/Fluoroscopy) and EMG as adjuncts to standard cystometry are discussed in an expert consensus meeting, concluding with recommendations(118,119) and also in a teaching module and a manuscript with the aim to improve practice(120,121).

1.4. Conclusions

The committee concludes that limits of normality in UDS are well established (Level 2). The committee also concludes that precise limits for abnormal (i.e.reduced) compliance are not exactly known (Level 3). The committee concludes that LPP has many variations (also without cystometry) and that standardization of technique is lacking (Level 3).

1.5. Discussion

Normal function and physiology of the LUT is the basis for diagnosis of abnormality and dysfunction. Based on the commonly accepted limits of normality a specific dysfunction can be diagnosed. Not every dysfunction needs treatment and treatment is selected on the basis of diagnosis, signs, symptoms, bother, prognosis and risk to the upper urinary tract, and patient preference.

There is a risk for urinary tract infection (UTI: <5%) after invasive UDS. A systematic review evaluated nine randomized controlled

trials and concluded that prophylactic antibiotics did reduce the risk of bacteriuria after UDS but there was not enough evidence to suggest that this effect reduced symptomatic UTI(122). The ICS standard(4) has recommended to advise the patient to drink extra amounts immediately after the test to prevent bacteriuria evolving into infection and inflammation.

1.6. Recommendations (Grade A):
Persons diagnosing LUT function and dysfunction should be sufficiently aware of normal LUT function and physiology, and its variability. They should also be familiar with the variability in the results of UDS. Persons performing UDS and persons interpreting the test results should have a thorough knowledge of normal physiology and its deviations, should be aware of the circumstances of the tests and their potential influence on LUT function and should be able to evaluate the tests with the reported representativeness in mind.

It is important that any new equipment used for UDS should have established reference values. It is particularly important to note that reference values between water-filled systems and air-filled systems are not interchangeable.

Antibiotic prophylaxis should not be routinely prescribed for UDS testing, The procedure should be performed with sterile catheters, tubes, fluids and aseptic technique as per good clinical practice. Local microbiological advice should be sought and protocols developed for the local UDS laboratory.

2. REPRODUCIBILITY OF AMBULATORY URODYNAMIC STUDIES

2.1. Summary of earlier conclusions and recommendations
Earlier consultations have not found published data on the reproducibility or test-retest differences of ambulatory UDS for patients with UI without relevant neurological abnormalities(84). A report on ambulatory UDS for patients with NLUTD was included in ICI2016 concluding fair reproducibility but with difficulties in zeroing of the pressures and balancing of the abdominal and vesical pressures(123). These technical difficulties may likely also occur in non-neurogenic dysfunction but it has not been studied or reported.

2.2. New evidence 2021
A single centre retrospective cohort study deemed ambulatory UDS to be useful for 430 patients out of 12,123 patients (3.5%) that underwent conventional UDS. In those patients ambulatory UDS changed the treatment plan in 75% of the cases (124).

2.3. Conclusion (Level 3)
The committee has not found studies that report reproducibility of ambulatory UDS for patients with non-neurogenic urinary incontinence. A reproducibility study in patients with neurogenic LUTD has observed difficulties in technical reliability of this test, though this has not adequately disproved ambulatory UDS for patients without neurogenic dysfunction. A new study has demonstrated that ambulatory UDS, when used for a sub-selection of patients, can change the treatment plan.

2.4. Discussion
Movement artefacts, pressure balancing and assessment of fill volume as well as prevention of urodynamic catheters from dislocating are challenging in ambulatory monitoring and standardization of the test is likely of relevance(125).

2.5. Recommendations (Grade B-C)
- The committee does not recommend ambulatory UDS as a routine first-line diagnostic test for patients with LUTD.
- The committee recommends greater attention to test-retest differences of ambulatory monitoring.
- The committee recommends standardization of the indication, the practice and the technical quality and analysis of ambulatory UDS.

3. INFLUENCE OF CATHETER ON VOIDING

3.1. Summary of earlier conclusions and recommendations
There is evidence that, in general, flow is reduced when voiding with a urodynamic catheter in the urethra and that this reduction is partially caused by the size of the catheter. It has been the opinion of earlier committees that single catheters 6-8 Fr incorporating both a filling channel and a pressure-sensing channel (i.e. double lumen catheters) should be used for intravesical pressure measurement during cystometry, as is also included in the ICS standard(4). PFS parameters and the subsequent PVR and Void % (voiding efficiency) should be interpreted together with the free flow voiding parameters.

3.2. New evidence 2021
A new study was published, confirming that the catheterized flow rate differs from the free flow in a cohort of patients(126) which in combination with an *in silico* analysis, again leads to the recommendation to always compare these two flow rates(127).

A study evaluated the test-retest reliability of uroflowmetry in a cohort of patients with various clinical incontinence syndromes. Test-retest differences were reported as insignificant in all groups apart from the patients with SUI and all uroflowmetry results were similar between the diverse syndrome groups. Although the number of abnormal, ineffective voiding, or reduced, intermittent or fluctuating flow rates was not provided, the authors have concluded that uroflowmetry with PVR requires further appraisal as a screening test for women with urinary incontinence(128).

3.3. Conclusion (Level 3)
Studies have confirmed that the transurethral urodynamic catheter causes an effect on voiding and flow rate that is proportional to the size of the catheter. Apart from these static effects, a dynamic effect is likely in a proportion of patients. The usefulness of uroflowmetry with PVR is not proven for women with isolated urinary incontinence. However, the pattern of flow on a flow curve may indicate straining and can be helpful.

3.4. Discussion
Both test-retest variation as well as variation in circumstances (e.g. position, privacy, bladder volume) play a role in 'dynamic differences' between two flow rates. The potential effects of position (for men and women) and privacy have not been reported in PFS. Also, differences may be large without clinical relevance in relatively high flow rates (especially when >15 mL/s). Double lumen 6 Fr catheters are ICS standard and PFS categories are based on measurements with catheters of this size, however only in male patients(4). Dysfunction of voiding has not been included in the scope of this

consultation however LUT function and dysfunction of storage and voiding are inextricably bound together.

3.5. Recommendations (Grade A-B)
- The committee recommends that investigators interpret pressure-flow study parameters and the subsequent PVR and voiding efficiency together with the free flow voiding parameters when relevant in the diagnosis of concurrent LUTD, together with the complaint of UI.
- Standard practice of dual lumen, as thin as possible catheters (8 Fr or less) for filling and pressure recording during UDS is recommended. If a dual lumen catheter is not possible, a two catheter technique can be an alternative during the filling phase, with removal of the filling catheter at the end of filling and prior to voiding.

4. URETHRAL PRESSURE MEASUREMENTS

4.1. Summary of earlier conclusions and recommendations
ICI committees have concluded that diverse studies have shown considerable test-retest variation and that urethral pressures depend on the pressure recording catheter used and its orientation within the urethra, and also depend on patient position, volume of fluid in the bladder and position of the patient. The clinical specificity of the results has never been demonstrated to be very high(84).

4.2. New evidence 2021
A pressure profile through the urethra has recently again been demonstrated with many sensors(129,130) or with an alternative to micro-tip sensors(131). There is no evidence that this solves the earlier problem of the lack of specificity for the type of urinary incontinence. Another recent study has again shown that there is a very substantial overlap in UPP results when a cohort of women was separated into diverse types of UI(132). Far more relevant, however, is the comment written in reaction to this research(133), which said that the pressure profile can never be an exact representation of the closure forces because technical limitations prohibit this, and measurement unavoidably affects function. An expert group has summarized many uncertainties around the assessment of urethral function and suggested areas for research(134) that should be scrutinized against the fundamental physics of intra-urethral assessment. That urethral closure function is not static *per se* was recently summarized by an expert group(116), as well as in a systematic analysis(115).

4.3. Conclusions and recommendations
Relatively high closure pressure in the bladder outlet can prevent incontinence in a normally functioning bladder. The premise of a UPP is not unjustified. The Committee concludes again that the very large overlap of urethral pressure values in clinical practice reduces the diagnostic value of the test due to low specificity. There is no evidence or plausibility that profilometry with more synchronous pressures or with alternative ways of pressure recording are of any potential advantage.
- The Committee discourages UPP as a single diagnostic test.
- The Committee recommends the use of standard UPP only in combination with cystometry and pressure–flow test, if deemed necessary, e.g. to confirm very low ‘urethral pressure’ or when leak point pressure has been very low during cystometry.
- Dual lumen catheters do not provide a precise measurement of urethral pressure profilometry as the eye holes are not opposite each other.

5. ABDOMINAL LEAK POINT PRESSURES

5.1. Summary of earlier conclusions and recommendations
ICI committees have concluded that diverse definitions and techniques to determine abdominal LPP exist and also that there is a variable association between abdominal LPP and the patient-experienced or measured severity of bother, or amount of UI. Studies have shown that different techniques and patient positions influence the results of abdominal LPP. Committees have not recommended abdominal LPP measurement as a sole test in female patients with UI. With regard to post RRP UI in men, Valsalva LPP was evaluated as a predictor before artificial urinary sphincter (AUS) insertion but did not show any relevance.

5.2. New evidence 2021
Apart from the above comments on UPP, a study has shown the plausible effect of an intra-urethral balloon catheter during the urodynamic stress testing(135). Cough stress testing with an air pressure balloon in the urethra results in higher LPP (or no leakage at all) compared to leak pressure testing without this. Also reconfirmed is that women with easier and larger amounts of leakage, more vaginal deliveries and older age have a larger chance of relatively low LPP(136).

5.3. Conclusion (Level 2-3)
Earlier and new studies showed no evidence that abdominal LPP is very specific to diagnose female patients with SUI or male patients with post RRP-I in subcategories.

5.4. Recommendation (Grade B)
• The committee does not recommend abdominal LPP measurement as a sole test in patients with UI without relevant neurological abnormalities.

6. PROVOCATIVE MANOEUVRES

6.1. Summary of earlier conclusions and recommendations
ICI committees have concluded that upright position, moving to a toilet, and hand washing are provocative of DO and recommended that the results of provocative cystometry are interpreted in the light of the patients’ symptoms, and to bear in mind whether the results obtained are representative. Also recommended earlier was that all circumstances and provocations during UDS should be reported. No standard for the diverse manners of provocation for patients with urinary incontinence is published, neither for the provocation of DO and nor for the provocation of stress urinary incontinence.

6.2. New Evidence 2021
The committee has not found new evidence regarding the position of the patient during cystometry although seated position is defined to be standard whenever possible(10). The latest ICS-GUP standard has introduced and defined the term ‘cough associated DO’ for one of the provocative tests during cystometry(4). A newly published evaluation has shown that this is applicable and relevant(137). Although clinical stress testing (as explained in the clinical assessment chapter of this consultation) is better standardized

at present(138) a standard for urodynamic stress testing and or leak point assessment is still lacking.

6.3. Recommendations (Grade C)

- The committee recommends that the results of provocative cystometry are interpreted in the light of the patient's symptoms and to bear in mind whether the results obtained are representative.
- The committee recommends the performance of UDS in the upright position (not supine); for females in the sitting position, and sitting or standing for males, whenever possible, because of the better sensitivity for filling phase abnormalities, but also because of the greater possibility of representative voiding and better patient comfort.
- The committee recommends that, when possible the filling position should be similar to the voiding position to avoid artefacts during recording of pressures.
- The committee recommends development of standards for provocations during UDS.

7. CLINICAL APPLICATIONS OF URODYNAMIC STUDIES; CORRELATION WITH SYMPTOMS AND SIGNS

7.1. Summary of earlier conclusions and recommendations

Numerous studies have demonstrated that symptoms and signs are not very predictive of the results of objective assessment. Objective assessment is the basis for almost every disease although symptom and signs may be helpful in initial management. Urinary incontinence is no exception; recognising the overactive bladder syndrome (OAB-S), SUI (and/or voiding dysfunction syndrome) may be helpful for initial conservative management(139), but good healthcare practice usually requires objective assessment when initial symptom or syndrome management fails. Earlier committees have always confirmed the guidelines that state that UDS is the gold standard to assess LUT function and dysfunction. All guidelines recommend UDS 'when necessary'. That UDS is fundamental in the objective assessment of urinary incontinence is never disputed although no guideline has ever been very specific in the indication for UDS. Earlier ICIs have recommended UDS as the gold standard assessment of patients with urinary incontinence.

7.2. New evidence 2021

A large study has confirmed that many patients with 'typical' SUI, as defined in earlier studies, did not have the 'typical' result on UDS. Even the most 'straightforward patients' with this syndrome could have diverse LUT dysfunctions(140,141). An *ad hoc* expert group has recently summarized the abundant evidence that confirms the mediocre specificity of symptoms, when resistant to initial management, for dysfunction and used this to underline another plea for objective assessment(142). Regrettably the ICI committee has found that no new studies have provided good guidance to define resistance to treatment or failure of pragmatic, syndrome-based management, neither for OAB-S(143), or for OAB-S incontinence or for SUI.

UDS may be help predict UI or delayed recovery of continence after radical retropubic prostatectomy (RRP) (144–146), which may be useful to counsel patients when they opt for surgical intervention. However, many confounders exist, especially the surgery and surgical technique itself. It is known and plausible that urodynamic parameters do not predict concomitant LUT problems when filling cystometry is done only up to leakage (e.g. (147)). The situation after intervention leads usually to larger capacity and to the need to void (without BOO and without PVR) as well. A balloon occlusion urodynamic technique, as was described in the earliest standards(148), is essential for many patients and occlusion (whether with a balloon catheter(149) or with manual closure of the urethra) should be applied as standard.

7.3. Discussion

Syndrome-based diagnosis of urinary incontinence has some diagnostic predictive value and is definitely of use in initial management. There is a lack of good prospective assessment of the diagnostic strategy after failure of initial management. It is plausible that objective UDS assessment may reduce the necessity of invasive second line management, and by reducing the number patients allocated to unnecessary invasive treatments would reduce failure rates, harm and costs, as well as increase success rates.

7.4. Conclusions and recommendation (Grade A)

- The committee recommends, in agreement with all guidelines, UDS as the gold standard test for patients with UI and LUTS.
- The committee recommends to precisely define 'failure' or 'treatment resistance' after initial (and syndrome-based) management.
- The committee recommends including red flags or alarms within the definition of the UI syndromes, potentially leading to a lower threshold for objective assessment of dysfunction, before any management.

8. QUALITY ASSURANCE IN URODYNAMICS

8.1. Evidence base

As in any medical test, monitoring and assurance of quality is vital. Urodynamic testing is frequently discussed with regard to its clinical quality and relevance. Technical quality has received attention for over 15 years.

In the UK health care system a single centre set of urodynamic traces were retrospectively evaluated for accuracy of baseline and cough pressures(150). Approximately 65% of the pressures were acceptable. An unexpected high rate of catheter loss around voiding was observed while using a separate single lumen filling catheter beside the pressure recording catheter. Initial resting pressures and cough responses, were also evaluated in other manuscripts reporting traces from different centers(151,152), with similar results, i.e. some imbalance in cough responses and errors in intravesical or abdominal initial resting pressures values, or both. Reviewing published traces and urodynamic traces found on the internet showed in addition to these errors lack of visible scales and other relevant elements of urodynamic testing(153,154). Another single centre retrospective study observed errors in interpretation and especially in flow rates, associated with insufficient voided volumes leading to unrepresentative results(155).

After publication of the 2016 ICS Good Urodynamic Practices and also after an ICS teaching module, helping to recognize errors and artefacts(15), a prospective multicenter study observed technical artefacts and errors, both in measuring quality as well as in clinical evaluation(156).

8.2. Conclusion
Evaluation of the technical quality of urodynamic testing shows that a relevant proportion of UDS has errors and artefacts.

8.3. Discussion
Technical artefacts occur, though do not always hinder diagnosis. It is demonstrably clear that many artefacts or errors seem not to be recognized, as becomes obvious when examining published tracings where urodynamic diagnoses are given based on obviously erroneous tracings, without discussing the reliability or validity of the measurement. Research questions to answer to help remedy this situation have been proposed(157).

8.4. Recommendation
Practical training of persons performing urodynamic testing (urodynamicists) is very relevant, including quality monitoring. However training and education of the persons establishing the diagnosis and management (the treating physicians) is even more important to prevent mis-interpretation, independent of technical measuring quality.

IV. PATIENT EVALUATION: WOMEN

1. STRESS URINARY INCONTINENCE IN WOMEN

1.1. Urethral Pressures and Severity of Stress Urinary Incontinence

1.1.1. Conclusions and Recommendations 2016
Various studies have shown a weak association between UI severity and urethral function tests (LPPs and urethral closure pressures) and cohort studies have shown that UI volume and intravesical volume at leakages are poorly associated with symptoms' severity and/or with patients' quality of life. In addition, studies have shown that urethral pressure and/or LPP did not have a predictive value towards outcome 6 months following TVT surgery, apart from the 6% patients with very low urethral pressures (<20 cmH_2O). However, it was also noted that there is a lack of evidence specifically for the management of patients with very low urethral pressures and that the many possible surgical solutions do not differ very much in outcome. In ICI2016, the committee recommended that LPP and urethral closure pressures not be used as a single factor to grade the severity of UI and did not recommend the use of urethral function tests for predicting the outcome of any surgical treatment for SUI (Grade C).

1.1.2. New Evidence for 2021
Two retrospective studies showed a correlation of SUI severity as determined by Stamey score with an abdominal LPP (ALPP) <60 cmH_2O which these studies defined as intrinsic sphincter deficiency (ISD)(136,158). In one study ALPP<60 cmH_20 was also associated with a positive empty bladder stress test. A large retrospective database study of women with urodynamically demonstrated SUI confirmed a lack of correlation of maximum urethral closure pressure (MUCP) and ALPP, showing only a weak association at 150 ml bladder volume that improved to a moderate association at bladder capacity(159).

1.1.3. Conclusions and Recommendations
- The committee considers that the term 'severity of incontinence' is not universally defined. Since it is not always clear whether severity refers to patient-reported bother or to physician-perceived therapeutic challenges (i.e. more difficult to treat), the committee suggests to better standardize the term.
- While there is increased evidence that higher degrees of subjective SUI and physical findings such as a positive empty bladder stress test are associated with ALPP<60 cmH_2O, the clinical relevance of this finding remains uncertain. The newer literature confirms the poor correlation of MUCP and ALPP, making it difficult to define ISD in a practical way by urodynamic parameters.
- The ICI2021 committee recommends assessing urethral function by at least one of the above methods, MUCP and ALPP if it will affect treatment. The committee reaffirms its recommendation that LPP and urethral closure pressures not be used as a single factor to grade the severity of UI. Furthermore, the committee does not recommend the use of urethral function tests for prediction the outcome of any surgical treatment for SUI. (Level of evidence 3, Grade of Recommendation C)

1.2. Aspects of Urodynamic Studies Relevant to Therapy for Stress Urinary Incontinence

1.2.1. Conclusions and Recommendations 2016
ICI2016 reported that prior ICIs concluded that UDS is not cost effective in the *primary* health care setting for women with symptoms that are likely associated with SUI ('SUI-predominant'). ICI2016 discussed the "VALUE" study that concluded that UDS does not influence the outcome of SUI treatment (7) and the "Investigate1" trial, a randomized controlled trial (RCT) designed to demonstrate the feasibility of a RCT into the role of UDS for patients with SUI(160). The investigators concluded such a trial was feasible and their pilot data indicated that there was a change in practice based on UDS with 80% versus 95% undergoing surgery. However, the study was not powered to demonstrate significance and the authors concluded that 450 patients would be needed in each arm to answer the question, which is more than the two prior prospective studies concluding that preoperative UDS was not necessary for uncomplicated SUI. Because a simplified accurate and reproducible system for anatomic changes and establishing the likelihood or presence of SUI was not in place, it was concluded that it is impossible to establish the need for UDS in a reliable manner in this setting. At present, the predictive value of a clinical diagnosis towards the selection and the outcome of management are unknown. UDS can only be disputed (or discarded) as the gold standard when prospectively compared to its alternative; a reproducible systematically derived clinical assessment or a well-defined 'stress urinary incontinence', and/or a precisely defined 'urgency urinary incontinence' (or 'overactive bladder – wet syndrome'). Thus, the committee recommended that UDS is kept in mind when discussing costs, risks, harm and benefit of the various methods (clinical or UDS) of diagnosis for LUTD and/or UI, in relation to the method of treatment.

1.2.2. New Evidence for 2021
There was minimal new information introduced to further support or oppose the use of preoperative UDS to predict outcomes of surgery in women with SUI. In a retrospective review of 71 women with DU and SUI undergoing retropubic synthetic sling, the authors found that successful treatment of SUI without the need for clean intermittent catheterization (CIC) was predicted by two independent variables: IIQ-7 score ≤6, and Q_{max} ≥6 mL/s(161). They also noted that Q_{max} ≤6 mL/s can predict needing CIC after surgery. However, their cohort included a mix of patients including those with neuro-

genic LUTD and procedures were modified based on UDS findings. However, in another larger retrospective study of 403 women the same senior author found that the presence of DO or DU did not affect continence rates at 5 and 10 years post-surgery versus patients with normal detrusor function(162). In a systematic review and meta-analysis of 4 randomized controlled studies with 150 women, the authors found that routine UDS prior to non-surgical management of UI or surgical management of SUI was not associated with improved treatment outcomes, when compared to clinical evaluation only(163). Data was limited and they suggested that well-designed clinical trials are needed to evaluate the clinical and cost-effectiveness of routine UDS prior to surgical management of SUI and OAB-S.

1.2.3. Conclusions and Recommendations

- The committee recommends that UDS be considered when discussing costs, risks, harm and benefit of the various methods (clinical or UDS) of diagnosis for LUTD and/or UI, in relation to the method of treatment. Care should be taken to determine if and how UDS will affect treatment and/or counselling. Recommendation Level of Evidence 2, Grade of Recommendation B.
- The committee suggests that in a patient with SUI symptoms and no other UDS cause for these symptoms failure to demonstrate urodynamic SUI does not exclude the diagnosis of SUI.

1.3. Prediction of Failure of Surgery

1.3.1. Conclusions and Recommendation 2016

ICI2016 did not find any new evidence for UDS predicting surgical failure. The committee, however, reviewed some studies that commented on the new onset or persistence of OAB-S in women with mixed symptoms of UI. An extensive review of the outcome of all minimally invasive surgical techniques after >=2 years showed that storage LUTS and voiding LUTS had an overall similar prevalence of about 15%.

1.3.2. New Evidence 2021

The committee did not find any new evidence that any specific urodynamic parameters can consistently predict surgical failure. Sections 1.1, 1.2, and 1.5 (above and below) which address specific areas do not add constistently and reliably to the evidence that specific UDS parameters do not predict surgical failure.

1.3.3. Recommendation

The committee recommends that studies evaluating the predictive value of UDS for failure of management include a strategy that is based on UDS results, including change of management and/or continuation of current management on the basis of UDS results, and include evaluation of an intention to treat principle.

1.4. Voiding Difficulties after Surgery

1.4.1. Conclusions and Recommendations 2016

ICI2016 confirmed the conclusions of ICI2013 that voiding dysfunction in women has been defined in many ways throughout many publications, but lacking consistency in UDS criteria and analysis. Also concluded was that test methods have been unable to reliably predict which patients will develop voiding difficulties after surgery for SUI. Normal UDS do not predict absence of voiding difficulties after sub-urethral tape. However, it was found that flow rates, if abnormal, may be useful in predicting post-operative voiding dysfunction and retention following retropubic and transobturator suburethral slings. It was recommended that patients are informed that it is difficult to predict who will develop voiding difficulty following surgery for SUI and recommended that patients with poor flow rates before intended surgery are informed that they have a higher likelihood of having voiding problems following suburethral tape placement for SUI. Also of importance, though not specifically mentioned in ICI2016, was that a large randomized, controlled trial of pubovaginal sling vs. Burch colposuspension showed that no preoperative UDS (including maximum urinary flow rate) was able to predict postoperative voiding dysfunction or the risk for surgical revision(164).

1.4.2. New Evidence 2021

A Cochrane review in 2017 found the presence of voiding dysfunction after transobturator and retropubic mid-urethral slings was 5.53% and was slightly higher in retropubic vs. transobturator slings(165). However, no specific predictors of voiding dysfunction were mentioned. There is no new evidence regarding other incontinence surgeries such as pubovaginal sling or Burch colposuspension.

1.4.3. Conclusions and Recommendations

The committee confirms the conclusions of the ICI2016 regarding definitions of voiding dysfunction after stress incontinence surgery and the lack of predictability of UDS in predicting voiding dysfunction after mid-urethral sling and furthermore extends these conclusions to other incontinence surgeries, specifically pubovaginal sling and Burch colposuspension.

The committee recommends that clinicians may use UDS to evaluate bladder contractility, bladder outflow obstruction, and bladder emptying prior to stress incontinence surgery, however there are no consistent predictors of postoperative voiding dysfunction for midurethral slings, pubovaginal slings and Burch colposuspension.

Level of Evidence 2, Grade of Recommendation B.

1.5. Urgency, Mixed Symptoms of Incontinence, or Overactive Bladder Syndrome after Surgery for SUI.

1.5.1. Conclusions and Recommendations 2016

The prospective studies that were available at ICI2013 indicated that OAB-S, mixed symptoms of UI (MUI) and/or DO at presentation have a negative effect on the outcome of all available surgical interventions for SUI. ICI2013 concluded that methods have been unable to reliably predict which patients will develop *de novo* urinary urgency (OAB-S) after surgery for SUI when the pre-intervention evaluation has been negative for DO (or for reduced compliance). *Post hoc* evidence suggests that procedures for the treatment of SUI which are more 'obstructing' produce a higher chance of *de novo* urinary urgency (OAB-S). The ICI2013 recommended (grade B) that patients with SUI are informed that the chance of developing urinary urgency (OAB-S) following surgery is unpredictable and recommended also that patients are counselled before surgical intervention regarding the possibility of a lesser success rate when OAB-S and/or UDS signs of DO (or reduced compliance and/or cystometric capacity) exist. For ICI2016, a study showed that also patients with 'obvious' symptoms of SUI may have DO, and that these patients are successfully managed without surgery and another study demonstrated that when TVT-O was done only in patients with USI without DO, the cure rate after 10 years was markedly higher (95%) than that usually reported ±75-80%(166). No new recommendations were given.

1.5.2. New Evidence for 2021

In a single retrospective study of 157 women with MUI undergoing mid-urethral sling surgery, authors noted an objective cure of 82.2%

in women with USI but no DO, versus an objective cure rate of 55.2% in those with USI plus DO/DOI(167). Subjective cures were 81.1% and 53.7% respectively. The type of incontinence surgery did not affect postoperative outcomes in either of the groups. The authors concluded that although there is evidence for a good cure of the stress component of MUI, urodynamic investigation with its findings prior to management of MUI could have greater implications for selective patient-centred counselling because the presence of DO or DOI resulted in poorer objective and subjective outcomes. The authors did not specifically report on other patient-reported outcomes. The ESTEEM trial, a randomized controlled trial to determine the effect of behavioural and pelvic floor muscle therapy combined with surgery vs surgery alone on incontinence symptoms among women with MUI in which UDS was not done, showed that patients in both arms had significant improvements in both stress and urgency incontinence after 1 year(168). Women with more severe urgency symptoms at baseline may benefit from perioperative behavioural and pelvic floor muscle therapy combined with mid-urethral sling(169). Among women with MUI, behavioural therapy and PFMT combined with mid-urethral sling (MUS) compared to MUS alone resulted in a small statistically significant difference in urinary continence symptoms at 12 months, but that difference did not meet a prespecified threshold for clinical importance. It should be noted that all women had moderate to severely bothersome SUI **and** UUI at least one episode of each on a 3-day diary.

1.5.3. Conclusions and Recommendations

- The committee recommends that patients with SUI are informed that the chance of developing urinary urgency (OAB-S) following surgery or the possibility of urinary urgency improving after surgery is unpredictable and recommends also that patients are counselled before surgical intervention regarding the possibility of a lesser success rate when OAB-S and/or UDS signs of DO (or reduced compliance and/or cystometric capacity) exist and also the possibility that pre existing overactive bladder symptoms may improve. Level of Evidence 2, Grade of Recommendation B
- The committee recommends invasive UDS after failure of initial non-invasive management of SUI. (Evidence Level 1 (guidelines). Grade of Recommendaition A.
- The committee recommends that UDS may be performed in patients with MUI prior to surgical treatment of SUI, if the results of the UDS will affect management or counselling. Level of Evidence 2, Grade of Recommendation B

1.6. The Role of Urodynamic Studies in Predicting Urinary Incontinence in Women after Surgical Management of Pelvic Organ Prolapse

1.6.1. Conclusions and Recommendations 2016

Various studies summarized for prior ICIs have shown that symptoms of SUI can appear after surgery for pelvic organ prolapse (POP). A variety of methods to uncover 'occult stress urinary incontinence' in women with POP have been reported and in prospective stud-ies it has been demonstrated that all have different sensitivities and specificities. Standardi-sation of these tests was considered necessary. The ICI2016 recommended that patients with POP be informed about the relatively unpredictable chance of developing SUI after surgery for POP. Also, noted was that although UDS is referred to as the gold standard for the diagnosis of LUTD in all teaching books (level 1), it is yet not precisely determined in which type of patients a UDS diagnosis (in addition to a clinical diagnosis) is needed for long term effective and safe management.

The following recommendations were made (Grade 2):

- Consider managing a patient with SUI without a UDS diagnosis, and to individually discuss the likelihood of success and/or the possibility of side effects or failure of surgical man-agement (with suburethral tape) based on the available clinical diagnosis.
- Considering UDS prior to surgical treatment in patients with SUI when clinical signs sug-gest atypical, not uncomplicated or complex SUI exists.
- Consider including the complete and systematically gathered results of UDS in the man-agement plan for patients with SUI when UDS is done.

1.6.2. New evidence 2021

One retrospective database review suggested that SUI may be more important than the demonstration of occult SUI (O-SUI) on invasive UDS. In a study of 274 women without O-SUI, de novo SUI developed at ≥6 months postoperatively in about 5% of women with no SUI and in 17% of those with SUI(170). Another retrospective observational study of 98 women without LUTS undergoing preoperative UDS assessment prior to POP surgery, re-ported that 20% of women had O-SUI and concluded that preoperative evaluation of POP is incomplete without UDS, but failed to show any outcomes benefit(171). In another retro-spective study of 392 women with a variety of LUTS undergoing preoperative UDS prior to POP surgery, the authors found that except for the demonstration of O-SUI, UDS rarely changed the surgical plan or counselling (3.5%). It was most useful for women with SUI that also had concomitant voiding symptoms and/or elevated PVR, where the decision to per-form or not perform an incontinence procedure or treatment of BOO was affected, although outcomes were not assessed(172). A prospective trial of women undergoing stage III and IV POP repair called into question the reliability of invasive UDS to diagnose O-SUI vs. physi-cal exam (PE). 60% of 105 consecutive women had O-SUI. Of these, in 48 (76.2%) O-SUI was identified by both tests, in seven (11.1%) women O-SUI was identified by UDS and not by PE and in eight (12.7%) women, O-SUI was identified only by PE. The sensitivity to de-tect O-SUI during PE and UDS was 88.9% and 87.3%, respectively. Twenty-nine percent of women with no SUI on PE had O-SUI. However there was no association with surgical outcomes(173). A retrospective study of 322 women undergoing POP repair showed that the negative predictive value of preoperative UDS for postoperative SUI in patients undergoing any POP repair was 97.9% [95% confidence interval (CI) 92.7–99.7%](174). This led the au-thors to conclude that their study supported using preoperative UDS as a screening tool to avoid unnecessary concomitant continence procedures.

A study on 164 women from a single center showed that occult urodynamic stress inconti-nence and previous history of SUI are significant predictors for de novo SUI following the single-incision mesh surgeries(175).

Regarding the predictive role of UDS to add a concomitant anti-incontinence procedure, a single-center retrospective study including 87 women with O-SUI showed that urodynamic parameters, obtained before POP repair surgery, were associated with O-SUI and could be useful in providing adequate counseling to facilitate decision making on whether to add a concomitant anti-incontinence procedure. However, another retrospective evaluation was undertaken of 155 patients with at least second-degree POP who underwent POP surgery after UDS assessment and found that clinically incontinent patients with MUCP ≤50 cmH2O will gain the greatest benefit from concomitant POP and SUI surgery(176). Finally van der Ploeg et al reported data from two RCTs comparing postoper-

ative SUI in vaginal POP repair with and without MUS(177). They evaluated those women without SUI not undergoing SUI surgery at the time of POP repair. Only 9% developed post-operative SUI, with only 3.5% undergoing surgery for de novo SUI. And furthermore, all women who underwent treatment for de novo SUI showed SUI during basic office evaluation.

1.6.3. Discussion

ICI2016 recognized some of the limitations of UDS in patients with POP with or without SUI prior to surgery. Absolute indications for UDS were not given but rather considerations for clinicians based on SUI in uncomplicated vs. complicated patients. Current evidence with respect to both UDS and surgical outcomes would suggest that clinicians should carefully discuss incontinence and potential incontinence after surgery and the relative risks and ben-efits of treating and not treating incontinence(178). In patients without SUI and no occult incontinence on physical exam, stress incontinence surgery is not indicated and therefore UDS will likely not be helpful. In patients with SUI, UDS evaluation may be helpful in guid-ance of invasive treatment and counselling when SUI is complicated or associated with voiding dysfunction.

Recent data adds to the uncertainty of surgical outcomes. Previous consultations had rec-ommended UDS for all patients with symptoms of SUI and POP. Based on the recent trials' conclusions, but also already before the publication of those trials, many patients under-went midurethral sling surgery after a diagnosis of SUI was established based on signs and symptoms. Systematically collected long-term follow up data is scarce, and difficult be-cause of patients lost to follow up, and the now available publications usually report single centre expert outcomes. Nevertheless, there has not been much epidemiological evidence that the management of patients with 'clinically uncomplicated SUI' without UDS is very risky. However, surgery is invasive, potentially morbid or irreversible, and therefore estab-lishing a confirmed diagnosis prior to that is in the patient's interests and needs careful counselling about the pros and cons of UDS and the surgery itself. It should also be borne in mind that the recruitment rate for the published trials evaluating the need of UDS, notably, in expert centres, has been fairly low. This seems to allow the interpretation that the inci-dence of patients with 'uncomplicated SUI' has been relatively low and that a large percent-age of patients with the complaint of UI, or with SUI symptoms plus other LUTS or compli-cating factors, deserves UDS.

1.6.4. Recommendations 2021:

- The committee recommends that clinicians may non-surgically manage a patient with uncomplicated SUI, or uncomplicated O-SUI on physical exam without a UDS diag-nosis. However, it recommends to discuss the role of invasive UDS in select pa-tients if considering invasive, potentially morbid or irreversible treatments after dis-cussing the likelihood of success and/or the possibility of side effects or failure of surgical management of stress urinary incontinence. Level of Evidence 2, Grade of Recommendation C
- The committee recommends that clinicians utilize UDS in a patient with complex SUI and POP with UDS in a manner similar to a patient without POP if the patient is considering surgery for the treatment of SUI. Level of evidence 3, Grade of Rec-ommendation C
- The committee recommends that clinicians may perform invasive UDS on patients without SUI and no O-SUI on physical exam if the patient would be interested in treating O-SUI and the results of UDS testing would help them make that deci-sion. Level of evidence 2, Grade of Recommendation C
- The committee recommends considering including the complete and systematically gathered results of UDS in the management plan for patients with POP and SUI when UDS is done. Level of Evidence 2, Grade of Recommendation B

2. URGENCY URINARY INCONTINENCE AND OVERACTIVE BLADDER SYNDROME

2.1. Frequent Voiding and Urgency; Overactive Bladder Syndrome

2.1.1. Recommendations 2016

Studies have not been able to show a strong association between OAB-S and DO. Various studies have directly or indirectly concluded that the individual prediction of the response to treatment for OAB-S, on the basis of the characterization or quantification of DO during UDS, is impossible. A single centre retrospective study with good power confirmed the lack of association between subjective symptom severity and bother and objective measure-ments reinforcing the need for objective assessment, especially in proof of principle stud-ies. However, it was also observed that UDS cystometric capacity, compliance, as well as onset of first contraction were associated with perceived severity of symptoms(179). An-other well powered multicentre study demonstrated that subjective symptom assessment for women with LUTS was not reliable to uncover the pathophysiology that caused the symp-toms(140).

The ICI2016 recommended (Grade B) that investigators and clinicians discuss with patients with DO that neither the quantity nor specific characteristics of DO predicts the response to any of the therapeutic approaches. Furthermore, the committee recommended that investi-gators and clinicians discuss with patients with OAB-S that when UDS is performed neither the quantity nor specific characteristics of DO predicts the response to any of the therapeu-tic approaches, but that the absence of DO is relevant for further management.

2.1.2. New evidence 2021

Since ICI2016, many studies have investigated the role of UDS in OAB-S and UUI, in an attempt to find UDS predictors of outcomes of treatment. Unfortunately, none have been successful. Thus, the principal role of UDS remains for the patient in whom the diagnosis is uncertain or an underlying secondary condition (e.g. voiding phase dysfunction, SUI) is suspected. In 2018 the International Consultation on Incontinence Research Society sought to determine if different patterns of DO are clinically relevant(180). Specifically, they re-viewed the literature on several defined patterns of DO: Phasic, Terminal, Sustained, Com-pound, and Post Micturition. They noted that some studies showed some correlation be-tween different patterns of DO and phenotypes of OAB-S. However, they concluded that there is not enough evidence in the literature that the different patterns of DO have clinical relevance and that more research studies are necessary. Two new studies added to the ex-isting body of literature have shown that urodynamic outcomes were not beneficial in pre-dicting response to OAB-S treatment: one for sacral neuromodulation(181) and one for mir-abegron(182).

2.1.3. Recommendations

The committee recommends that investigators and clinicians discuss with patients with DO that neither the quantity nor specific characteristics of DO predicts the response to any of the therapeutic approaches (Grade B).

Furthermore, the committee recommends that investigators and clinicians discuss with pa-tients with OAB-S that when UDS is performed neither the quantity nor specific characteris-tics of DO predicts the response to any of the therapeutic approaches, but that the absence of DO is relevant for further management (Grade B).

The committee also recommends that UDS be considered in the patient with OAB-S in whom voiding dysfunction in suspected (Grade B).

2.2. Urgency Urinary Incontinence

2.2.1. Recommendations 2016 (Grade B)

The committee recommended UDS in the following circumstances:

- Whenever there is doubt about the pathophysiology causing LUTS (including UI) whether the UI is uncomplicated or not.
- For patients that have had failed conservative and medical therapy.
- For women that have LUTS and/or UI and representative ineffective voiding (i.e. significant PVR) and or reduced flow rate.

2.2.2. New Evidence 2021

New evidence regarding UUI is concordant with new evidence on OAB-S, as many patients with OAB-S in studies also have UUI (see above). UDS parameters and DO characteristics do not reliably predict response to treatment in patients with UUI. The diagnosis of BOO or other voiding phase dysfunction remains an important indication for UDS in women with OAB-S and UUI. One new study showed a high incidence of voiding phase dysfunction in women with OAB-S, 87% of whom had MUI. In this group 19.7% of women had BOO and 3.3% had DU(183). Not surprisingly, the presence of DO and higher PVR were independent predictors of BOO, but the only independent predictor in the pressure-flow study was a smaller voided volume. One large, longitudinal prospective study of 687 women with OAB-S assessed the impact of UDS on treatment outcomes(184). It should be noted, however, that the intent of the study was to assess the diagnostic accuracy of bladder ultrasound in diag-nosing DO. Almost all women had UUI (61% had urgency predominant MUI, 33% had UUI). Women were eventually treated with either bladder relaxants alone, SUI surgery, DO surgery, or no treatment. Those who were treated concordant with UDS diagnosis (DO surgery – DO on UDS; SUI surgery – SUI on UDS; bladder relaxants – DO or normal UDS; no treatment – normal UDS) were more likely to report improvement in bladder symptoms (57%) then those whose treatment was not based on UDS findings (45%) on follow-up questionnaires (re-sponse rate 69%). The study was not an RCT, and by the authors' admission results are subject to unknown confounders, which may bias the results, including decisions to treat being based on information from sources other than UDS.

2.2.3. Recommendations (Grade B)

- The committee recommends UDS in women with UUI whenever there is doubt about the pathophysiology causing UI, for women who have failed empiric initial therapy, and for women in whom voiding phase dysfunction (BOO or DU) is suspected based on clinical history, elevated PVR, or reduced urinary flow rate.
- The committee recommends to include specific recommendations in the guidelines for management, based on proof of principle or specific evidence, of patients with OAB-S that have normal filling phase results on UDS, especially no DO.

V. PATIENT EVALUATION: MEN

1. URODYNAMIC TESTING OF MEN WITH SYMPTOMS AND SIGNS OF LOWER URINARY TRACT DYSFUNCTION

1.1. Conclusions and recommendations 2016

UDS for men with LUTS has demonstrated relevance for the diagnosis of bladder sensation, bladder compliance and detrusor relaxation. It has also demonstrated relevance in the quan-tification of BOO. UDS is in all guidelines referred to as the gold standard test to evaluate men with signs and symptoms of LUTD. Most elderly men who present with OAB-S have voiding symptoms also and a consistently reported large percentage have UDS evidence of BOO. BOO, DO, reduced cystometric capacity, PVR and/or DU can occur in any combina-tion per individual, independent of the symptoms presented, and can all be quantified on the basis of UDS. Specific evidence that UDS improves outcomes is limited, and pragmat-ic, symptom-based management is demonstrated to be very possible in many men. Never-theless, UDS is the basis for therapy when it is directly aimed at the pathophysiology that is responsible for the symptoms if the patient and/or the physician consider that relevant.

1.2. New evidence 2021

A pilot MRI study, observing the bladder during voiding in a cohort of healthy men and men with BPH and LUTS showed the greatest bladder wall displacement at the bladder dome in healthy men, compared to a decreased and asymmetric bladder wall motion pattern in BPH/LUTS men(185).

Ambulatory UDS might have a role in predicting sacral neuromodulation (SNM) in patients with bladder emptying problems. A single centre retrospective study, not using standardized criteria, found that in their hands, UDS overestimated the number of patients diagnosed with DU or acontractile bladder. Patients with reduced contractility on ambulatory UDS had a lower chance of SNM success. Hence, ambulatory UDS may be apliccable to select pa-tients with a truly acontractile bladder and predict SNM failure, especially when patients are unable to void as usual during UDS in clinic(186). In patients with OAB-S in whom SNM is considered, UDS parameters are not predictive of therapy outcome. Both cohorts however, contained only a very small subgroup of males and grade of outflow obstruction was not considered(181,186). Cystometric capacity and bladder compliance are improved with beta-3 agonists and vesicoureteral reflux grade was observed to decrease in patients with low-compliance bladder in a single centre retrospectively selected cohort of patients with neuro-genic LUTD on CIC(187).

A meta-analysis using nine Asian articles including a total of 932 patients with BOO with a median number of 92 patients per study (range 40-190) evaluated the finding of preoperative DO on outcomes following BOO surgery . The nine studies included conventional tran-surethral prostatectomy in four studies, photoselective vaporization of prostate in three studies, and other surgical modalities in two studies. In patients with DO, the pooled mean difference

in the IPSS was not significant for a better or poorer improvement. These results demonstrated that preoperative DO, as the single predictor, had no significant effect on subjective outcomes after treatment for obstruction in male patients The analysis has not evaluated or reported prostate size, grade of BOO and/or voiding contraction(188). For oth-er conservative management options, no new reports exist about whether or not UDS influ-ences the outcome of management.

1.3. Recommendations 2021 (grade C)

- The committee recommends invasive UDS for a male patient for whom objective elucidation of the pathophysiology of the LUTD is deemed relevant, especially when conservative options fail.
- In general, UDS is relevant when invasive management is considered, but it may al-so be relevant in symptomatic men of a relatively young age and/or relatively small prostates, relatively good flow rates and/or with relatively large PVR, when initial management fails.
- The committee recommends invasive UDS for patients that have experienced failure of surgery for LUTS and/or incontinence after treatment for obstruction.

2. LUTS AND OAB-S IN MALE PATIENTS

2.1. Conclusions and recommendations 2016

LUTS in men >50 years of age are highly prevalent and storage LUTS are frequently report-ed. In male patients, OAB-S-wet symptoms are associated with DO. UI in the elderly male may also be a sign of dysfunction in which DU, elevated PVR and/or BOO may exist. UDS is the gold standard to diagnose storage dysfunction (DO, reduced compliance) and/or bladder outflow dysfunction (bladder neck obstruction, DU and BOO) or combinations of these, in men with LUTS. Storage symptoms, with or without UUI, diminish gradually over time following TURP but this also has been demonstrated after vaporisation of the prostate. Patients with preoperative terminal DO might have less rapid improvement of OAB-S symp-toms after TURP. Nocturia is an important and highly prevalent cause of LUTS. Epidemio-logical studies have shown that non-urological causes for nocturia are prevalent and noctur-nal polyuria can be diagnosed with a 24 h frequency-volume chart in a significant number of patients. UDS in elderly men indicate however that DO and BOO with inefficient voiding do also play a role in a significant proportion of patients with nocturnal enuresis and/or UI. New onset, night-time UI, in an elderly male, warrants clinical assessment, including rectal exam and UDS-PFS. UDS studies have shown that use of a phosphodiesterase inhibitor does not objectively change LUT function in men, although it does often favorably affect symp-toms.

2.2. New evidence 2021

The committee has again specifically concentrated on LUTD within the scope of UI, to be within the scope of this consultation.

In an attempt to predict DO in male patients with LUTS, higher OAB-S symptom score (OAB-SSS) urgency UUI subscores, as well as greater intravesical prostatic protrusion, were found to be useful parameters(189). However in another study intravesical mid-lobe prostatic ob-struction was not a good predictor for OAB-S, but indicated a higher frequency of nocturia(190).

Several studies looked at the possible predictive role of bladder wall thickness (BWT) or detrusor wall thickness (DWT) in male patients with LUTS. A first study showed that BWT and Qmax can non-invasively predict the presence of DU in patients with LUTS and BPE, and presents the first available nomogram for the prediction of DU in patients with LUTS(191). In another study, BWT or DWT was associated with BOO in men aged 70 years or older, sug-gesting, according to the authors, that BWT or DWT thickness might serve as a non-invasive parameter in the management strategy decision for elderly men with LUTS(192). To evaluate the role of BWT as a predictor of DO in patients with LUTS/BPE without BOO, a study showed how BWT in male patients may be a consequence of DO other than BPO(193).

Subjectively successful treatment outcomes of intravesical onabotulinum toxin-A injection for OAB-S patients were associated with improvement in OAB-S symptoms but not with increased bladder capacity(194).

In patients with DO, adding trigone, and bladder neck/prostatic urethra as sites of onabotu-linum toxin-A injection produced 1-2 points larger reduction in OAB-SSS score and less residual urine volume with a 15 mL difference in cystometric capacity but a lower volume at urgent desire to void in comparison with detrusor only injections(195,196).

Males with DO in addition to DU had higher age and number of daily micturitions and were more likely to report urgency with or without urgency incontinence than males with DU with-out DO. They also had lower volumes for first desire to void, volume voided, and post void residual urine, lower abdominal pressure at Qmax and were less likely to report a history of retention or reduced bladder filling sensation than males with DU without DO(197).

To evaluate the impact of OAB-S on patients diagnosed with retrograde ejaculation, a clini-cal study revealed the coexistence of retrograde ejaculation with OAB-S upon performing UDS and showing that anticholinergic treatment is effective in selected patients(198).

2.3. Recommendations 2021

- The committee recommends considering UDS for the objective diagnosis of male LUT storage function, especially in elderly men with UI or in young men with LUTS and relatively small prostates not responding to management or medical treatment based on clinical examination. Recommendation grade C
- The committee recommends considering UDS for objective diagnosis of LUT func-tion in men with prostate enlargement to ensure specific management of the dys-function causing the LUTS. Recommendation grade C

3. URINARY INCONTINENCE AFTER TRANSURETHRAL RESECTION OF THE PROSTATE AND OPEN PROSTATECTOMY FOR BENIGN DISEASE

3.1. Conclusions and recommendations 2016

Many case series show that sphincter weakness is the most common aetiology of male UI after prostatectomy for benign disease (eg. TURP). However, case series and reviews show that other LUTD besides sphincter incompetence play an incident role in post radical prosta-tectomy incontinence (PRRP-I). Case cohorts

showed conflicting evidence whether DO be-fore prostatectomy is an important indicator for post-operative persistence of UI, or for the outcome of interventions to treat the UI.

3.2. New evidence 2021

The urodynamic alterations after sub-urethral sling surgery (SUSS) in patients with PRRP-I was evaluated during free uroflowmetry, and no parameters showed any statistically signifi-cant difference pre- and postoperatively. During cystometry, there were also no statistical differences and the same was observed at PFS; the exception was detrusor pressure at maximum flow rate (pdetQmax), that was lower post-operatively (p=0.028). In relation to the presence of urinary dysfunctions associated with post-prostatectomy incontinence (PPI), there was a significant reduction of DO (p=0.035) in relation to the pre-operative period. In conclusion, SUSS surgery significantly reduced DO and PdetQmax; however, there were no alterations of other evaluated UDS parameters(199).

The clinical and UDS parameters affecting the treatment outcomes of PRRP-I surgery were reviewed in patients with PPI who received an artificial urinary sphincter (AUS) or adjustable male sling (MS). Previous pelvic irradiation, prior PPI surgery, and volume of incontinence were inversely, significantly associated with the success of PPI surgery. In patients who received AUS, a history of neurological disease was inversely associated with treatment success. Also, in patients with an adjustable MS, previous pelvic irradiation, prior PPI sur-gery, and degree of incontinence were inversely associated with treatment success. From these results, adjustable MS should be avoided in patients with previous pelvic irradiation, prior PPI surgery, or severe symptoms. The treatment outcome of AUS might be compro-mised in patients with neurological disease. One centre confirms that these parameters are relevant(200), but isolated UDS parameters were on average not predictive of the outcome.

3.3. Recommendations 2021

The committee recommends UDS be considered in male patients have persistent LUTS and/or UI after surgical treatment for prostatic BOO if further surgical or invasive treatment is planned. Grade D recommendation.

4. RETROPUBIC RADICAL PROSTATECTOMY

4.1. Conclusions and recommendations 2016

The main cause of UI after retropubic radical prostatectomy (RRP) is sphincter weakness, but reduced compliance and DO with or without neo-bladder neck outflow obstruction con-tribute in an unknown proportion of these patients. UDS have demonstrated value to identify the aetiology of LUTD after surgical or radiotherapy treatment of prostatic carcinoma. Both urethral and detrusor function are prone to be affected after RRP. Decreased bladder com-pliance, lower detrusor pressure during voiding, higher Qmax, and reduced MUCP can be seen immediately after RRP. DU is commonly observed in patients with UI after RRP and may be a risk factor for the development of neo-bladder neck (stricture).

LPPs and urethral pressures, measured in their various ways, are consistently reported to be improved after anti-incontinence treatment using the various surgical techniques, and their improvement is associated with cure or reduction of UI volume and/or pad use. Clinical indi-cators for reduced chance of success of post RRP UI surgery are lesser amounts of urine loss, less pad use, and higher preoperative Valsalva LPP; however precise actionable val-ues for these are not precisely or universally defined. Anastomotic stricture (which may also prevent UI from being demonstrated during UDS), reduced compliance and DO as well as Valsalva voiding are UDS predictors of failure although with unknown specificity. Retro-grade LPP may be a good tool for the setting of male sling tension by adjusting the re-sistance during post-RRP UI surgery.

4.2. New evidence 2021

A prospective data collection study in 1814 patients identified the following factors as pre-dictive to develop post retropubic radical prostatectomy incontinence (PRRP-I): preopera-tive severity of LUTS, higher age, extent of nerve-sparing surgery and surgeon experience. The authors also provided an online prediction tool(201). In another study, the preoperative perfusion quality of the levator ani was studied by multiparametric MRI and found to be related to the postoperative continence status. This could according to the authors facilitate the preoperative patient consulting and decision making(202).

To examine chronological changes in urethral and bladder functions before, immediately after, and 1 year after robot-assisted radical prostatectomy (RARP), UDS were prospective-ly performed. Urethral sphincter and bladder storage function were observed to worsen im-mediately after RARP and to recover over time, when patients with and without incontinence were grouped together. However, the urethral sphincter function did not return to its pre-operative level and was considered the most prevalent factor for urinary incontinence after RARP(203).

Studies have been done to demonstrate the anatomical and functional changes in inconti-nent men after radical prostatectomy compared to continent men, as well as to evaluate the use of UDS in the work-up for PRRP-I prior to treatment. UDS have been used to have a better understanding of the anatomical and functional changes in incontinent men after RRP; however, the role of UDS to select a treatment recommendation is still to be determined(204).

SUI is a frequent adverse effect for men who have undergone prostate surgery. Artificial urinary sphincter (AUS) insertion or a synthetic sling for men which elevates the urethra are used for treatment after failure of conservative measures. The UK-NHS MASTER trial aimed to determine whether the male synthetic sling is non-inferior to implantation of the AUS for men who have SUI after prostate surgery (for cancer or benign disease), judged primarily on clinical effectiveness but also considering relative harms and cost-effectiveness, however, regrettably without considering UDS as a predictor of success or failure(205).

To examine which preoperative factors, including UDS, and operative procedures could predict continence status after RARP, a study was conducted. Univariate and multivariate logistic regression analyses of pre-operative factors predicting 24-hr pad test >2 g/day at 1 year after RARP were examined in 111 patients enrolled in this study. The number of pa-tients with incontinence at 1 year after RARP was 39 (35.1%). The only predictive factor for urinary continence was nerve sparing (NS) grade. To investigate the contribution of NS to urinary continence, 84 patients underwent UDS three times: before, immediately after, and 1 year after RARP. Chronological UDS revealed that recovery patterns of storage and voiding functions were the same among non-NS, unilateral-NS, and bilateral-NS groups, and that higher degrees of NS contributed to lesser decreases in MUCP and longer functional ure-thral length (FUL) after RARP. It was concluded that preoperative factors, including the re-sults of UDS, could not predict continence 1 year after RARP. The NS procedure contribut-ed to continence status. NS favourably

affected MUCP and FUL; however, it did not affect bladder function after RARP(145).

The storage symptoms following RARP, focused on de novo OAB-S and the factors related to de novo OAB-S occurrence. 245 patients without OAB-S who underwent RARP were pro-spectively examined. At 3 months after RARP, the patients were divided into two groups: patients with de novo OAB-S (de novo OAB-S group) and those without OAB-S (OAB-S free group). De novo OAB-S was observed in 37.8% (87/230) of patients. Post-operative conti-nence rate was significantly higher in the OAB-S free group (79.7%) than in the de novo OAB-S group (8.0%). There was a significant difference in preoperative IPSS-QoL score, continence rate, pre-and post-operative MUCP, and postoperative functional profile length (FPL) between both groups. Multivariable logistic regression analysis showed preoperative IPSS-QoL score and postoperative MUCP were significant predictive factors for de novo OAB-S. The incidence rate of de novo OAB-S after RARP was about 40% and seemed un-expectedly high. Decreased urethral function was significantly related to de novo OAB-S after surgery(206).

4.3. Recommendations 2021 (grade C)

- The committee recommends that invasive UDS for patients with RRP UI is not only done to evaluate SUI but that it is also done specifically to evaluate bladder storage function as well as voiding dysfunction.
- The committee recommends that UDS should be considered, in cases where it will help in diagnosing or counselling and follow-up.
- The committee suggests to perform UDS in patients with PRRP-I with an outlet closed by penile clamp or cuff if early fill volume leakage occurs, to better evaluate filling properties until capacity.

5. UDS FOR PATIENTS WITH POST (RADICAL) PROSTATECTOMY URINARY INCONTINENCE AND PERSISTENT SYMPTOMS OF LOWER URINARY TRACT DYSFUNCTION AND/OR FAILED SURGICAL MANAGEMENT

5.1. Conclusions and recommendations 2016

The committee has recommended UDS for patients with post RRP UI and failed surgical management when co-existing dysfunctions of the LUT cannot be excluded on the basis of clinical history, e.g. radiotherapy, signs and/or non-invasive UDS and symptoms.

5.2. New evidence 2021

A study investigated UDS findings in prostate cancer patients with self-reported persistent severe PPI as well as the outcome of incontinence surgery. The main aim was to evaluate the ability of preoperative LUT dysfunctions to predict the outcome of incontinence surgery. Of the 94 men with severe PPI more than 12 months after RRP, 76 patients (81% response rate) presented for clinical examination. Among them, 99% had intrinsic sphincter deficien-cy, and 67% had coexisting bladder storage dysfunction. The presence of preoperative bladder dysfunction was not predictive of the outcome of PPI surgery. Preoperative use of fewer pads (contrary to ICI 2016 conclusion), less severe PPI, and a longer interval between RP and PPI surgery were associated with the successful outcome of one or fewer pads/day. Longer duration from RP to PPI surgery was the only preoperative factor associ-ated with the successful outcome of satisfaction. Hence, presence of preoperative LUTD was not considered predictive of the outcome of PPI surgery in this study (146,207).

The concept of 'urethral atrophy', which is often cited as a cause of recurrent incontinence after initially successful implantation of an artificial urinary sphincter (AUS), and the specific cause of the malfunction of the AUS in severe PPI patients was investigated. UDS was used in this analysis and DO was reported to be relevant, however without further details about DO. The remaining results speculated that recurrent PPI, years after initially success-ful implantation of an AUS, is because of material failure, probably attributable to its age and consequent loss of its ability to generate pressure, and that urethral atrophy does not occur(208). The mid-term (mean 3 y) durability of the AdVance sling for PPI and impact of prior radiotherapy and storage dysfunction was assessed in a retrospective single center review of 80 men. Men with radiotherapy or DO were reported to have significantly poorer outcomes indicating a return to baseline degree of incontinence. Preoperative UDS (specifi-cally exclusion of DO), and prior radiotherapy were considered important when counselling men for AdVance sling. Compliance and maybe PdetQmax are predictors of outcome following artificial urinary sphincter (AUS) implantation for PPI. An internally validated nomogram has been developed that may be used to determine an individualized likelihood of AUS suc-cess. This nomogram may be used as a counselling tool to objectively set realistic expecta-tions of continence post-AUS implantation(149).

On the basis of a systematic literature review, it was confirmed that DO could be considered as another possible (or co-existing) underlying mechanism for PPI although sphincter in-competence and weakness are the most prevalent and/or important mechanisms(209). A single centre article argued that retrograde LPP could be used as an objective and potential-ly more reliable substitute to pad weight to objectify and stratify UI in PRRP-I patients(210), but also found that cystometric capacity and DO during cystometry up to normal capacity (done with an occluded urethra to prevent fluid loss when leakage at early volumes occured) were predictive of the outcome of AUS implantation.

A study evaluated the filling phase of men with PPI and used a penile cuff to prevent early leakage as a way of mimicking the situation after surgery for PPI-UI. DO was observed as well as reduced compliance, affecting outcomes (149).

LUTS are common following RP or curative radiotherapy in prostate cancer patients. One quarter of those treated with RP experience biochemical failure and are subsequently of-fered salvage radiotherapy (SRT) to the prostatic bed. Long-term LUTS after surgery and SRT are common and need further elucidation. In a study to evaluate long-term UDS charac-teristics in patients treated with SRT, several UDS parameters were affected. This indicates that SRT primarily affects bladder compliance, maximum cystometric capacity and BOO. LUTS were proven to be strongly related to UDS parameters(211).

Another study reported that UDS was performed before surgical treatment of PPI UI and that patients with DO were excluded. Regrettably no further details were given(212).

To compare the UDS in patients presenting with social continence (0-1 pads/day) after AMS800 or ZSI375 insertion, vesical pressure (pves), FUL, maximum urethral pressure (MUP), MUCP and Qmax were recorded with standard urodynamic equipment. 27 male patients with AMS800 and 28 with ZSI375 were recruited. Results of UDS were reported to be similar for both types of AUS(213).

To evaluate the effect of radiation on male SUI and to assess the relative value of preopera-tive UDS in radiated vs nonradiated men with SUI, a retrospective chart review was conduct-ed of all male patients with SUI who underwent UDS testing. The impact of UDS findings on treatment decision making was assessed. Radiation therapy appears to increase the likeli-hood of bladder dysfunction in male patients with SUI. The UDS findings did, however not alter the plan to treat SUI in any patients in this series, and consequently the role of UDS (and reported history of radiation) before SUI surgery in male patients was not examined in the reported practice(214).

5.3. Recommendations 2021 (grade C)

- The committee recommends that UDS should considered in cases where it will help in diagnosing or counselling and follow-up when RRP UI has not spontaneously im-proved, and conservative measures have failed.
- The committee suggests to perform UDS in patients with PRRP-I with an outlet closed by penile clamp or cuff if early fill volume leakage occurs, to better evaluate filling properties until capacity
- The committee recommends UDS for patients with post RRP UI when co-existing dysfunctions of the LUT (neo bladder neck BOO, valsalva voiding, significantly re-duced bladder compliance and/or DO) cannot be excluded on the basis of clinical history, e.g. radiotherapy, signs and/or non-invasive UDS and symptoms.

6. NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

6.1. Conclusion and recommendations 2016

Case series indicate that it is possible to monitor patients with neurogenic lower urinary tract dysfunction (NLUTD), without (congenital) anatomic abnormalities of the LUT (especially adult age spinal cord injury (SCI)) with cystometry and ultrasound of the UUT. Uncontrolled cohort studies indicate that non-invasive tests are less sensitive to relevant abnormalities in comparison with UDS and investigators have concluded that UDS is necessary when LUTS arise in patients with neurological abnormalities. The optimal frequency and techniques of follow-up UDS in patients with NLUTD are still debated. Furthermore, there is no conclusive evidence on the predictive value of ice-water testing or ambulatory UDS towards better di-agnosis or the outcome of treatment.

Nocturia, nocturnal enuresis or LUTS may be the first, or an early, sign of Parkinsonism in elderly male patients, and may occur also in other neurological conditions (e.g. multiple sclerosis (MS),). UDS is of value to establish a diagnosis of the LUT dysfunction(s) re-sponsible for the symptoms. LUTD in male patients with Parkinsonism (or other neurological conditions) can be the result of DO, benign prostatic BOO, dyssynergic voiding, DU or elevated PVR or any combination thereof. DO and DU, with or without urethral sphincter (pseudo-) dyssynergia, are commonly found in male patients with Parkinson's disease.

6.2. Recommendations 2016

- This committee recommends that UDS evaluation should be considered at the time of first evaluation of patients with signs and symptoms or with suspicion of NLUTD and that VUDS is considered when anatomical abnormalities with the NLUTD are not unlikely.
- The committee recommends that the frequency of testing and the techniques ap-plied in the follow up of patients with NLUTD be critically analysed and optimised and continues to recommend that guideline recommendations on the basis of those analyses should be developed.
- The committee recommends that UDS in patients with NLUTD is done with special attention to the specific needs of the patients. It is highly preferable that all profes-sionals involved are specifically trained for that purpose.

6.3. New evidence 2021

NLUTD is very common in patients with multiple sclerosis, and it might jeopardize renal function and thereby increase mortality. Although there are well-known urodynamic risk fac-tors for UUT damage, no clinical predictive parameters are available.

High Expanded Disability Status Scale (EDSS) score is significantly associated with urody-namic risk factors for UUT damage and allows a risk-dependent stratification in daily neuro-logical clinical practice to identify MS patients requiring further neurourological assessment and treatment(215).

Neurogenic bladder dysfunction after SCI is generally irreversible. One proof of principle animal study and a phase 2 human study have suggested that initiation of SNM immediately following SCI can prevent neurogenic DO and preserve bladder capacity and compliance(216,217). A multicenter randomized clinical trial was designed to evaluate the effectiveness of early SNM after acute SCI, but currently no data have been reported(218). In a prospective cohort study in 54 patients with NLUTD due to acute spinal cord injury who underwent urodynamic investigation within the first 40 days after injury at a single university spinal cord injury centre, an acontractile detrusor was observed in only 20 of the 54 patients (37%) but unfavourable urodynamic parameters in 34 (63%). The authors found DO in 32 patients, detrusor sphincter dyssynergia in 25, maximum storage detrusor pressure greater than 40 cmH2O in 17, vesicoureteral reflux in 3 and low bladder compliance (less than 20 ml/cmH2O) in 1. More than one unfavourable urodynamic parameter per patient was possi-ble. In contrast to the common notion of an acontractile detrusor during acute spinal cord injury (spinal shock phase), almost two-thirds of the studied patients showed unfavourable urodynamic parameters and "active" detrusors within the first 40 days after spinal cord inju-ry. Considering that early treatment of NLUTD in patients with acute spinal cord injury might improve the long-term urological outcome, the authors recommended that urodynamic in-vestigation should be performed promptly to optimize patient tailored therapy (219).

Another study assessed which urodynamic parameters are associated with renal deteriora-tion over a median of 41 years follow-up after traumatic spinal cord injury. Renal deteriora-tion was diagnosed as split renal function ≤30% in one kidney or relative glomerular filtration rate ≤51% of that expected according to age and gender. Detrusor function, presence of detrusor sphincter dyssynergia, maximum detrusor pressure, post-void residual volume, and cystometric bladder capacity were obtained. In patients with DO, a DO/cystometry ratio was calculated using duration of detrusor contraction(s) during filling cystometry divided by total duration of

filling cystometry. A total of 73 patients were included in the study, and the me-dian follow-up time was 41 years after injury (range 24-56). Sixty-four patients (88%) used reflex triggering or bladder expression as bladder emptying method for the longest period after injury. During follow-up 60% changed to clean intermittent catheterization. The majority of the patients (68%) had neurogenic DO. In 35 patients, a DO/cystometry ratio could be calculated and a ratio > 0.33 was significantly associated with renal deterioration ($p < 0.02$). No significant association was found between maximum detrusor pressure or other urody-namic parameters and renal deterioration. The authors concluded that the duration of DO longer than one third of the duration of cystometry is associated with renal deterioration after spinal cord injury(220).

6.4. Recommendations 2021 (grade C)

- This committee recommends that UDS evaluation should be considered at the time of first evaluation of patients with signs and symptoms, or with suspicion of NLUTD and that VUDS is considered when anatomical abnormalities with the NLUTD are not unlikely.
- The committee recommends that in SCI patients, VUDS should be considered at the latest after 6 weeks after trauma.
- The committee recommends that the frequency of testing and the techniques ap-plied in the follow-up of patients with NLUTD be critically analysed and optimised and continues to recommend that guideline recommendations on the basis of those analyses should be developed.
- The committee recommends that UDS in patients with NLUTD is done with special attention to the specific needs of the patients. It is highly preferable that all profes-sionals involved are specifically trained for that purpose.

VI. PATIENT EVALUATION: CHILDREN

1. INTRODUCTION

1.1. Conclusions and Recommendations 2016

ICI2016 concluded that retrospective and prospective studies have shown that symptoms and signs (of UI) do not adequately represent LUTD and UDS diagnosis in children. This is observed in healthy children with LUT signs and symptoms, in children with myelomeningo-coele (MMC), anorectal malformation (ARM), spinal cord injury (SCI), spinal cord tethering, cerebral palsy/spasticity, sacro-coccygeal teratoma, and in children with urethral valves, vesico-ureteral reflux (VUR), bladder exstrophy, nocturnal enuresis (NE) and OAB-S.

Retrospective and prospective studies have shown that a UDS-diagnosis is relevant in chil-dren with the above-mentioned pathologies, but also that initial conservative management of (otherwise healthy) children with UI is possible without UDS-diagnosis. No good evidence existed in 2016 to support optimal selection of VUDS (versus standard UDS) in most situa-tions of children with UI, apart from MMC and VUR or to support individual decisions re-garding UDS or VUDS for follow-up in children.

The ICI2016 committee recommended that non-invasive UDS including voiding diary and flowmetry with PVR measurement, is utilized to evaluate the voiding function prior to any invasive procedures. Flowmetry plus EMG is recommended in the ICS- Children's Good Urodynamic Practice(221). Furthermore, ultrasonography of the urinary tract is considered a useful tool with acceptable reproducibility for initial assessment when evaluating LUTS in children. Ultrasound LUT-studies in children include not only PVR and bladder volume but also bladder wall thickness (BWT). Ultrasound has been used to evaluatie both morphology of the LUT, functional change of bladder wall, as well as pelvic floor muscle function.

The committee recommended to consider VUDS when relevant anatomical abnormalities are expected and recommended the need to improve pelvic patch surface-EMG technique, standards, and evaluation/reporting. The committee recommended that patients with NLUTD receive (V)UDS when it is considered possible to initiate treatment as a consequence of the diagnosis based on the (V)UDS and when first line management has failed. They also rec-ommended ambulatory UDS in patients with relevant neurological abnormalities.

The committee recommended the International Children Continence Society (2015) guideline on the use of UDS in children, summarized the available evidence and expert-based knowledge, and provided expert recommendations, and presented in 2016 a specific stand-ardized expert report for VUDS. A meticulous and complete history, physical examination including a clinical neurological one and assessment by voiding diaries, are essential.

1.2. New Evidence 2021

During invasive UDS, a pressure recording catheter needs to be inserted into the bladder either transurethrally or suprapubically (222). The indications for UDS evaluation in children include neurological, anatomical and/or functional abnormalities,with the types of studies to be performed being based on the presumed underlying patho(physio)logical conditions rather than on the presenting symptoms. Retrospective and prospective studies have shown that UDS has been popularly used in the evaluation of paediatric UI, not only in the diagno-sis, but also in the follow-up of the treatment response, in making treatment protocols, pre-dicting disease evolution, and assessing the effect of treatment. In addition, not only the literature on children with UI induced by NLUTD, MMC, ARM, SCI, spinal cord tethering, cer-ebral palsy / spasticity, sacro-coccygeal teratoma, urethral valves, VUR or bladder exstro-phy, but also that induced by OAB-S and NE increased.

Non-invasive UDS are more acceptable and applicable to children. It is able to identify clini-cal conditions that will benefit from further invasive UDS.It has been recommended to eval-uate all children with UI by UDS. These include voiding diary, flowmetry with PVR measure-ment and/or EMG, andupper tract ultrasound evaluation. Remote or Internet-based voiding diaries have been recommended to make it an easier and more precise recording of chil-dren's voiding pattern (223). A consensus has been reached that non-invasive UDS (uroflowmetry ± simultaneous EMG, assessment of PVR, renal/bladder ultrasound, and pel-vic ultrasound) when used appropriately can provide valuable information to facilitate deci-sion making during the evaluation of children with LUTD. The exact role and reproducibility of uroflowmetry is still under consideration, but flows plus PVR measurement and/or pelvic floor EMGis recommended (224). To exclude NLUTD in infants less than 6-months-old, sa-cral spinal ultrasound or anteroposterior lumbosacral X-ray or MRI are recommended to find (occult) spinal dysraphism or spinal bifida occult.

It has been recommended that ultrasonography is a useful tool with acceptable reproducibil-ity for initial and follow up assessment of LUTS in children before and after treatment. Ultra-sound LUT-stud-

ies in children not only include PVR and bladder volume but also bladder wall thickness(BWT) (225,226). They are not limited to a morphological analysis of the LUT, but also to dynamic analysis, with evaluation of the full and of the empty bladder (227), and evaluation of the pelvic floor muscles movements and muscular endurance(228).

However, more research in this area in children are scarce although recently similar studies in adults have been reported which suggested a significant relationship between the pre-treatment BWT and the success of urinary incontinence treatment. The mean BWT may be used as a benchmark in assessing the responsiveness to treatment of urinary incontinence types (229). For validating BWT ultrasound measurements, a study on cadaveric bladder wall caliper measurements has been performed and found that high-frequency ultrasound is more accurate for assessing BWT (230). Lack of standardization of BWT measurements remains a potential confounding factor. BWT measurements of the ventral and dorsal walls in children with spina bifida at pre-defined points during video-UDS showed a lack of corre-lation with pressures suggesting that such measurements might not be a suitable substitute (231).

The aim of invasive UDS in children is to provide objective knowledge about LUT function, to identify the underlying causes for voiding symptoms, and to quantify related pathophys-iological processes. It also provides understanding to the caregiver and to the patient (and her or his parents). It includes filling cystometry and pressure/flow study (PFS). It is indicat-ed when history and clinical examination raises a suspicion of either anatomical and/or NLUTD involving primarily the storage phase (filling cystometry) or the voiding phase (PFS), or when there is a question that cannot be answered by less invasive testing (222,232). VUDS give additional information on morphologic changes of LUT and whether DSD exist or not.

Invasive UDS is used to establish as clearly as possible a baseline, so that changes result-ing from treatment and/or growth can be assessed (indicating that the investigation may need to be repeated), and to provide some guidelines for the choice of treatment (although results of UDS may not necessarily be the deciding factor) (232). Paediatric UDS show many differences from those in adults. However, a validated guideline on the use of UDS in children is still lacking although educational modules and terminology of ICCS have been published (222,232–235). Furthermore, a specific standardized expert report for VUDS was presented in 2016 (236) as well as a review on urodynamic application on children with cere-bral palsy (237).

The reliability and variability of measurements in children can be influenced by developmen-tal effects as well as by the unfamiliar clinical environment. Alternatively, ambulatory UDS is less influenced by this because it is measured over a prolonged period and is conducted in a child-friendly environment. Recently, an analysis showed that more diverse voiding pat-terns were identified in ambulatory UDS compared with conventional in office UDS, with a lack of consistency in identified voiding patterns in both methods. Therefore, the urodynam-ic findings in children may have to be analysed in more detail, taking the variations into ac-count (238,239).

The parameters used in UDS in children are far from established. Children's growth and de-velopment make it difficult to have an identical standard procedure and interpretation of the UDS evaluation and results(240) compared to adults. More research is needed to establish the normal criteria for UDS in the different age groups. It's known that voiding symptoms and signs do not adequately represent LUT dysfunction in children especially in infants who are still in the developmental stage of voiding control (240). There are specific challenges in making a diagnosis of detrusor sphincter dyssynergia (DSD) due to the lack of reliability of patch EMG recording and difficulty in differentiating an involuntary phasic contraction from a volitional void (241).

UI in children is relatively more often seen (compared to adults) in combination with other LUT (or lower bowel or pelvic floor) dysfunctions. On the other hand, UI and the develop-ment of 'full-grown' LUT function are the result of a normal maturation process that can be delayed in some and may 'spontaneously cure' (or 'resolve') without requiring medical inter-vention. UDS is used to establish as clearly as possible the baseline situation where needed, so that changes resulting from treatment and/or growth can be assessed, and some guid-ance is obtained in the choice of treatment.

2. NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

More than 85% of NLUTD in children is due to spinal dysraphism which is an incomplete fusion of the spine during embryologic development and encompasses a spectrum of con-genital anomalies that can affect the spinal cord, nerve roots, and vertebral column. These anomalies can be categorized into open and closed spinal dysraphism. Open spinal dysra-phism is also known as spina bifida aperta. The neural tissue in these lesions is exposed, Myelodysplasia is mainly seen in open spinal dysraphism (meningoceles and myelomenin-goceles. Closed spinal dysraphism is also referred to as occult spinal dysraphism (OSD)(242). Urological abnormalities, prenatally and congenitally induced by these condi-tions are variable with regard to anatomy and dysfunction and, often need evaluation with UDS before treatment and later during follow up.

2.1. Myelodysplasia

2.1.1. ICI2016 Conclusions and Recommendations

The bladder volume at which leaking occurs should be noted, as it may be important for a particular patient to organize their clean intermittent self-catheterization (CIC) regimen (243).

Retrospective and prospective studies have shown that the UDS diagnosis of (neurogenic) DO and/or reduced detrusor compliance in patients with myelodysplasia or (occult) spinal dysraphism is not predictable based on clinical signs or symptoms. Both initial and follow-up evaluation often reveals clinically relevant results with regard to management and surgical or medical treatment. Evidence for the optimal interval and frequency of (V)UDS follow-up in patients with children with NLUTD is lacking.

VUDS testing is preferable as compared to conventional UDS but the exact advantage of repeated VUDS in the follow-up of children with known (morphological or anatomical) ab-normalities is not substantiated. Various studies have shown that LUT function in children with myelodysplasia or (occult) spinal dysraphism may change over time (and with physical growth).

Comprehensive UDS is advised in all symptomatic patients with myelodysplasia or (occult) spinal dysraphism throughout the entire life on a regular basis from earliest childhood. UDS should also be considered when changes in signs and symptoms occur in the lower limbs, pelvis and/or urinary tract or when significant (surgical or medical) treatments have been instigated. The advantages and disadvantages of the addition of video (x-ray/fluoroscopy) to UDS

should be considered in children with myelodysplasia or (occult) spinal dysraphism on an individual basis. The timing and technique of UDS in patients with myelodysplasia or (occult) spinal dysraphism must be selected on an individual basis. To help identify children at risk for subsequent urinary tract deterioration or a changing neurological picture, initial UDS very early in the neonatal period (e.g. starting from 3 months age), should be consid-ered for children with myelodysplasia or (occult) spinal dysraphism. Anorectal function or dysfunction is recommended to be simultaneously evaluated with LUT function in children with myelodysplasia or (occult) spinal dysraphism (see also the chapter on faecal inconti-nence in the book). The committee recommended research to determine the optimal interval and frequency of follow-up UDS in children with NLUTD.

2.1.2. Discussion and New Evidence 2021

Many retrospective and prospective studies have recommended that UDS should be used to evaluate all cases with myelodysplasia, before and after treatment during follow up. What types of UDS (conventional UDS or VUDS) should be chosen depends on severity of cas-es and the underlying mechanism the clinician would like to evaluate. The parameters ob-tained from UDS are helpful in the decision of treatment protocol. It is recommended to follow classification based on UDS to make a treatment protocol in patients with UI(244). After initial invasive urodynamic evaluation, non-invasive UDS are recommended for the follow up in those cases with symptoms but no significant increase in PVR and normal UUT ultrasound findings. Otherwise, VUDS should be considered also in the follow up.

To identify the risk of subsequent UUT deterioration, initial UDS in the neonatal period had been recommended for children with myelodysplasia(245). This concept has been confirmed by ICCS recommendations and EAU guideline(244) for congenital neuropathic bladder(246).

The updated EAU/ESPU guideline advocates more proactive use of UDS to evaluate chil-dren with myelodysplasia. For those with intrauterine closure of the defect, UDS are recom-mended to be performed before the patient leaves the hospital; those with closure after birth UDS should be done within the next 3 months. Close follow-up including ultrasound, bladder diary, urinalysis, and UDS are necessary within the first 6 years and after that, time intervals can be prolonged, depending on the individual risk and clinical course. In all other children with the suspicion of NLUTD due to various conditions such as tethered cord, in-flammation, tumours, trauma, or other reasons as well as those with anorectal malformations, UDS and preferable VUDS, should be carried out as soon as there is a suspicion of NLUTD. Conservative treatment should be started soon after confirmation of the diagnosis of neu-rogenic bladder. If the UDS confirmed DO, oxybutynin (dosage 0.2-0.4 mg/kg weight per day) should be applied(244).

Based on expert opinion, VUDS testing is preferable above conventional UDS because the anatomy and morphology can be evaluated simultaneously. The significance of bladder morphological changes was studied in 81 children with myelomeningocele at video-UDS. The authors calculated the ratio of the maximum height of the bladder to the maximum width at maximum cystometric capacity. Children categorized as high risk (those with maximum detrusor pressure of ≥40cm H20) were noted to have a higher ratio (1.50 vs 1.37, p=0.004). A cut-off of 1.40 was associated with sensitivity of 87% and specificity of 57% for predict-ing high risk findings(247).

Various studies have shown that LUT function in children with myelodysplasia may change over time and with physical growth. No studies have been published that precisely deter-mine the optimal timing and frequency for follow up myelodysplasia. UDS and the presence of neurological impairment were considered to have had crucial roles in determining the optimal timing of surgery in patients with lipomeningocele, and in diagnosing the onset of tethered cord(248).

Because renal transplantation in patients with myelodysplasia and persistent LUT dysfunc-tion carries increased (post –renal) risks for the grafted kidney, the existence or creation (augmentation cystoplasty) of a UDS confirmed low pressure bladder with adequate cysto-metric capacity before transplantation is deemed necessary(249).

UUT deterioration (UUTD) is a life-threatening complication of NLUTD. Early identification of risk factors for UUTD and institution of remedial measures may probably prevent UUTD. A cross-sectional, observational study over 2 years including 30 children found that delayed presentation with palpable bladder lump, recurrent UTI, increased BWT, bilateral VUR, in-creased PVR, and DLPP > 40 cmH2O were identified as potential risk factors for UUTD. This study highlights the potential of BWT as a predictor of UTD in neurogenic bladder. A limita-tion of this study is the small number of patients and heterogeneous clinical diagnosis(250). Another study of 637 children with myelodysplasia found that lack of bladder sensations, long duration of symptoms, reduced maximum cystometric capacity, reduced compliance and elevated residuals were independent risk factors for UUTD(251).

Currently due to the good responses towards early combination of drugs and/or intermittent self-catheterization, bladder augmentation is performed less frequently. However, selected patients with spinal dysraphism and children with congenital malformations like bladder ex-strophy and resulting small bladder capacity might require bladder augmentation(252). UDS can play a key role in decision of bladder augmentation and later follow up the treatment results, but the exact UDS parameters as well as frequency and interval of the UDS remains undefined. Bladder augmentation is performed to relieve or prevent UUTD and/or VUR (usu-ally without necessity of simultaneous anti-reflux repair) when conservative treatment op-tions (CIC, anticholinergic drugs and botulinum injections) are not sufficient(253). However, the studies in the adult population are controversial. A recent retrospective study in 160 adult patients indicates that ureteral reimplantation concomitant with augmentation cysto-plasty may be beneficial in patients with low pressure or high-grade vesicoureteral reflux and/or severe upper urinary tract dilatation(254). In another study, 29 patients with a poorly compliant bladder associated with VUR had undergone bladder augmentation with no cor-rection of the existing reflux. VUDS showed a significant improvement of bladder capacity, diminution of intravesical pressure, and resolution of reflux after bladder augmentation in more than 90% of patients during 2 years follow up. Thus, in the latter study, ureteral reim-plantation was found not to be necessary when augmentation enterocystoplasty was rec-ommended for patients with high-pressure, low-compliant bladder and VUR(255). Therefore, whether simultaneous reimplantation in patients with augmentation is mandatory needs to be further investigated in the future. Expert reviews have recommended follow up of the pa-tients with UDS, but interval and frequency of follow up UDS after operation are not precise-ly established.

UDS have been used to follow children with NLUTD who underwent bladder outlet enhance-ment surgery (bladder neck myofascial sling or bladder neck reconstruction using the Young-Dees-Ledbetter technique) without augmentation cystoplasty. Two recent stud-

ies showed the limited value of this approach with substantial risk for needing follow up sal-vage therapy: 40% children needed augmentation cystoplasty in follow up with the devel-opment of hydronephrosis and reflux in one study(256) while 53% needed salvage botuli-num toxin injection or augmentation at a mean follow up of 5 years in the other(257).

The efficacy of intradetrusor injections of botulinum toxin has been confirmed in patients with myelomeningocele at recent few years. A systematic review on the efficacy of intra-detrusor injections of Botulinum Toxin A (BTX-A) in spina bifida patients with neurogenic DO refractory to antimuscarinics included 12 studies covering 293, all <18 years old. There were no randomized studies comparing BTX-A versus placebo and most studies had no control group. Most studies reported a clinical and urodynamic improvement with resolution of in-continence in 32-100% of patients, a decrease in maximum detrusor pressure from 32 to 54%, an increase of maximum cystometric capacity from 27 to 162%, and an improvement in bladder compliance of 28-176%. Two studies suggested lower efficacy in patients with low compliance bladder compared to those with isolated DO. Obviously, intra-detrusor in-jections of BTX-A could be effective in children with spina bifida but this assumption is not supported by high level of evidence studies(258).

A study in 19 children showed that repeated botulinum toxin injections are a safe treatment modality and can be offered as an effective alternative, instead of more invasive surgery, in children with neurogenic DO due to myelodysplasia. The detrusor compliance and the max-imum detrusor pressure significantly improved following injections(259). Another study in 31 children with myelodysplasia and all had VUR (22 unilateral), botox injection resulted in in-creased bladder capacity, enhanced continence, and prevented VUR. Although above re-sults are promising, a larger group of long-term prospective studies are warranted to inves-tigate this method of treatment(260).

The efficacy of mirabegron has (off label) been studied by UDS in 37 children (mean age 12.7y) with NLUTD (31 myelomeningocele). Patients were studied in two groups, one which was refractory to antimuscarinics alone (Group A) and another was refractory to abobotuli-num toxin A (Group B). Treatment with mirabegron 25mg resulted in significant improvement in maximum cystometric capacity (increase of 136ml and 133ml respectively, both $p<0.001$) and a fall in end fill pressure (reduction of 10 and 19 cm H20 respecitvely, both $p<0.001$) in both groups(261). (Long term) Results considering effects of this management on blood-pressure cardiac function or other side-effects are at present not available. Especially also in this group of patients renal function should closely be monitored (and included in the indication for this treatment).

A single centre study on 39 patients with myelodysplasia, classifying patients according to detrusor and sphincter behaviour, found that the early evaluation and treatment of patients is essential for decreasing renal impairment, reducing the need for surgery and improving the continence options(262).

Tarcan et al investigated more accurate cut-off levels for the detrusor leak point pressure (DLPP) in terms of UUT protection in a cohort of children with myelodysplasia. They found that more than half of the children with myelodysplasia had normal UUT function even with a DLPP of 40 cm H2 O and over. Therefore, DLPP, should not be the sole decision-making parameter to rely for more invasive therapies in children with myelodysplasia. On the other hand, a DLPP cut-off value of 20 cm H2 O showed a higher sensitivity to predict UUTD instead of 40 cmH2O in patients with myelodysplasia (263).

An expert review discussed 9 papers addressing routine spine ultrasounds for children with sacral dimples and showed that 3.4% of the 5166 patients had abnormal spine ultrasounds, compared with the 4.8% reported by another study for children without sacral dimples. The authors concluded that sacral dimples do not predict underlying spinal cord malformations, and spine ultrasounds should not be performed for neonates with simple sacral dimples(264). Whether BWT is useful in predict the UUTD is still controversial and far from established. In 2015, Kim et al(265) found that even if bladder wall thickness is measured at specifically defined bladder volumes, it cannot predict video-urodynamic findings other than bladder trabeculation in children with spina bifida. A total of 23 males and 30 females with spina bifida (median age 7.8 years) underwent measurement of bladder wall thickness at maximum cystometric capacity. In a later editorial comment, it was suggested that specific aspects of the study methodology and population might have contributed to a lack of cor-relation with high-risk urodynamic findings. The application of non-invasive modalities to LUT assessment of NLUTD remains a promising and relevant area of future research to pre-vent progression to end stage LUT changes for all individuals with spina bifida(266).

Approximately 90% of children born with MMC will have a preserved UUT at birth. Over time, in the absence of proactive urological care, DO, reduced bladder compliance, detrusor-sphincter dyssynergia and/or high LPP will result in UUT and/or LUT deterioration. The main identified UDS risk factors are: decreased bladder compliance of <9 mL/cmH2O, increased DLPP of >40 cmH2O and presence of an acontractile detrusor(267). Bladder wall thickness measurement was also found as a predictor of LUT impairment. When conservative treat-ment such as CIC, anticholinergic drugs and botox injections are not sufficient, bladder augmentation is performed to relieve or prevent UUTD and/or VUR, usually without necessi-ty of simultaneous anti-reflux repair. UDS follow-up should be used to evaluate the effect of this treatment.

Expert reviews have recommended periodic UDS when new onset VUR, hydronephrosis, or UI develops in children with myelodysplasia. However, the interval and frequency of follow up UDS are not precisely established. UDS and the presence of neurological impairment were considered to have had crucial roles in determining the optimal timing of surgery in patients with lipomeningocele. Also in diagnosing the onset of tethered cord, UDS were more relevant towards the outcome of neurosurgical interventions (untethering) than pelvic floor muscle needle EMG.

UDS have been relevant to evaluate the treatment efficacy of drugs in the long-term. Over a period of 15 years, intravesical oxybutynin treatment showed adequate suppression of de-trusor activity, increase in cystometric capacity, and mean end-filling pressure had returned to the safe zone(245).

Adam et al retrospectively reviewed patients born with myelodysplasiathat received follow up before 1 year old and treated with clean intermittent catheterization (CIC), anticholinergics, surgical interventions according to the results of ultrasound and VUDS. The study reported that the initial high incidence of hydronephrosis resolved in the first decade of life. The 8-11-year incidence of kidney disease and upper tract changes was low(268).

2.2. Occult spinal dysraphism

2.2.1. New evidence

Most common pathologies of occult spinal dysraphism (OSD) are isolated vertebral defects which arethe least severe forms. Others include neuroenteric cysts, split notochord syn-drome, split spinal cord malformation, sacral meningeal cysts, spinal lipomas, caudal re-gression syndrome, dorsal dermal sinus tracts and cysts, and tethered cord syndrome. It is recommended that all OSD with LUTS should be evaluated by conventional UDS. If UUT morphological changes are found by ultrasound, VUDS should be considered.

As awareness and frequency of tethered spinal cord (TSC) has increased with magnetic resonance imaging (MRI), variability exists in its evaluation and management. Tethered spi-nal cord syndrome (TSCS) is a clinical entity that presents with neurological, urological, and/or orthopaedic symptoms caused by primary or secondary tethering of the spinal cord, which may result in ischemic damage of the neural tissue and symptom development. There is relative agreement that patients with symptomaticTSC will require surgical intervention. However, it is still debatable as to how to approach asymptomatic patients with primary TSC. A study in 22 cases with TSC (8 of them were asymptomatic) showed that spinal cord un-tethering is beneficial in terms of clinical and UDS outcomes with statistically significant improvement in the median percentage of change of actual bladder capacity, median in-travesical pressure for patients with pre-operative pressure ≥40 cmH2O at total cystometric bladder capacity, and median bladder compliance at 75% bladder capacity (269).

The International Children's Continence Society (ICCS) published level I data and summa-rized the current recommendations for diagnosis and treatment of OSD. It is suggested that infants with classic cutaneous markers of OSD, with progressive neurologic, skeletal, and/or urologic findings, present no diagnostic or therapeutic dilemma: they routinely undergo MRI and spinal cord untethering (SCU). Conversely, in asymptomatic patients or those with fixed, minor abnormalities, the risk profile of these OSD cohorts should be carefully considered before SCU is performed. Irrespective of whether or not SCU is performed, patients at risk for progression should be followed carefully throughout childhood and adolescence by a multidisciplinary team (270).

Tarcan et al investigated the role of magnetic resonance imaging (MRI) in detecting OSD in children with LUTD and a normal neurological examination in a cohort of children over 5 years of age who did not respond to an initial treatment of 6 months (271). A spinal MRI was performed in 61 children with ongoing LUTS or UTI. Nineteen of 61 children (31%) had cuta-neous stigmas. MRI detected spinal abnormality in 2/42 children with a normal sacral exami-nation in comparison to 7/19 children with an abnormal sacral finding (Chi-squared test, $P < 0.005$). The sensitivity and specificity of an abnormal sacral finding in predicting MRI ab-normality were 0.76 and 0.77, respectively. Urodynamic parameters did not predict an ab-normal spinal MRI. The authors concluded that abnormal sacral findings, but not urodynamic studies, were strong predictors of OSD. A normal sacral examination did not rule out OSD(271).

It has been reported that UDS before neurosurgical intervention is able to identify LUTD in clinically silent cases and also to identify deterioration in these patients(272). However, an-other study showed that pre and post untethering UDS did not predict continence status(273), but UDS and prone MRI were considered to be the best tools for screening those patients at risk of symptomatic retethering(274). The utility of UDS in preoperative work-up, monitoring for retethering, and long-term urologic follow-up is confirmed but re-quires further examination.

Lipomyelomeningocele (LMM) may present with no obvious functional concerns. Indications for and timing of tethered cord release in LMM are therefore controversial. Yerkes, et al performed a retrospective study that identified 143 patients from the multidisciplinary clinic who underwent tethered cord release for LMM between 1995 and 2010. Fifty-six patients were studied. Median age at tethered cord release was 4.4 months (range 1.0-224.0) with a median follow-up of 10.7 years (range 1.3-19.1); In this series of primary tethered cord re-lease for LMM, 93% of patients were urologically asymptomatic before tethered cord re-lease, and prospects for continence were excellent. Families can anticipate 23% likelihood of CIC, which is considerably less than in meningomyelocele, but long-term urologic follow-up is still strongly recommended. Clear predictors for continence after tethered cord release will require additional long-term patient outcomes(275).

A total of 130 expectantly managed infants/young children with spinal dysraphism and initial DMSA and UDS before age 2 were reviewed. They found that VUR, bladder trabeculations, end-fill pressure (EFP) ≥ 40 cm H20, initial volume (IV) drained at UDS catheter placement ≥50% of EBC, and detrusor pressure at initial volume (DPIV) >10 cmH2O were associated with subsequent DMSA abnormalities managed expectantly. Many of these parameters were associated with febrile UTI and early CIC. The combination of trabeculations and/or VUR outperformed other UDS parameters in identifying those high and low-risk for adverse uro-logic outcomes. Routine DMSA scan may have limited utility in patients with a non-trabeculated bladder without VUR, as none developed an abnormal DMSA. Most (71%) abnormal DMSAs were in patients with trabeculations and/or VUR following a febrile UTI. Given these findings and that incidence of febrile UTI may be lower in those with trabecula-tions while on CIC, patients with trabeculations and/or VUR should be managed aggressive-ly to protect kidneys (276).

2.2.2. Conclusions (Level 2/3)

- Retrospective and prospective studies have confirmed that in patients with myelodyspla-sia or (occult) spinal dysraphism UDS play a unique role in detecting DO and/or reduced bladder compliance, which is not predictable on the basis of clinical signs or symptoms; also, UDS both initial as well as in the follow-up reveals clinically relevant results with regard to management and surgical or medical treatment.
- Repeated routine VUDS as opposed to non-video UDS in the follow-up of children with known (morphological or anatomical) abnormality is not substantiated. Exact timing of re-peat UDS (and in select cases VUDS when clinically indicated) in children with NLUTD are currently at the discretion of the clinician as no studies have been published that help to determine the optimum of timing and frequency of UDS follow-up. This should be guided by the necessary to know how UDS parameters that might affect decision on changing treatment.
- Based on expert opinion, regular non-invasive UDS is encouraged to be used at follow up whenever possible.
- Various studies have shown that LUT function in children with myelodysplasia or (occult) spinal dysraphism may change over time (and physical growth) (Level of Evidence: 3). Therefore, invasive UDS should be performed every year in symptomatic patients with MMC, non-invasive UDS in asymptomatic cases is recommended.

2.2.3. Recommendations in children with myelodysplasia or (occult) spinal dysraphism

- Comprehensive UDS is advised in all patients with myelodysplasia or symptomatic (oc-cult) spinal dysraphism throughout the entire life on a regular basis from earliest childhood. Once non-invasive UDS find unexplained abnormal UDS parameters, invasive UDS or VUDS is recommended. The committee recommends research the application of non-invasive UDS in these cases and to determine the optimum of interval and frequency of follow up UDS. (Grade B/C)
- UDS should also be considered when a change in signs and symptoms, or relevant lower body half and/or urinary tract clinical or neurologic signs or symptoms arise or when signifi-cant (surgical or medical) treatment changes have been instigated. (Grade B/C)
- VUDS is recommended when non-invasive UDS indicated bladder morphology changes and UUT dilatation and timing and technique of UDS must be selected on an individual ba-sis. (Grade C)
- UDS is a validated procedure to evaluate tethered cord release results. (Grade B/C)
- To help identify children at risk for subsequent UUT deterioration, initial UDS very early in the neonatal period should be considered. (Grade C)
- Anorectal function or dysfunction evaluation simultaneously is recommended. (Grade C)
- UDS guided CIC (safe bladder capacity determined by UDS) should be considered when this procedure is used. (Grade C)

2.3. Sacral Agenesis

2.3.1. ICI2016 Conclusions and Recommendations

- UDS of LUT function in children with (partial) sacral agenesis reveals a substantial inci-dence of clinically hidden dysfunction.
- Approximately one third of children with anorectal anomalies (ARM) have MMC and/or tethered spinal cord, associated with UDS demonstrable and clinically relevant LUTD.
- Clinicians should consider UDS in all children with sacral agenesis and also after (surgery for) sacrococcygeal teratoma. (see section f – Tumours)
- Clinicians must consider that in children with LUTD, otherwise clinically silent sacral agene-sis can exist.

2.3.2. Discussion and New Evidence 2021

Sacral agenesis (SA) or caudal regression syndrome, is a congenital malformation of the spine of varying degree of severity, refers to the absence of part or all of two or more lower sacral vertebral bodies. Urinary and/or faecal incontinence usually manifests at an older age when the child fails to toilet train on time. A careful physical examination noting flattened buttocks and a short gluteal crease is pathognomonic for the diagnosis. It can be associat-ed with neurogenic bladder dysfunction that does not necessarily correlate with the level of spinal or skeletal defect.

It is recommended that symptomatic patients with SA should undergo UDS to guide LUT management. Whether asymptomatic patients with SA should undergo UDS to find bladder dysfunction in time need more investigation to clarify in the future.

A retrospective study in 43 infants and children with SA evaluated by UDS including cysto-metrogram and electromyography, and showed that in 30% neurogenic DO, but none devel-oped end-stage renal disease or required spinal cord detethering(277). However, another study concluded that symptomatic neurogenic bladder due to SA may cause renal damage in a similar way as ARM. The UDS study that children with SA had poor compliance (6.7 ml/cmH2O, interquartile range [IQR] 4-13.6 ml/cmH2O), reduced age-adjusted bladder capaci-ty (59%, IQR 22-85%), elevated end-fill pressure (22 cmH2O, IQR 11-28 cmH2O), hydro-nephrosis (88%), and reduction in eGFR (29%), all comparable to ARM or cloacal malfor-mation without the SA (22 cases) indicated(278).

Sacral agenesis also shows variable association with ARM and/or spinal cord anomalies . These studies reveal that 30 to 40% of these patients have a lesion type with DO and an intact, but dyssynergic sphincter, 25 to 50% have areflexic detrusor and denervation in the sphincter, and 15-20% may have normal LUT function(282). MRI is recommended for the evaluation of all patients that have sacral agenesis (279), and the extension of the sacral defect can serve as a prognostic factor for retethering(283). When MRI shows sacral or spi-nal cord anomalies, UDS should be considered, preceded by neurological exam and con-sidering neurophysiological (evoked potentials) testing. The authors of this and subsequent studies recommend a non-invasive evaluation for all other children, and UDS when NLUTD is suspected(284).

2.3.3. Conclusions (Level 3)

- Case series have shown that UDS of LUT function in children with (partial) sacral agenesis reveals a substantial incidence of clinically hidden dysfunction.
- Approximately one third of children with anorectal anomalies (ARM) have MMC and/or tethered spinal cord, associated with UDS demonstrable and clinically relevant LUTD.

2.3.4. Recommendations (Grade C)

- UDS should be considered in all SA children with voiding symptoms and also after (sur-gery for) sacrococcygeal teratoma. (see section f – Tumours)

2.4. Spinal Cord Injury

2.4.1. ICI2016 Conclusions and Recommendations

- Retrospective studies have shown that UDS in all children with SCI is relevant.
- Retrospective studies have shown that UDS in children with SCI results in diagnoses and treatment similar to adults with SCI.
- The committee recommends that UDS in children with SCI is planned on an individual ba-sis, but should be considered at the latest after 6 weeks after injury.

2.4.2. Discussion and New Evidence 2021

Patients with SCI have a higher risk of developing UUTD. Reduced compliance and high DLPP were major risk factors for UUTD. It had been demonstrated that the mandatory role of UDS in the management of NLUTD, standardization and better implementation of as-sessments in daily practice may further improve outcomes of neuro-urological patients in-duced by SCI based on objective measurements(285). UDS of children with SCI results in diagnosis and treatment is similar to adults with SCI. It is important to measure detrusor compliance in order to determine the potential risk for VUR and hydroureteronephrosis(286).

All studies are single centre, retrospective and use historical controls for comparison. In the presence of elevated UDS filling and voiding pressures, a 30% incidence of UUT deteriora-tion can be

expected(287), while effective voiding with pressures below 40 cm-H2O in the absence of detrusor-sphincter dyssynergia ensures a stable UUT(288). UDS monitoring has been demonstrated to be relevant in the follow up and prevention of UUT deterioration(289). In another study on 17 children aged 6 months-18 years with cervical (4), thoracic (8) and lumbar (5) SCI, all but one showed DO on first evaluation, which was changed to acontrac-tile and/or compliant detrusor pattern by medical treatment; 7 had increased cystometric capacity and 8 decreased DLPP at follow-up; only 2/17 developed minor UUT impairment(290). As in adult patients autonomic dysreflexia can occur also in children and adolescents(291).

2.4.3. Conclusion (level 2/3)

- UDS is relevant to all children with SCI, which shown an important value in diagnoses and treatment strategy making SCI children similar to that of adults.

2.4.4. Recommendations (Grade C)

- The committee recommends that UDS in children with SCI is done with special attention to the specific needs of the patients (e.g. autonomic dysreflexia and positioning). It is highly preferable that all professionals involved are specifically trained for that purpose.

2.5. Cerebral Palsy

2.5.1. ICI2016 Conclusions and Recommendations

- Some studies have shown that clinically unexpected LUTD can occur in children with cere-bral palsy (CP), especially when voiding symptoms are present.
- Observation and non-invasive testing are helpful, but UDS should be considered when UTIs or UUT dilation occurs in children with cerebral palsy.
- Clinicians should evaluate voiding in children with cerebral palsy and should consider complete UDS when dysfunction is suspected.
- UDS is to be considered in all patients with spastic cerebral palsy. Undiagnosed and un-treated patient's bladder dysfunction remains pathological and potentially dangerous and may damage the UUT.

2.5.2. Discussion and New Evidence 2021

In a recent study on the urodynamic findings in children with CP, 24 boys and 10 girls (mean age 6.6 years) diagnosed with CP who were scheduled for a dorsal rhizotomy operation were evaluated(292). The most common complaints of the study group were urinary inconti-nence (58.8%), encopresis (32.4%) and constipation (17.6%), and 41.2% of the patients were on diapers. The most common urodynamic findings were low bladder compliance (85.3%), DO (67.6%), hyposensitive bladder (52.6%), and low bladder capacity (41.2%). No patient had UUTD.

A recent systematic review on 27 studies, describing prevalence of LUTS or UDS findings, found that 55% of the patients have at least one LUTS: storage symptoms are more com-mon, and patients with pelvic floor overactivity are more prone to progress to UUT dysfunc-tion in adult life(237).

Uroflowmetry and PVR are considered first line evaluation of LUT function in children with cerebral palsy(293) UDS can direct management. Negative prognostic factors are the spas-tic subtype with quadriplegic distribution, moderate to severe functional impairment and severe cognitive impairment(237). A careful study by uroflowmetry on 57 patients showed that the symptomatic children (52%) had lower Qmax (P .013) and abnormal flow rate curves (P .022) (294), indicating non-invasive testing as a good screening tool. The vast majority of the children with cerebral palsy tend to gain normal LUT function, but often at an age that is later than expected for from DO(295). Bladder (cystometric) capacity is decreased in most children with cerebral palsy, and PVR is present in an important proportion.

It has been suggested based on expert opinion that cystometry and sphincter EMG are to be considered, but only when frequent toileting or anticholinergic therapy fails to control incontinent episodes, the child develops UTI from ineffective voiding, or when ultrasonog-raphy reveals hydronephrosis. VUDS assessment can be considered in all patients with infantile cerebral palsy as at least half of the children with spastic cerebral palsy have clini-cally silent bladder dysfunction. 100% of children had clinical improvement postoperatively (selective dorsal rhizotomy), 71% who were incontinent preoperatively became continent and none had deterioration on UDS(296,297).There is a spectrum of clinical and UDS LUT (dys)function in children with cerebral palsy; e.g. 77% void spontaneously but have UI. Chil-dren with UI have a significantly lower age related cystometric capacity(290), and also lesser than expected for age voided volumes on uroflowmetry (plus PVR)(298).

2.5.3. Conclusion (Level 3)

- Some studies have shown that clinically unexpected LUTD can occur in children with cere-bral palsy, especially when voiding symptoms are present.
- Observation and non-invasive testing are helpful, but UDS should be considered when UTIs or UUT dilation occurs in children with cerebral palsy.

2.5.4. Recommendations (Grade C)

- Clinicians should evaluate voiding in children with cerebral palsy and should consider complete UDS when dysfunction is suspected.
- UDS is to be considered in all patients with spastic cerebral palsy. Undiagnosed and un-treated patient's bladder dysfunction remains pathological and potentially dangerous, and may damage the UUT.

2.6. Tumours

2.6.1. ICI2013 Conclusions and Recommendations

According to ICI2016, it was shown in single centre cohorts that UDS testing is relevant after resection of a sacrococcygeal teratoma. A study showed that all children with central nerv-ous system tumours can have LUTD regardless of the location of the tumour. LUTD exists after sacrococcygeal teratoma resection and recently again it was proposed, on the basis of a single centre cohort, that UDS is necessary for those children(299,300). A recent study showed that children with central nervous tumours can have UDS abnormalities, whether the tumour is in the spinal cord or not. A single centre and selected cohort study concluded that a child with a central nervous system tumour needed urological investigation including UDS regardless of tumour location(301). A controlled cohort study of 17 patients with sacrococ-cygeal teratoma and 85 healthy control patients shown that uncontrolled voiding, difficulty in bladder emptying, pyelonephritis, and constipation were more common in patients with sac-rococcygeal teratoma than in healthy children.

Dysfunctional outcome was more prevalent in children with large and immature teratomas(302).

2.6.2. Conclusion (Level 3)

- It was shown in single centre cohorts that UDS is relevant after resection of a sacrococ-cygeal teratoma.
- A study showed that all children with central nervous system tumours can have LUTD re-gardless of the location of the tumour.

Recommendations (Grade C)

- It is recommended that UDS should be considered before and after resection of sacro-coccygeal teratoma and central nervous system tumours.

3. ANORECTAL MALFORMATION AND PERSISTENT CLOACAL ANOMALIES

3.1. ICI 2016 Conclusions and Recommendations

Various studies have shown that a significant proportion of children with anorectal malfor-mations (ARMs) have primary or secondary LUTD, LUT innervation abnormalities or pelvic floor dysfunction. Clinicians should consider UDS in children with imperforate anus when clinical signs of LUTD exist. Clinicians should consider UDS in children where, based on an MRI, or based on clinical examination, relevant neurological abnormalities exist, before and/or after reconstructive surgery independent of (the existence of) LUTS.

3.2. Discussion and New Evidence 2021

UI and LUTD may result from iatrogenic injury or from a pre-existing congenital neurological lesion in children with ARM. With the advent of the posterior sagittal anoplasty, this compli-cation has been eliminated as a cause for subsequent UI, although bladder neck incompe-tence may be a consequence of extensive mobilization of the sigmoid colon to transfer the rectum to its final location(303). UI after definitive repair is reported as to be the result of ineffective emptying causing ‘overflow urinary incontinence’ and DU or acontractile detrusor, rather than urinary sphincter injury. Similarly, it has been reported, on the reconstruction of cloacal anomalies, that the main clinical characteristic of bladder dysfunction was a failure to empty(304,305), presumably due to iatrogenic injury from extensive dissection, which can lead to peripheral nerve damage.

In a prospective study on children with ARM, prior to, and following definitive procedure, only 9 of the 19 patients had normal UDS pre-operatively, and LUT function worsened post-operatively(306). UDS is required to evaluate LUTD in patients following repair of ARM (and cloacal anomalies). The reliability and reproducibility of findings among the various studies analysed confers an important role for VUDS as an integral part of the evaluation and man-agement of these children. Even asymptomatic children with high ARM often have an unsafe intravesical (detrusor) pressure suggesting the need for an aggressive evaluation approach for these children(307).

A retrospective cohort study showed again that children with ARMs have a high proportion of bladder dysfunction and/or genitourinary anomalies. In patients who had been treated for a recto-bladder neck fistula, the most urodynamic findings included the presence of DO in 30 (75%) patients, median leak point pressure of 56.0 cmH2O (range, 14-140), median func-tional cystometric capacity at 40 cmH2O of 125.5% age-expected capacity (range, 36-473%), and median maximum cystometric capacity of 131.0% age-expected capacity (range, 44-473%). A mildly decreased GFR or worse developed in 13 (24%) patients. Of the 52 (78%) patients who were followed by paediatric urology with a median follow-up of 30.9 months (range, 0.0-86.8), 35 (67%) were at least 4 years of age and could be assessed for continence. Continence was achieved in five (14%) patients voiding spontaneously and 15 (43%) performing CIC. Recurrent urinary tract infections (UTI) were an independent predictor of incontinence, while urethral anomalies were an independent predictor of chronic kidney disease (CKD) on multiple logistic regression analysis(308).

Spinal cord tethering screening in all patients with ARM is recommended although the preva-lence of tethered cord in these children is still unknown. A survey was performed in a large cohort of European paediatric centres, supporting tethered cord screening in all patients with ARM and conservative management of the tethered cord. However, the definition of tethered cord, screening tools, and complementary tests are controversial(309).

It has been reported that spinal MRI’s reveal a 35% incidence of distal spinal cord abnormal-ities in children with an imperforate anus(310) NLUTD occurs in 50%(279), and 40-60% of those patients who have tethered cord needed untethering(283). Evaluation of all patients with ARM using MRI is recommended and when MRI shows sacral or spinal cord anomalies, non-invasive should be done, and UDS when NLUTD is suspected(280). To detect spinal cord abnormalities in neonates, spinal ultrasound has been largely used as a screening test up in children to 5 months of age; a study on 244 ARMs showed a 100% specificity but a very low sensitivity (15%), thus stating that ultrasound is not suitable as a screening test for MMC in ARM, with MRI being necessary when symptoms occur(311). By combining the inci-dences in 3 studies it was found that the presence of an abnormal sacrum increases the likelihood of LUTD to as high as 76% (38 of 50 children)(279,312,313). When the rectum ends above the levator ani muscle there is a much greater chance of LUTD than when it ends below the pelvic floor(280) and the older the child is at the time of UDS the more likely he/she is to have abnormal LUT function(314).

Patients with cloacal anomalies have a high incidence of associated urinary tract and spinal anomalies. Although the majority of cloaca patients can achieve faecal and urinary conti-nence with the surgical reconstructive procedures performed today, many require addition-al/multiple urological procedures to achieve continence, treat bladder dysfunction and to protect renal function. One half of patients will develop renal failure, so regular and lifelong monitoring bladder function is mandatory(315–317).

A study on 466 persistent cloaca (PC) and 229 cloacal exstrophy (CE) cases found that 45.6% of CE patients have myelomeningocele. Varies of urological procedure has used to treat the LUTD in the neonatal and infantile periods, the respective rates of bladder dysfunc-tion, clean intermittent catheterization, and permanent enterostomy were 32.6, 22.5, and 7.3% in PC patients and 60.7, 28.4, and 73.8% in CE patients. The clinical outcomes of PC and CE remain unsatisfactory and the treatment guidelines is still lacking(318). Obviously, UDS should be considered to follow up LUT function before and after above procedures.

3.3. Conclusions (Level 3)

A significant proportion of children with ARM has primary or secondary LUTD or pelvic floor dysfunction. The incidence of congenital urachal, bladder, and cloacal anomalies is low, but has a high

incidence of associated anomalies most commonly in urinary tract and spinal.

3.4. Recommendations (Grade C)
- Clinicians should consider UDS in children with ARM (cloacal anomalies) when clinical signs of LUTD exist.
- Clinicians should consider UDS in children where, on the basis of an MRI, or on the basis of
- clinical examination, relevant neurological abnormalities exist, before and/or after recon-structive surgery independent of (the existence of) LUTS.
- Spinal cord tethering screening in all patients with ARM is recommended

4. ANATOMIC ABNORMALITIES OF THE URINARY TRACT

4.1. ICI2016 Conclusions and Recommendations
In children with posterior urethral valves (PUV), urethral stricture, ectopic ureterocele, VUR or with bladder exstrophy, the frequent UDS abnormalities are predominantly DO and reduced bladder compliance or large cystometric capacity with impaired filling sensation. Invasive UDS has been shown to be of help to determine when further medical or surgical manage-ment is indicated in children with these abnormalities.

The use of UDS has aided in an objective measurement of treatment success or failure for these abnormalities. Therefore, clinicians should consider complete UDS of the filling and voiding function, at least once, in children with above anatomical abnormality. UDS in chil-dren should be done with special attention to their specific needs, and with careful attention to minimize mental trauma and to ensure reproducing symptoms as much as possible. Clini-cians should consider regular uroflowmetry and PVR assessment in the follow-up and fur-ther management of children with PUV, urethral stricture ectopic ureterocoele, VUR or with bladder exstrophy, and the necessity of follow-up UDS should be decided on an individual basis and as less frequent as possible.

4.2. Discussion and New Evidence 2020
Literature available has recommended to use non-invasive tools as much as possible in conditions which are not treated with surgical correction (i.e VUR and/or valve patients); while major abnormalities (i.e. exstrophies or ARM or cloacal anomalies) need UDS evalua-tion prior to decide complex corrections. The evidence still consists of uncontrolled case series and expert opinions although many clinicians now feel its usefulness is beyond ques-tion.

4.3. Posterior Urethral Valves
UDS are not only a basic tool to understand voiding function, persistence of UI and UUT (and renal) impairment evolution, but also help in judge the results of treatment procedures in boys with PUV. In a series of UDS after valve ablation, the type of bladder function ob-served, correlates with the time elapsed from surgery; DO was the predominant pattern ini-tially(319) but changes are noted in both DO and compliance over time(320–322). Despite early valve ablation, a large proportion of boys treated for PUV have gradual detrusor ‘de-compensation’, persisting DO and/or secondary bladder neck outflow obstruction leading to obstructive voiding and finally DU or acontractility.

A retrospective study on 28 consecutive patients treated for PUV who underwent foetal intervention or postnatal surgery. Pre- and postnatal treatment modality included foetal vesico-amniotic shunt, endoscopic valve ablation, and vesicostomy. UDS showed that the mean maximum detrusor pressure was significantly lower in patients with a foetal shunt than in others (37.7 vs 73.0 cmH2O, P = .019). Bladder capacity was greater and residual urine volume was lower in the postnatal vesicostomy group than in the primary valve ablation group, but without statistical significance. Vesicostomy is more beneficial in the recovery of renal function and is not inferior in terms of bladder function, even in patients with severe PUV disorder. It is a reliable surgical option that can spare renal function and guarantee adequate bladder function in the long term(323).

The importance of bladder neck secondary obstruction which may require further interven-tion on the basis of the UDS observation that DO and high maximum voiding detrusor pres-sures decreased consistently after bladder neck incision(324). Singh et al. summarized 81 children with PUVs including 40 cases underwent bladder neck incision (BNI) in addition to valve fulguration (Group I), and the remaining 41 patients underwent conventional tran-surethral valve fulguration (Group II). UDS follow up showed no statistically significant dif-ference regarding DO, compliance, end-filling pressure, and max Pdet at Qmax in the both groups. However, improvement of peak flow and postvoid residue (PVR) in Group I in com-parison to Group II was significant(325).

In addition, VUDS is useful for many aspects of valve bladder, and is increasingly used in cases with vesicoureteral reflux, changing or inconsistent urodynamic studies, and bladder neck obstruction. VUDS has also been used in pre-operative evaluation of patients with end-stage renal disease receiving a kidney transplant. However, additional research is re-quired to better define the proper circumstances for its use(326). The role of VUDS in diag-nosis of the condition that late-presented PUVs is still unclear although cystoscopic exami-nation is still the preferred for those cases to diagnose this condition(327).

The persistence of UUT changes is related to the bladder’s unresponsiveness to medical therapy for the DO and/or for DU (usually CIC). However, it is possible that this condition is secondary to insufficiently frequent voiding in the face of increased urine production. BOO from a secondary hypertrophied bladder neck can also occur, requiring further intervention(328). Several studies have shown the predictability of the development of renal failure based on specific detrusor patterns seen on UDS: persistent poor compliance, high detrusor pressures, BOO and/or chronic failure of the detrusor to adequately contract during voiding with increased PVR(329,330). In a study on 54 cases, it was found that the non-symptomatic PUV patients had lager filling volume (135 ± 46% of EBC) than the sympto-matic PUV patients. PUV patients with LUTs had a higher rate (19/28, 67.9%) of impaired bladder compliance than non-symptomatic PUV patients (11/26, 42.3%, p = 0.0489). The PUV patients with LUTs had a trend of worse kidney functions in lower GFR, higher serum creatinine and lower estimated GFR(331).

Whether pressure pop-offs, such as high-grade vesicoureteral reflux with renal dysplasia, is beneficial for renal and bladder outcomes in boys with PUV, or beneficial for renal function is still controversial. A retrospective study of 48 cases with PUV show that patients with pop-offs required more extensive interventions to achieve continence and achieved conti-nence and toilet-training less frequently than patients without pop-offs. Their study conclud-ed that pop-offs do not appear to impart significant benefit to bladder outcomes and may indicate more severe bladder dysfunction(332).

A respective study on the correlation of bladder contractility index (BCI) with development of chronic kidney disease stage IIIB or more in 270 boys with PUV who underwent valve fulguration between 2000 and 2010 was followed up by recording BCI, end filling pressure (EFP), compliance (ΔC), bladder outflow obstruction index, and bladder volume efficiency, and the authors concluded that BCI may be a useful tool for early detection of boys with PUV who are likely to progress to chronic kidney disease stage IIIB or more(333). It is im-portant to note that the BCI was not validated for use in children or women.

It is well known today that the LUT conditions are at risk for UUT deterioration, therefore it is reasonable to follow the patients who underwent neonatal valve ablation and aggressive and early bladder training, by non-invasive UDS exams. In a multivariate analysis study, detrusor thickness greater than 1.3 mm was considered the only independent risk factor for later impaired bladder function(334). Non-invasive UDS seems to be as safe and effective as invasive UDS in the long-term management of boys with PUV, and invasive UDS may be reserved for cases of progressive deterioration of LUTD or renal function.

4.4. Bladder Exstrophy

Once the bladder exstrophy (BE) is closed it may be difficult to manage persistent UI, UUT dilation or VUR. In addition, as more children undergo complete primary repair of the BE in the neonatal period, the most accurate assessment of bladder function is by UDS; compli-ance reduces in up to 50% after surgery(335,336). Studies have correlated UI with age relat-ed cystometric capacity, compliance, DO and/or LPP(337). UDS remain helpful to evaluate LUT before (and after) further surgical procedures and for research matters. To check poten-tial injury to pelvic neuro-urological anatomy after complete primary repair of bladder ex-strophy, needle EMG was done in 13 children to evaluate the external urethral sphincter re-sponse to sacral reflex stimulation and during voiding, finding normal individual motor unit action(338).

The role of UDS on prediction of certain risks in BE has been reported. A retrospective mul-ti-institutional review of bladder perforation in seven male and two female patients with clas-sic bladder exstrophy-epispadias (E-E) showed that UDS may identify those at risk. CIC with or without augmentation should not be delayed once poor bladder emptying and/or high pressure are identified(339).

UDS has also been used to evaluate the long-term efficacy of Young-Dees bladder neck reconstruction (YDBNR) alone versus YDBNR plus bladder neck injection in patients with BE(340). A multi-institutional cohort assessed the probability of bladder augmenta-tion/diversion and CIC in 216 patients with classic bladder exstrophy. On long-term follow-up probability of bladder augmentation/diversion increased with age, with 1 in 2 patients by age 10 years and the majority in adulthood. Almost a third of patients, including adults, with a closed native bladder performed clean intermittent catheterization. Considering all adults only 14% did not perform clean intermittent catheterization(341). Obviously, BE needs life-long care and UDS assessment.

4.5. Ectopic Ureterocele

The literature on UDS application in ectopic ureterocele is still limited. UDS in babies with an ectopic ureterocele had shown that several cases had a larger than normal cystometric ca-pacity and DU(342), but in a multicentre analysis of 616 children it was found that LUTD is present only in ectopic ureterocele(343). Recently, there is an increasing agreement in favour of conservative management of paediatric duplex system ureteroceles, by mean of simple endoscopic puncture followed by close surveillance: VUR can resolve spontaneously in a significant number of patients, and bladder function should be conserved(344), and even if secondary bladder surgery is needed, significant bladder dysfunction is rare(345,346).

4.6. Vesicoureteral Reflux

VUR may be a secondary phenomenon resulting from LUT dysfunction(347). There is evi-dence that DO may lead to VUR in a marginally competent ureterovesical junction mecha-nism(348). This DO may be a natural phenomenon in the infant bladder(349) and/or a learned dysfunction in older children. Among UDS parameters, high bladder pressure at the onset of VUR was found a positive prognostic factor for spontaneous resolution of VUR, inde-pendently of VUR grade(350). The highest degree of VUR was found associated with high-est detrusor pressure in the group with 'urgency syndrome'(351), and no differences in reso-lution rates observed from grades I to V VUR in children with LUT conditions, patients with dysfunctional voiding having the most improvement and greatest(70%) resolution of VUR(352). A study on 153 children with vesicoureteral reflux and accompanying non-neurogenic LUTD were retrospectively evaluated. It was found that the absence of signifi-cant post-void residual urine volume, and a low Dysfunctional Voiding and Incontinence Symptom Score increase the likelihood of spontaneous resolution rates of vesicoureteral reflux in children with non-neurogenic LUTD(353).

Another prognostic finding regarding the spontaneous resolution of VUR is intravesical vol-ume at the onset of VUR: large cystometric capacity correlated with VUR during filling, while VUR at voiding correlated with low cystometric capacity, with the first pattern showing a lower resolution rate within the third year of life, in a longitudinal study by videocystometry(354). There is ample evidence to show that treating the DO and/or voiding dysfunction leads to a faster rate of resolution of VUR (63-92% within 1 year) than treating only with antibiotics(25-54%)(355). We now understand that sterile VUR is benign and most reflux spontaneously resolves over time, the initial approach in majority of children is non-surgical with continuous antibiotic prophylaxis (CAP) and correction of bladder and bowel dysfunction(356).

UUT damage is more likely to occur in children with abnormal LUT function(357). In this set-ting, history taking about voiding habits and accurate non-invasive UDS evaluation become paramount. A study on 50 children has shown the usefulness of the non-invasive test and the classification of urinary dysfunction in children aged over 3 years prior to the first endo-scopic treatment of VUR(358). A prospective study with simultaneous performance of filling cystometry and cystosonography in 43 children showed that cystosonography can replace conventional cystourethrography as an imaging test associated with UDS. It has been able to indicate the treatment to our patients, subjecting them to a single catheterization and without exposing them to ionizing radiation(359).

Question remains if cystometry with PFS in older children are advised. In a study on 40 pa-tients, VUDS showed LUTD in 76% of the children(360), and in a recent prospective study of 147 children with high grade VUR, normal patterns were found in only 23% of them(361). In patients who had post-treatment UDS, biofeedback, pelvic floor muscle training and treatment with antimuscarinics effectively decreased detrusor pressure, increased cystomet-ric capacity and maximum flow rate, and reduced the grade of VUR(362). It is nowadays reasonable to diagnose LUTD by non-invasive tests and to consider VUDS in therapy re-sistant patients, paying attention to bladder neck dysfunction, which was shown to be rele-vant

in a randomized trial(363). Many clinicians advocate UDS especially for those patients that still have UI, renal damage, or who are about to undergo surgical correction(364,365), even if precise UDS (pressure-flow) criteria for outlet conditions in children are still unde-fined.

4.7. Urethral Stricture

Congenital urethral stricture disease in boys is rare(366). Paediatric urethral stricture is aris-ing from a previously unsuspected straddle injury or the late result of hypospadias repair, even the modified procedures have been used nowadays(367). Some meatal stenosis is due to circumcision(368), bladder outflow obstruction comprising PUV, urethral atresia, and urethras with variable degrees of stenosis.

Uroflowmetry can accurately predict the presence of a urethral stricture in 88% of affected males(369). A urethral (meatus or stricture) outflow obstruction after hypospadias repair may develop as symptomatic and uroflowmetry can be helpful(370), demonstrated by signifi-cantly different pre- and post-meatotomy findings of Qmax (P .001) and voiding times (P.03)(371). Follow-up uroflowmetry, analysing and comparing the maximum flow rate, void-ing times and curve pattern may alert the clinician to early signs of (re-) stricture formation but the precise interval, frequency (and efficacy) of periodic uroflowmetry testing in these patients has not been corroborated(372). A prospective study following 25 symptomatic toilet-trained boys before and after meatotomy showed that symptom evaluation and physi-cal examination should be the hallmark assessing children with meatal stenosis. Uroflowme-try provides objective assessment as well as surgical success(373).

4.8. Conclusions (Level 3)

- Frequent UDS abnormalities, predominantly DO and reduced bladder compliance or large cystometric capacity with impaired filling sensation, in children with PUV, urethral stricture, ectopic ureterocele, VUR or with bladder exstrophy.
- Proper UDS has been shown to be of help to determine when further medical or surgical management is indicated and evaluating the treatment results during follow up in children with these abnormalities.
- The use of UDS has aided in an objective measurement of success or failure of treatments for these abnormalities.

4.9. Recommendations (Grade C)

- VUDS at least once, in symptomatic children with PUV, urethral stricture, ectopic ureterocele, VUR should be considered before invasive treatment is adapted
- UDS in children should be done with special attention to their specific needs, and with careful attention to minimize mental trauma and to ensure to reproduce symp-toms as much as possible
- Clinicians should consider regular uroflowmetry and PVR assessment in the follow-up and further management of children with PUV, urethral stricture ectopic uretero-cele, VUR or with bladder exstrophy.
- Clinicians should consider the necessity of follow-up UDS on an individual basis and as less frequent as possible.

5. FUNCTIONAL DISORDERS OF THE LOWER URINARY TRACT

5.1. ICI2016 Conclusions and Recommendations

Various studies show that treatment for children with functional UI can be initiated based on history, clinical exam, bladder diaries, bladder ultrasound and uroflowmetry with PVR as-sessment. It has been suggested that UDS should be considered in children with UI and nocturnal enuresis resistant to initial (conservative) treatment. Epidemiological studies have shown that several neurological/cognitive/behavioural disorders (i.e. genetical diseases, autism, ADHD) have an association with LUTS and UI. Social and/or behavioural conditions (i.e. obesity, bullying) have a significant incidence of high LUTS-score and/or UI. The neuro-logical diseases and social conditions with potential LUTS and UI should be evaluated at least by bladder diaries and questionnaires, possibly by non-invasive UDS. The potential risk factor for adult women to have UI if they suffered from LUTS as girls may require long-term accurate follow-up.

Uroflowmetry with pelvic floor EMG and PVR assessment as ‘non-invasive urodynamic’ screening and evaluation in all children with LUTS, UI and/or with nocturnal enuresis resistant to first line therapy. Urological signs and symptoms should be assessed in children with chronic constipation and/or faecal incontinence. Complete UDS in children with UI and/or with nocturnal enuresis resistant to conservative treatment should be performed if invasive or clinical (dry-bed training) treatments are contemplated. In addition, the committee gave some suggestions for research. The further integrated approaches to the diagnosis (and management) of children with bowel dysfunction, in combination with LUTD should be un-dertaken. Longitudinal studies on persistence of LUTS/UI in adults are suggested, to be integrated with retrospective studies in adults suffering of UI, in order to evaluate if having LUTS in children is a risk factor for UI in adulthood.

5.2. Discussion and New Evidence 2021

Many infants experience chronic incontinence into childhood. UDS, especially flowmetry and PVR measurement has been used frequently in evaluation of voiding function of chil-dren(374). When assessing LUTD in children, one must consider the dynamics of the matur-ing nervous system, learned habits of elimination for bladder and bowel function and social influences.

5.3. Diurnal Incontinence

LUTD is a broad term describing the full spectrum of disorders in any of the stages of bladder function-storage or voiding including OAB-s, voiding postponement, stress inconti-nence, giggle incontinence, and dysfunctional voiding and they are common in childhood(375).

In all children with non-neurogenic LUTS, non-invasive UDS is warranted to determine the presence of different forms of disorder, and to assess bowel dysfunction as well. Uroflow-metry with a PVR measurement and/or simultaneous EMG recording are first choice to eval-uate the voiding dysfunction in children. Voiding diary might be considered in cases to know the patient’s voiding “Frequency/ Volume”. Both small bladder volume and overfilling the bladder might decrease the Qmax. The residual urine in normal infants and children, with an average time delay due to catheterization of 4–5 min, is less than 10 ml, unrelated to age, sex or bladder capacity(222,376,377). The uroflow is considered normal if the bladder emp-ties at least once during two uroflow measurements(232). A retrospective survey of 153 children who were diagnosed with vesicoureteral reflux and accompanying non-neurogenic LUTD showed

that the absence of significant post-void residual urine volume together with a low "Dysfunctional Voiding and Incontinence Symptom Score" increased the likelihood of spontaneous resolution rates of vesicoureteral reflux in children with non-neurogenic LUTD(353).

Pressure / flow study has a limited place in diurnal (day and night) UI. History and clinical investigation are very important in evaluation of UI. Therefore, it is imperative to formulate a 'urodynamic question(s)' following a comprehensive history, careful physical examination, and standard urological investigations, possibly with the aid of validated questionnaires (378–380).

UI resistant to conventional therapy may require (V)UDS. UDS is helpful for us to under-stand the aetiology of diurnal UI and improved making strategy of treatment. Pre-treatment UDS is recommended in any case with UI before invasive treatments. Approximately 6% of 7-year-old children and 1% older adolescents affected by daytime urinary incontinence (DUI) which contains a wide variety of subtypes. Effective treatment requires precise identification of the subtype (381,382).

Different UDS findings have been reported, with DO (in 57%), dysfunctional voiding (in 22%) and also normal findings in 14%(383,384). Dysfunctional voiding was also reported associated with DO in up to 76%. If a low PVR is demonstrated during free flow uroflowme-try then any raised PVR during the urodynamic assessment can be considered as an artifact due to the artificial circumstances of the test and the presence of an in-situ urethral catheter(232).

Several recent studies, well designed by validated questionnaires, including a case-controlled one on autism spectrum disorders(385) and another in children with attention def-icit-hyperactivity disorder (ADHD) have shown a significant incidence of LUTS(386). Other social and behavioural conditions were investigated in children referred with signs and symptoms of LUTD, such as obesity or underweight(387); 415 bullying (a quarter of Ameri-can school children are regularly bullied)(388); and sexual abuse and found these to have a higher LUTS score and/or a higher incidence of UI (389,390).

Greater attention has been recently paid to check the prevalence of LUTS and UI in a series of genetic disorders with cognitive/behavioural or potential neurological problems, such as children with Down's syndrome, to reassure the families and to screen the cases which may require treatment. It was found that there is a marked delay in toilet training (average 5.5 years), and UI was reported in 46% of (versus 24% in controls) previously toilet trained children(391).

OAB-S, defined by urinary urgency, usually accompanied by increased urination frequency and nocturia, with or without urinary incontinence. The prevalence of paediatric OAB-S in 5–13-year-olds is as high as 16.6%, but the pathophysiology and epidemiology have not been sufficiently elucidated. A retrospective study on 126 children with OAB-S evaluated by bladder pressure and urethral pressure recording simultaneously (synchro-cysto-urethrometry) found that urethral instability plays an essential role in the pathogenesis and progression of OAB-S in children. The authors concluded that synchro-cystourethrometry is a useful urodynamic technology to precisely diagnose OAB-S, and transcutaneous electrical pudendal nerve stimulation may be an effective treatment for OAB-S children induced by urethral instability(392).

Fuyama et al. observed 117 children with OAB-S including neurogenic LUTD (spina bifida) aged between 5 and 15 years by abdominal ultrasound and uroflowmetry. The recovery pe-riod (=time to cure =incontinence reported <1/month, achieved by 67% of the children.) was significantly shorter in the group with bladder wall thickness ≥5 mm than with bladder wall thickness <5 mm. Children with a tower-shaped curve on uroflowmetry had a significantly shorter recovery period than those with a bell-shaped curve. The authors concluded that bladder wall thickness and uroflow curve shape are related to the recovery period of paedi-atric OAB-S(393).

UI are commonly associated with gastrointestinal co-morbidities, such as constipation or faecal incontinence in children. Bowel dysfunction, in the absence of any anatomical or neu-rological deficit, often affects LUT function. Constipation had been shown in the past to be associated with DO and a reduced functional bladder capacity(394). Understanding and eliminating this possible aetiology can normalise LUT function, as stated by the report from the Standardisation Committee of the International Children's Continence Society(395). In a recent prospective study from urological and gastroenterological clinics in one centre, 68% of subjects referred with UI, and/or constipation and/or faecal incontinence and included, had at least a 50% reduction in number of daytime UI episodes and 27% became complete-ly urine -continent by successful relief of bowel (constipation and/or faecal incontinence) dysfunction(396).

Whether minimal invasive UDS should be used evaluating the voiding function before treat-ing these Bladder / Bowel Dysfunction(BBD) with non-invasive procedures such as behav-ioural modification, biofeedback training, drug therapy is still controversy(397,398).

5.4. Nocturnal Enuresis

Nocturnal enuresis (NE) is a common complaint in children, with a prevalence of around 15% at age 6 years(399). It has been categorized as monosymptomatic nocturnal enuresis (MNE) and non-monosymptomatic one (NMNE). Multiple risk factors have been reported related to NE, including genetic factors, maturational delays, sleep disturbances, social causes, psy-chiatric conditions(386), LUTD and/or abnormal vasopressin secretion(233,400). Recently, the delay of elimination communication has been found to be one of risk factors to contrib-ute to the increase of EN prevalence in China(401).

Minimal invasive UDS (flowmetry + ultrasound PVR) is recommended for evaluation of void-ing function before medical treatment(402). The role of uroflowmetry in evaluation of NE might be limited. A retrospective study on 93 children who underwent uroflowmetry three times on the same day showed that uroflowmetry did not reflect the urinary symptoms of children with NE. The abnormal uroflowmetry curve patterns did not differ significantly be-tween NE children with and without DI. However, the DVSS questionnaire scores differed significantly(403).

A study on 100 children with NE found that elevated PVR was a significant predictor for lower chance of complete response to treatment whether they had high "Dysfunctional Void-ing Symptom Score" (DVSS) or not(404). Pressure/flow study or VUDS were indicated for refractory cases. An abnormal micturition history, or dysfunctional voiding symptoms like squatting and/or abnormal voiding charts, predicted abnormal UDS results correctly, with a sensitivity of 81% and specificity of 86%(405). A bladder volume and bladder wall thickness index less than 70 was a predictor for the presence of DO at cystometry in one cohort(406). In a double-blind, placebo-controlled study, 24 children with severe OAB-S and DUI (mean

age 8.5 ± 1.2 years) underwent 48h natural fill UDS. No immediate objective effect of transcutaneous electrical nerve stimulation (TENS) on bladder activity was found. There was no significant difference in the proportion of different bladder contraction types between the two groups. TENS did not significantly influence the number of bladder contractions not leading to a void(407).

A study on total of 184 NE and 180 control patients showed that spina bifida occulta (SBO) is more common in NE patients than in non-NE patients. Response to NE treatment is lower in SBO patients with severe LUTS; for this population, advanced treatment options may be considered earlier(408). Whether the NE patients with SBO needs UDS is still unknown.

Both maximal VV and nocturnal urine volume were lower (P < 0.001) in patients with NMNE compared to MNE. Out of 500 patients who were initially referred as desmopressin resistant, 33% of these became dry on desmopressin monotherapy, demonstrating how relevant the UDS diagnosis of enuresis is in subtyping them for treatment selection(402). On this regard, it was shown that treating the non-monosymptomatic child using antimuscarinic agents can be very effective (as high as 77% cure) when based on the findings of UDS(409,410). An emerging issue which requires further research, is the progression of enuretic children into adulthood. Enuretic children were found more likely to have nocturia and urinary urgency if they had nocturnal enuresis when> 12 years of age(411) A retrospective, descriptive cohort study, concerning 907 patients aged 11 years and older, suffering from enuresis of at least one wet night per fortnight showed that both small maximum voided volume (MVV) and nocturnal polyuria (NP) were found frequently in adolescent and adult enuresis patients, which is in line with the current thoughts on causal factors(412).

A retrospective cross-sectional chart study comprising 52 Ataxia telangiectasia patients showed that secondary enuresis affecting 15% of the cases heralding loss of ambulatory capacity, tough its pathophysiological mechanism is largely not understood(413).

Recently, laser acupuncture, a non-invasive, painless tool, with no side effects and lower recurrence rate, has been reported more effective than desmopressin acetate in treatment of NE becoming potential therapy for patients with NE(414). However, the effect of laser acu-puncture on the bladder function might need evaluating by UDS in the future.

5.5. Conclusions (Level 2/3)

- Treatment for children with functional UI can be initiated on the basis of history, clinical exam, bladder diaries, bladder ultrasound and uroflowmetry with PVR assessment.
- UDS or VUDS is relevant in children with refractory UI and NE resistant to conservative treatment.
- Synchro-cystourethrometry is a useful urodynamic technology to precisely diagnose OAB-S related to DO or urethral instability.
- There is evidence from epidemiological studies, carried out by validated questionnaires, that several neurological/cognitive/behavioural disorders (i.e. genetical diseases, autism, ADHD) have an association with LUTS and UI.
- There is evidence that also social and/or behavioural conditions (i.e. obesity, bullying) have a significant incidence of high LUTS-score and/or UI.
- The potential risk factor for adult women to have UI if they suffered from LUTS as girls may require long-term accurate follow-up.
- The delay of elimination communication and occult spina bifida might be a risk factor for children suffering from primary nocturnal enuresis.

5.6. Recommendations (Grade B/C)

- Uroflowmetry with PVR assessment by ultrasound as ‘non-invasive urodynamic screening and evaluation should be considered in all children with LUTS, UI and/or with NE.
- Pressure /flow study and/or synchro-cystourethrometry should be considered in children with UI and/or with NE resistant to conservative treatment, if invasive procedures are con-templated.
- The committee suggests urological signs and symptoms assessment in children with chronic constipation and/or faecal incontinence.

5.7. Suggestion for Research

- Longitudinal studies on persistence of LUTS/UI in adults are suggested, to be integrated with retrospective studies in adults suffering of UI, in order to evaluate if having LUTS in children is a risk factor for UI in adulthood.
- The potential risk factors such as delay of elimination communication or prolong usage of disposal diaper of UI and/or NE should be investigated in the future.
- The committee suggests that further integrated approaches to the diagnosis (and manage-ment) of children with bowel dysfunction, in combination with LUTD are undertaken.

6. TECHNICAL CONCERNS: RELIABILITY AND REPRODUCIBILITY OF TESTS

6.1. ICI2016 Conclusions and Recommendations

The ICI2016 concludes that UDS in children is reliable and reproducible; the limitation is same as that of adult. Non-invasive tests are gradually achieving more evidence level, by constructing normative values and more standardized performing of the tests. Although, it is plausible and considered useful to reduce filling speed and catheter size in relation to pa-tient size, the exact values cannot be given and the influence of the transurethral catheter size on voiding is unknown in children. The committee concludes that standards for Pres-sure/flow study (PFS), and information on non-invasive PFS in children are lacking.

The ICI2016 recommended (Grade C) that the specific demands of children, physically as well as psychologically are considered, before UDS is carried out as well as during the test-ing. The specialized workers, units and equipment needed to ensure this. Non-invasive diag-nostic tests should be preferred, and invasive ones should be done only if indicated by the results of non-invasive procedures, in neurogenic LUTD to discover risk conditions, and when the outcome will or can alter management. The variability and test-retest differences of UDS in children and the effect of the (apparent psychologically stressing) laboratory-situation on the child’s behaviour, and the implications for the results of the tests should be take into account.

In addition, the ICI2016 suggests elaborating on standardization of UDS evaluations and on criteria to judge how the ‘laboratory’

circumstances have influenced the child's (LUT) behav-iour, with the aim to better include how well UDS have represented the actual LUTD, in the evaluation of the test, to verify if, how and when non-invasive tests can substitute UDS in the accuracy of diagnosis of functional LUTD in children.

6.2. Discussion and New Evidence 2021

With the popularization and clinical application of guidelines and standard terminology, dif-ferences in UDS parameters existing from one study to another are decreasing. However, the standard criteria of UDS parameters in children are far from established. The reliability of UDS could be influenced by development effects and measurement variability, as well as by the unfamiliar clinical environment in children.

A recent study, comparing (conventional) UDS with ambulatory UDS: found that even if flow rates were similar between methods, more diverse voiding patterns were identified in ambu-latory UDS, suggesting that UDS may not be sensitive enough to the variability of LUT pathophysiology in children(239). 'Functional' bladder capacity (as derived from the voiding diary, without the first void in the morning) is presented as a relevant parameter for the clini-cian in the ICCS definitions(415,416).

Bladder diary, uroflowmetry with or without EMG, pelvic floor muscle activity (PFMA) has been recommended as first line procedure to evaluate voiding dysfunction in children. They have been used to evaluate the efficacy of biofeedback-assisted pelvic floor muscle thera-py (PFMT) on symptoms, bladder capacity, uroflowmetry before and after treatment in 24 children with refractory OAB-s(417). Bladder diary has been used in a prospective, random-ized study in 64 children to evaluate the efficacy of biofeedback and para-sacral electric nerve stimulation (TENS) for the treatment of children with LUTD(418). Uroflowmetry plus EMG for evaluating the voiding pattern of children with VUR is also reported to guid under-stand the abnormality and making treatment protocol(419).

A prospective treatment study (Level I: Randomized controlled trials with adequate statistical power to detect differences (narrow confidence intervals) and follow up >80%) comprised of 46 anatomically and neurologically normal children with non-neuropathic urinary inconti-nence. By using uroflowmetry with electromyography (EMG), a complete voiding diary and a dysfunctional voiding scoring questionnaire at the baseline, the combination of biofeedback therapy and transcutaneous interferential electrical stimulation had been demonstrated a potential effective modality in treating non-neuropathic urinary incontinence in children(420).

Daily pads use and episodes of urinary incontinence (UI) were recorded in a 3- day voiding diary had been used to evaluate the prevalence and types of bladder and bowel disfunction (BBD) in young and adult patients affected by autism spectrum disorder (ASD). It has been found that young and adult patients with ASD present with a high prevalence of BBD and concomitant antipsychotic medications could to play a contribution in induction and/or maintaining of BBD(421).

An observational study comparing data values, reliability, consistency and compliance col-lected by electronic and paper diaries of differing durations from patients with OAB-S, showed that 7-day or continuous electronic diaries improved the accuracy and reliability of micturition and incontinence frequency data compared with shorter collection periods and paper diaries(422).

Available evidence has demonstrated that children with suspected LUTD should be evaluat-ed properly by detailed history taking, validated questionnaire on voiding and defecation, voiding and bowel diary, urinalysis, screening ultrasound, uroflowmetry and post-void resid-ual measurement. Invasive urodynamic study such as VUDS should be reserved for children in whom standard treatment fails(398). Uroflowmetry is an indispensable first-line test for children with suspected LUT dysfunction, must be accompanied by ultrasound PVR meas-urement. More accurate nomograms were recently stated for uroflowmetry analysing, 721 records(423), and for PVR, analysing (single and dual) PVR in healthy school children(424). Unfortunately, there is still a tremendous amount of intra- and interobserver variation in de-fining the shape of curves, but studies are showing how uroflowmetry-analysis can be more reproducible using standardized evaluation and using a 'flow index'(425). Uroflowmetry may be also more reliable if performed with simultaneous EMG(426,427).

Ultrasound bladder wall thickness measurement has been reported a good sensitivity (based on anterior wall thickness: 67% and based on posterior wall thickness 83%) for symptoms of dysfunctional voiding in a study of 324 children, both healthy and dysfunc-tional voiders(227). Another study in children with BOO (PUV), found detrusor thickness greater than 1.3 mm as the only independent risk factor for later impaired bladder function in a multivariate analysis(334). Dynamic pelvic floor ultrasound is under evaluation for norma-tive values of endurance and direction of pelvic floor movements(228). A cut-off diagnosis for specific non-neurogenic dysfunction for any of the non-invasive tools would be desira-ble.

Filling cystometry is indicated when history and clinical examination raises a suspicion of either anatomic and/or NLUTD involving primarily the storage phase, or when there is a question that cannot be answered by less invasive testing. Additionally, filling cystometry is relevant when BOO (PFS) (eg, valve bladder syndrome, detrusor-sphincter dyssynergia as-sociated with N-LUTD), or congenital anomalies of the bladder (exstrophy, ureteroceles, multiple bladder diverticula) may be causing symptoms and signs of dysfunction that may need further delineation(222,416). The indications for PFS are similar to that for cystometry. PFS should be considered as one procedure, along with a "free" voiding uroflowmetry and filling cystometry, but not the only one, to clarify the diagnosis and to make therapeutic decisions as well as to follow up treatment responses to the voiding dysfunction, when less invasive studies are inconclusive. To understand the characteristics in PFS, normal voiding parameters as well as following Good Urodynamic Practice (GUP) recommendations from the ICS and ICCS are the basis of successful testing(232).

To assess the voiding phase, PFS studies are performed immediately after filling cystome-try. In children, the transition from filling to voiding is not as easily managed as in adults. To avoid missing this important transition, cystometry and pressure-flow/EMG measurements should preferably be performed as one continuous study(392). Available literature has shown that average detrusor pressure at voiding a wide range, to be 127cmH2O in boys and 72 cmH2O in girls on standard fill cystometry(428), similar to what found in a natural fill cys-tometry(429). It was supposed to be physiological dyscoordination, probably due to imma-ture detrusor-sphincter function, also to the different anatomy of the urethra(428,429). Later, it was demonstrated that high voiding pressure is related to DSD(430). The maximum detru-sor pressure (mean±SD) during voiding was 66.1 (13.1) and 56.6 (14.7) cmH2O and the max-imum voiding pressure was 73.9 (16.6) and 62.7 (16.2) cmH2O in symptom free boys and girls without DSD(376,431). A high voiding

detrusor pressure (usually >74 cmH2O in boys, 63 cmH2O in girls7) with a low urine flow indicates BOO; low pressure with a low flow indi-cates DU. A PFS-plot is useful to evaluate the pressure and flow relationship in this regard, although clinical calibration is not yet available for children(232,377).

When filling by catheter, slow fill cystometry (5–10 percent of estimate bladder capacity per minute, or <10 ml/min) is recommended, as compliance (predominantly) and DO (possibly) may be significantly altered by faster rates of filling(432). Room temperature normal saline is still the most common used in UDS. Most children readily tolerate a 6, 7 and 8 Fr. double or triple lumen transurethral catheter to fill the bladder and record pressure (bladder and/or urethral). In selected cases, a suprapubic catheter may be inserted under general anaesthe-sia the previous day or several hours earlier on the same day, but risks need to be juxta-posed against benefits of this approach(221). Use of 5F air-charged catheters has been shown to be safe and easy in children but comparative data with traditional water-filled cath-eters is not available(433). Avoiding general anaesthesia is important as this affects the natural state and eliminates the chance for voiding(221). Most children can undergo UDS without pre-medication; only the most agitated may require some degree of sedation(434). Cooperation is important for successful UDS. To reduce anxiety, the study may also be performed with the child seated, watching a video or DVD and accompanied by one or both parents. A study examining anxiety in children undergoing UDS showed that maximum anxi-ety was induced by EMG needle electrode insertion and insertion of the urethral catheters. Not knowing what to expect was also associated with enhanced distress(435). Difficulty with catheter placement and pre-test anxiety was noted to predict pain as measured by a VAS scale in children above 3 years of age. However, perception of pain was not influenced by the age of the child or the duration of the test(436).

In children with neurogenic LUTD, repeat cycles of testing can give variable results. The ICCS recommends two cycles of testing to ensure an accurate assessment. A recent study examined 3 cycles of testing in 80 children myelodysplasia and found that while maximum cystometric capacity and DO remained unchanged, detrusor pressure during storage was significantly lower in the second and third cycle of testing as compared with the first and DLPP was also noted to be lower in the third cycle. At the least, these findings suggest the importance of repeat cycles in children with impaired compliance(437).

Following previous consultation recommendation(362,438,439), the ICCS standardization on UDS studies of the LUT in children confirmed that UDS in children are best performed under the auspices of a knowledgeable urologist or trained aerodynamicists; so that children should receive comprehensive UDS in a laboratory that is specialized in paediatric UDS with appropriately trained personnel(221,440). However, it is sobering that substantial variation in performance, interpretation and terminology was noted even across experienced centres during the UMPIRE Study for children with myelomeningocele across the USA(441).

Uncorrected bowel dysfunction can influence urodynamic findings through pelvic organ cross-talk. In a series of children with spina bifida, aggressive bowel management resulted in substantial improvements in cystometric bladder capacity (237ml vs 183ml), age-adjusted bladder capacity (0.75 vs 0.54), reduced maximum detrusor pressure (64.3 vs 46.4 cm H20) and a reduction in detrusor leak point pressure from 62cm H20 to 39cm H20 all of which were statistically significant(442).

6.3. Conclusions (Level 3)

- The committee concludes that UDS in children is reliable and reproducible, within the limits also provided for adults
- Non-invasive tests are gradually achieving more evidence level, by constructing normative values and more standardized performing of the tests
- PFS should be considered when history and clinical examination raises a suspicion of either anatomic and/or neurologic LUTD involving primarily the storage phase, or there is a question that cannot be answered by less invasive testing.
- Synchro-cystourethrometry might be considered to evaluate DSD and urethral instability.
- The standards for pressure flow analysis in children have been partially established by ICCS and ICS, but information on non-invasive PFS in children are lacking.

6.4. Recommendations (Grade C)

- The non-invasive diagnostic tests should be preferred, and invasive ones should be done only when indicated by the results of non-invasive procedures, or in neurogenic le-sions to discover risk conditions, or when the outcome will or can alter management.
- The specific demands of children, physically as well as psychologically are taken into account, before UDS is carried out as well as during the testing. The committee advises specialised workers, units and equipment to ensure this.
- Clinicians should take into account the variability and test-retest differences of UDS in children and also take into account the effect of the (apparent psychologically stressing) laboratory-situation on the child's behaviour, and the implications for the results of the tests.

6.5. Suggestion for research

- The committee suggest to verify if, how and when non-invasive tests can substitute min-imal invasive UDS in the accuracy of diagnosis of functional LUTD in children
- The standards for uroflow and PFS analysis in children should be investigated, with the aim to better include how well UDS have represented the actual LUTD, in the evaluation of the test.

VII. URODYNAMICS IN FRAIL ELDERLY PATIENTS WITH URINARY INCONTINENCE

1. INTRODUCTION

UI is common in the elderly with significant implications for physical and mental health in the individual and challenges for the health care system. The prevalence and severity of UI in-creases with age and it is most often mixed UI in type(443–445). While newly occuring UI is common, about one-third of both men and women may experience spontaneous remissions when observed for at least five years(446,447). Unfortunately, under-reporting of UI remains common(448). UI has a negative impact on HRQoL and is associated with depression, so-cial isolation(449–451) and diminished sexual activity(452). UI continues to be regarded as an inevitable consequence of ageing both among patients as well as health care workers(453). The resultant delay in diagnosis leads to use of coping

strategies in the elder-ly(454,455), although individual or group pelvic floor muscle training (PFMT) can improve the complaints(456).

DO and UI are associated with frailty(457,458) and show correlation with its severity(459). Lack of physical activity(460) as well as changes in body morphology and composi-tion(460–462) are associated with a diagnosis of UI in the elderly. Specifically, there is a decline in balance while standing(463–465). Hence, UI is an independent risk factor for falls(466). Nocturia and sleep disturbance are common and may contribute to this risk(467–469).

PFMT is effective in the elderly(470) and combining behavioural strategies with physical activity is more effective(471). Group therapy with a team approach or home-based training might be more effective(456,472,473). Antimuscarinic therapy for the older individual is modestly effective but cognitive dysfunction is a concern(474) and caution is recommended in the frail and elderly. Combination of antimuscarinics with mirabegron is effective and safe in the older individual(475). Patients with refractory OAB-S syndrome may benefit from in-travesical injection of Onabotulinum toxin-A (100U) but older age might be a risk factor for retention(476). Sacral neuromodulation can also be considered. In elderly women with stress UI, minimally invasive mid-urethral slings are effective(477). Concerns regarding use of syn-thetics need to be balanced against the minimally invasive nature of these procedures and lack of long-term outcomes. Use of bulking agents may be a viable alternative in the elderly(478) who often prefer less invasive treatments(479).

Delivery of health care to the elderly patient remains a challenge(480). Integrated health care programs and better training of health care staff might be critical to improving the delivery of care(481,482). The economics of health care has an important impact(483).

2. SUMMARY OF EARLIER CONCLUSIONS AND RECOMMENDATIONS

ICI 2016 concluded that UI is common in the frail elderly and is associated with impaired mental health and HRQoL. Despite this, the rates for seeking treatment remain low. OAB-S is common in the elderly and has a diverse etiology. Patients are also more likely to have associated voiding dysfunction that may worsen with treatment. Evaluation by a skilled cli-nician is vital and consideration must be given to general health, mobility, cognitive func-tion, neurological disease, associated urological disease and concomitant medication. Signs and symptoms are not entirely reliable for predicting LUT dysfunction. Hence, UDS is recommended prior to invasive therapies and is more likely to show DO and/or DU in the elderly. Asymptomatic bacteriuria is common but there is no evidence that elderly patients are more prone to harm from UDS.

The 2016 committee concluded that PVR measurement by a non-invasive method is recom-mended before institution of pharmacological or surgical treatment and uroflowmetry is recommended before any invasive treatment. When required, a comprehensive standard UDS is recommended.

3. URGENCY URINARY INCONTINENCE IN FRAIL ELDERLY PATIENTS

3.1. New Evidence 2021

Elevated PVR is not uncommon in women with overactive bladder syndrome (OAB-S) (484). In fact, PVR has been shown to increase with age in women presenting for a urogynaecolo-gy consultation(485). Older men may harbour large PVR of up to 400ml for years without apparent harm(486). However, voiding efficiency (487) may be more relevant than isolated PVR. Therapy with antimuscarinics has been noted to be associated with impairment of voiding in the elderly with an increased risk of urinary retention as compared with placebo (RR3.60; CI 1.67–7.76)(488). In contrast, mirabegron has been shown to be safe even in elderly OAB-S patients with DU. In a study of 25 elderly patients (mean age 79.3years) with UDS-confirmed DO associated with DU, treatment with mirabegron was associated with improvements in symptom scores, voiding efficiency (40% versus 63% at 3mo) and PVR (153ml versus 86ml at 6 mo) (489). In another study of 60 elderly women with OAB-S, treat-ment with mirabegron resulted in improvement in OAB-S symptoms with objective improve-ments in cystometric capacity. DO disappeared in 40% without impact on any urodynamic voiding parameters(490). The effect of transcutaneous posterior tibial nerve stimulation in the treatment of urgency and mixed urinary incontinence in elderly individuals in residential and nursing homes was examined across 37 centers in the UK. This large sham-controlled randomized trial of 408 men and women failed to find any benefit in the overall study popu-lation as well as various sub-analyses(491).

Elderly women with OAB-S often demonstrate an interrupted voiding pattern. Although ab-normal voiding patterns were noted more often in women with OAB-S having an elevated PVR (77.4%), 47.4% of women with low PVR also showed an abnormal voiding pattern suggesting that PVR measurement may fail to identify some at-risk patients(484).

Among the elderly population (≥65 years) DO has been shown to be associated with frailty independent of age. The adjusted odds ratio for DO was noted to be 2.1 (95% CI 1.3-3.4) and 2.1 (95% CI 1.1-4.0) for pre-frail and frail elderly individuals, respectively(492). DO was noted to be associated with impaired contractility in 18.8% and 5.5% of community-dwelling elderly men and women, respectively. Storage and voiding parameters tended to be worse in these individuals(493).

At the central level, functional brain MRI suggests that UUI might be heterogeneous and differences in the brain response between controls, treatment-responders and non-responders might indicate differences in etiopathology(494). Successful treatment of UUI is associated with a decrease in ventral attentional network activity(495).

3.2. Conclusions

- The committee concludes that PVR elevation is not uncommon in the elderly (LE 3).
- The committee also concludes that lack of voiding symptoms is not a reliable predictor of a low PVR in the elderly (LE 3).
- The committee concludes that uroflow identifies patients with abnormal voiding who might not have an elevated PVR (LE 3).
- The committee concludes that antimuscarinics are associated with increased residuals in the elderly (LE 1).

- The committee concludes that invasive UDS identifies lower urinary tract abnormalities in the elderly that can impact treatment decisions (LE 3).

3.3. Discussion

Voiding dysfunction in the elderly can confound diagnosis and impact treatment. Patients with chronic retention may have symptoms indistinguishable from OAB-S. Additionally, prostatic bladder outflow obstruction (BOO) is common in elderly men and prolapse may be relevant in elderly women. Use of medication (for other diseases) is prevalent and phar-macogenic LUT (voiding) dysfunction is very common. Symptoms are not entirely reliable in identifying patients with voiding dysfunction. Pharmacotherapy with antimuscarinics has the potential for aggravating voiding dysfunction. Beta-3 agonists, such as mirabegron, have not been shown to have such a propensity. PVR and uroflow measurements may help iden-tify patients at-risk and may also enable a more informed decision regarding choice of drug therapy. However, non-invasive tests are not entirely reliable at excluding alternate diagno-ses. Invasive therapy with intravesical Onabotulinum toxin-A injection or sacral neuromodula-tion carries significant implications. In this context, invasive UDS provides accurate charac-terization of LUT function in the frail elderly.

Invasive UDS can result in a clinical urinary tract infection. While some guidelines have rec-ommended routine prophylaxis for elderly patients(496,497), this has been questioned(498,499). Most of the available evidence is based on identification of bacteriuria after invasive UDS rather than symptomatic infection. A careful assessment of the risks and benefit of using antimicrobial prophylaxis is warranted for each individual.

3.4. Recommendations (Grade B-C)

- PVR measurement is recommended in the evaluation of UUI in frail elderly patients with symptomatic voiding difficulty or a history of urinary retention. Assessment of prostate size and assessment of prolapse as well as of current use of all medication (see chapter Clinical Diagnosis) should be taken into account while considering PVR.
- PVR measurement is recommended before initiation of antimuscarinics in the frail elderly patient with UUI
- Uroflow and PVR measurement is recommended in the frail elderly patient with urgency UI prior to invasive therapy.
- Invasive UDS is recommended in the frail elderly patient with urgency UI prior to invasive therapy
- The decision for antimicrobial prophylaxis in the elderly should be based on a considera-tion of the risks and benefits in each individual patient.

4. STRESS URINARY INCONTINENCE IN FRAIL ELDERLY FEMALES

4.1. New Evidence 2021

Detrusor contractility declines with age(500,501). Accordingly, invasive UDS in elderly wom-en with SUI is more likely to show associated voiding abnormalities. In a study of 625 wom-en with stress incontinence, a reduction in maximum flow rate and detrusor contractility and an increase in PVR was noted with advancing age(502).

Invasive UDS often shows unfavourable storage and voiding characteristics in the elderly. In a large retrospective study of SUI outcomes (Age groups ≤50y, 296; 51-69y, 680; ≥70y, 488), elderly women were noted to be more likely to have a low abdominal leak point pres-sure (93, 82 and 70cmH20 respectively, p<0.001), intrinsic sphincter deficiency (64%, 71% and 76% respectively, p=0.002) and DO (12%, 13% and 28% respectively p<0.001). Howev-er, this did not translate into a lower treatment success rate in the elderly(503).

Contrarily, in a study of 688 women (Age groups ≤64y 554; 65-74y 98; ≥75y 36) evaluated at one year following mid-urethral sling, older women showed lower objective (91%, 81% and 67% respectively; p<0.001) and subjective (89%, 78% and 58% respectively; p<0.001) cure rates compared with a younger cohort; these women were more likely to have intrinsic sphincter deficiency (4%, 14% and 28%, respectively; p<0.001).Older women with ISD were also more likely to fail surgery (OR 2.60; 95% CI 1.10-6.18)(504).

4.2. Conclusions

The committee concludes that elderly women with SUI are more likely to have unfavourable findings on invasive UDS (LE 2). The committee concludes that standard recommendations for non-invasive testing before surgery for uncomplicated stress UI are not applicable to the frail elderly woman (LE 4).

4.3. Discussion

UI associated with chronic retention can confound the diagnosis of stress UI and may result in a positive stress test in women. Asymptomatic elevation of PVR is common in the elderly (vide supra). While this does not always appear to carry health implications, measurement becomes clinically important in patients presenting with UI. Guidelines often regard the el-derly woman as a non-index patient for stress incontinence surgery and the usual recom-mendations for surgery without invasive UDS may not be appropriate.

4.4. Recommendations (Grade B-C)

- PVR measurement is recommended in the diagnostic evaluation of SUI in the frail elderly women.
- Invasive UDS is recommended prior to surgery for SUI in frail elderly women.
- The decision for antimicrobial prophylaxis in the elderly should be based on a considera-tion of the risks and benefits in each individual patient.

5. STRESS URINARY INCONTINENCE IN FRAIL ELDERLY MALES

5.1. New Evidence 2021

Elderly men seldom present with stress urinary incontinence unless they have undergone prostate surgery although men with overflow incontinence associated with chronic retention might mimic stress UI. Urinary incontinence is common after radical prostatectomy and de-spite spontaneous improvement, 4-31% of men need pad protection at one year (505). Stress UI is the commonest finding but presence of other forms of LUT dysfunction may dictate a different clinical pathway for management. In a study of 860 men following robotic-assisted RP (RARP), 64 (7.4%, median age 66 years, median 19 months after surgery) pre-sented with post-prostatectomy incontinence (PPI). UDS showed USI alone in 64%, DO alone in

3% and mixed USI with DO in 17%. Poor compliance was noted in 5%. PFS showed weak detrusor contractility in 46% (BCI<100). Five men had associated anastomotic strictures. Among those avoiding further intervention were the 16% of patients with normal UDS findings (506).

A study examining long-term effects in patients receiving salvage radiation therapy after surgery (n=16; median interval from radiation to UDS 7.7y; median age at UDS 73y) found reduction in compliance and capacity with strong correlation of LUT symptoms to the UDS findings (507).

Peri-catheter leak during UDS can mask storage pressure abnormalities and must be recog-nized. Use of penile compression is effective and enables adequate bladder filling without apparent compromise to pressure recording (508). Presence of a passable anastomotic stricture can lead to a spurious negative stress test with the urethral catheter in situ but this might not impact results of surgery(509).

UDS has also been used for assessing the severity of PPI. Low retrograde leak point pres-sure (RLPP) correlated well with higher pad leakage (Spearman's correlation coefficient r.0.56, P<0.01) in a study of 61 patients. RLPP avoids the effect of fluid intake and activity that can confound the pad test(510).

Results of invasive UDS have been shown to predict the outcome of surgery for PPI. Of 99 patients who underwent artificial urinary sphincter implantation, 68 men (mean 68y) who had a successful outcome had higher compliance (112 versus 34ml/cmH20; p<0.01) and were less likely to show DO (18% versus 55%; p<0.01) compared with 31 men (mean 70y) who had failure. When noted, peak DO pressure was lower in the success group (15 versus 36 cmH20; p<0.01)(511). Presence of preoperative DO was also associated with a lower suc-cess rate after sling surgery. In a multivariate analysis of 80 men (mean 68y) preoperative DO and prior radiation therapy were associated with higher pad use at 36 months(512).

Invasive UDS with standard evaluation (history, examination and cystoscopy) was noted to be cost-effective as compared with standard evaluation alone in elderly men with PPI(513). Crucially, this benefit was contingent upon the assumption that invasive UDS was perfectly accurate for making a diagnosis.

5.2. Conclusions

- The committee concludes that stress urinary incontinence is the commonest cause for PPI (LE 2).
- The committee concludes that other important LUT abnormalities may be seen in isola-tion or association (LE 3).
- The committee concludes that presence of other urodynamic abnormalities can impact treatment decisions and outcome (LE 4). Radiotherapy may be a marker for LUT abnor-malities (LE 3).
- The committee concludes that special manoeuvres during invasive UDS can help im-prove the utility of the test (LE 4).

5.3. Discussion

Elevated PVR may suggest associated voiding dysfunction or anatomical obstruction in patients with PPI and trigger further testing. However, a low PVR does not exclude voiding dysfunction. Invasive UDS testing allows for a precise diagnosis of LUT function. Inconti-nence by the side of the urethral catheter or vesicoureteral reflux may mask poor compli-ance. Also, chronic under-filling due to continuous catheter drainage may result in a spuri-ously low compliance. PFS may show BOO due to the vesicourethral anastomosis. Such obstructions might not always be clinically relevant if the catheter-free uroflow is normal. A uroflow should always be available prior to surgery. While it is logical that DO and DU would be more common in the older patient with PPI, no studies have been undertaken to directly study this issue.

There are very few published studies on the impact of radiation on UDS findings in frail elderly men. While an earlier study failed to show adverse impact on compliance, UDS eval-uation in that study was performed at 3 months, possibly too early to detect changes in compliance(514).

5.4. Recommendations (Grade B-C)

- PVR measurement is recommended in the evaluation of frail elderly men presenting with post radical retropubic prostatectomy UI especially when invasive management is con-sidered.
- Uroflow and PVR measurement is recommended prior to invasive treatment for post-prostatectomy (stress) UI in frail elderly men.
- In frail elderly men with suspected voiding or associated storage dysfunction or those with a history of radiation therapy, invasive UDS is recommended prior to surgery for post prostatectomy stress UI.
- In frail elderly men with post retropubic radical prostatectomy urinary incontinence, inva-sive UDS should be considered prior to surgery for post prostatectomy stress UI, pref-erably with a (e.g. penile cuff-) closed outlet when early fill leakage is noticed.
- The decision for antimicrobial prophylaxis for UDS in the elderly should be based on a consideration of the risks and benefits in each individual patient.

6. NEUROLOGICAL CONDITIONS ASSOCIATED WITH URINARY INCONTINENCE IN THE FRAIL ELDERLY

6.1. New Evidence 2021

OAB-S and urgency UI are common in patients with Parkinson's disease. A study of 42 pa-tients (29 men, 13 women; 74.5y old) with OAB-S symptoms showed DO in all patients (ter-minal 45%). PFS abnormalities were common: DU in 47% and BOO in 37%. 17% had in-creased PVR. These findings suggest that DO might not be exclusively responsible for the OAB-S symptoms(515). Mirabegron was noted to be effective in patients with OAB-S symp-toms although there was a small increase in postvoid residual urine(493). In patients with refractory storage symptoms, intra-detrusor botulinum toxin injection resulted in improved cystometric capacity. 40% patients failed to respond and 28% needed intermittent catheteri-zation(516). Degeneration of the dopaminergic neurons as measured by 123I-Ioflupane SPECT imaging shows an inverse relationship with urodynamic bladder capacity(517). Pa-tients with nocturia may benefit from sustained release melatonin administration at night with a reduction in nocturnal urine volume and bother(518). A recent study suggested that sphinc-ter bradykinesia, the delayed relaxation of striated urethral sphincter seen in patients with Parkinsonism, might not be bothersome and may not progress(519).

UI is also common in multisystem atrophy, a differential diagnosis for Parkinson's disease. UI is typically earlier in onset in multisystem atrophy and voiding abnormalities are more common. Unlike Parkinson's disease, results of surgery for the prostate are uniform-

ly poor(520). PVR may be more reliable than sphincter EMG for differentiating Parkinson's disease from multisystem atrophy. In a study of 241 patients, PVR was noted to be higher both on free flow evaluation (113ml versus 40ml, p<0.01) as well as during PFS (230ml ver-sus 72ml, p<0.01) in patients with multisystem atrophy. In contrast, there was considerable overlap in the EMG picture limiting its diagnostic ability(521). While delayed relaxation of the striated sphincter may be noted in Parkinson's disease, genuine detrusor sphincter dyssyn-ergia is rare(520).

UI is a defining symptom for another geriatric condition, normal pressure hydrocephalus(522,523). Urgency UI and nocturia are the most bothersome symptoms and DO is common(524). Shunting of cerebro-spinal fluid (CSF) can improve LUTS and lead to improvements in UDS findings(525). In a study of 48 patients (33 men, mean age 79 years) who underwent a shunt surgery, compliance and capacity improved significantly with resolu-tion of DO in 7 of 37 patients in whom it was noted. However, there was no change in void-ing function(523).

LUTS are common after stroke with half the patients complaining of bothersome urgency UI(526). DO incontinence is the commonest urodynamic finding(527). However, other forms of LUTD such as chronic retention, impaired awareness or severe global functional disability may also manifest with UI(528). LUTS show a correlation with cognitive and functional status and improve progressively in the initial few months following an acute stroke(526,529).

UI is common in patients with Alzheimer's disease. In an insurance database study of 933 patients compared with an age-matched cohort, patients were more likely to have UI (hazard ratio 1.54; 95% CI 1.13-2.09). Annual incidence of UI was noted to be 6.2%(530). The com-monest form of UI is urgency UI with DO noted in 58% in a study of 144 patients (58 wom-en)(531). A positive correlation has been noted between urgency UI and clinical dementia rating scores(532,533).

6.2. Conclusions

- The committee concludes that functional abnormalities of the lower urinary tract are common in geriatric neurological conditions (LE 3).
- The committee concludes that findings of invasive UDS may impact decisions and out-come of invasive treatments (LE 4).
- The committee concludes that cognitive and functional status may be important deter-minants of treatment choice (LE 4).
- The committee concludes that elevated PVR is common in the elderly and impacts ther-apeutic decisions (LE 3).

6.3. Discussion

Several neurological conditions are common in the elderly. Alzheimer's disease, stroke, Parkinson's disease and allied disorders, and normal pressure hydrocephalus are all asso-ciated with a higher risk of UI and show an increased prevalence with age. Evaluation and management are complicated by associated LUT pathology both functional and structural, co-morbid conditions, polypharmacy, impaired cognition, psychological disorders, physical disability, and the available social support structure. Patients may be more prone to the adverse effects of medication and invasive therapies, and it is important to consider the harms associated with treatment.

In view of multiple LUT abnormalities in men with Parkinson's disease, UDS is preferable prior to invasive surgery for the bladder outlet. When available, video-UDS is the preferred modality of UDS testing in this setting. In men with suspected voiding dysfunction, UDS may be preferable prior to intravesical injection of Onabotulinum toxin-A for OAB-S.

While a recent guidelines document recommended antimicrobial prophylaxis for patients with neurogenic bladder, the recommendation was based on literature pertaining to spinal cord injury(496). The applicability of this recommendation in geriatric neurological conditions is uncertain.

6.4. Recommendations (Grade B-C)

- PVR measurement is recommended before initiation or escalation of drug therapy for UI in geriatric neurological conditions
- Uroflow is recommended prior to any invasive therapies for UI in geriatric neurologi-cal conditions.
- Invasive UDS is recommended in UI in geriatric neurological conditions prior to in-vasive therapies or surgery for the prostate.
- The decision for antimicrobial prophylaxis in the elderly should be based on a con-sideration of the risks and benefits in each individual patient.

6.5. Subjects for Future Research

- Evidence with regard to the utility of UDS in elderly individuals with UI is lacking. This would require high quality studies designed specifically for the elderly.
- Defining changes in the normal lower urinary tract with aging.
- Functional studies of the neuronal tracts and their impact on lower urinary tract.
- Functional MRI of the brain to better define the symptom of urgency and the ex-plore different subtypes of patients with UI.
- Impact of urodynamic findings on the results of PPI surgery.
- The role of invasive testing in frail elderly neurological conditions.

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COMMITTEE 6

IMAGING, NEUROPHYSIOLOGICAL TESTING AND OTHER TESTS

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Shobeiri, Seyed Abbas (United States)
Tubaro, Andrea (Italy)
Vodušek, David (Slovenia)

Consultants
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Betschart, Cornelia (Switzerland)
Broughton, Sophie (United Kingdom)

COMMITTEE 6

IMAGING, NEUROPHYSIOLOGICAL TESTING AND OTHER TESTS

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ABBREVIATIONS

2D two dimensional
3D three dimensional
4D four dimensional
AA African American
ACC anterior cyngulate cortex
ACG anterior cyngulate gyrus
ADH anti diuretic hormone
AI anal incontinence
ARJ anorectal junction
ATFP arcus tendineus fascia pelvis
ATLA arcus tendineus levator ani
ATT alpha-1 antitrypsin
BBI bladder base insufficiency
BCR bulbocavernosus reflex
BMI body mass index
BOO bladder outlet obstruction
BS bulbospongiosus
BWT bladder wall thickness
CCC concordance correlation coefficient
CCP cystocolpoproctography
CE clinical examination
CIN contrast induced nephropathy
CKD chronic kidney disease
CL cardinal ligament
CM contrast medium
CMAP compound muscle action potential
CMCT central motor conduction time
CNEMG concentric needle electromyography
CT computerised tomography
DMSA dimercaptosuccinic acid
DO detrusor overactivity
DLPP detrusor leak point pressure
dMRI dynamic magnetic resonance imaging
DTI diffusor tensor imaging
EAS external anal sphincter
EAUS endoanal ultrasound ultrasound sonography
ED erectile dysfunction
eGFR estimated glomerular filtration rate
EMG electromyography
EPI echo planar imaging
FI faecal incontinence
FISP fast imaging with steady-state precession
FOV field of view
HASTE single-shot turbo spin echo
HOXA Homebox A
IAS internal anal sphincter
ICC intraclass correlation
ICM iliococcygeal muscle
ICTP carboxy-terminal telopeptide of type I collagen
IIQ-7 incontinence impact questionnaire
IP interference pattern
ISD intrinsic sphincter deficiency
IVU intra venous urography
IVS intravaginal sling
LAM levator ani muscle
LLM longitudinal layer muscle
LMR longitudinal muscle of the rectum
LUT lower urinary tract
LUTD lower urinary tract dysfunction
LUTS lower urinary tract symptoms
MCC maximum cystometric capacity
MEP motor evoked potential
MMPS matrix metalloproteinases
MRI magnetic resonance imaging
MPL midpubic line
MSA multiple system atrophy
MU motor unit
MUP motor unit potential
NSF nephrogenic systemic fibrosis
PA puboanalis
PAG periacqueductal grey
PCL pubococcygeal line
PD Parkinson's disease
PET positron emission tomography
PFMT pelvic floor muscle training
PGPI patient global perception of improvement
PICP propeptide of type I procollagen
PIIINP amino-terminal propeptide of procollagen III
PIVS posterior intravaginal slingplasty
PMC pontine micturition centre
POP pelvic organ prolapse
POP-Q pelvic organ prolapse quantification
PFMT pelvic floor muscle training
PNTML pudendal nerve terminal motor latency
PRM puborectalis muscle
PUV posterior urethrovesical (angle)
PVM pubovisceral muscle
PVR post-void residual
QST quantitative sensory testing
RCT randomised controlled trial
SCP sacrocolpopexy
SCr serum creatinine
SE spin echo
SEP somatosensory evoked potential
SERMS selective estrogen-receptor modulators
SFEMG single fibre electromyography
SII symptom impact index
SMA supplementary motor area
SO symphysis orifice (distance)
SSF sacrospinous fixation
SSFSE single-shot fast spin echo
STP superficial transverse perineal muscle
SSI symptom severity index
SSR sympathetic skin responses
STARD Standards for Reporting of Diagnostic Accuracy
SUI stress urinary incontinence
T/A turns/amplitude
TE echo time
TGF-β transforming growth factor-β
TIMP tissue inhibitor of metalloproteinases
TOT transobturator tape
TPUS transperineal ultrasound
TR repetition time
TVT tension free vaginal tape

UAR urethral axis at rest
UAS urethral axis straining
UEBW ultrasound estimated bladder weight
UI urinary incontinence
UP urethropelvic (angle)
UPP urethral pressure profile
USI urodynamic stress incontinence
USL uterosacral ligament
USS ultrasonography
UTI urinary tract infection
UUT upper urinary tract
VB vestibular bulb
VCCU voiding colpo cystourethrography
VCUG voiding cystourethrogram
WA white American

I. INTRODUCTION

The Committee was given the task of updating the evidence on imaging, neurophysiological testing and other tests in the field of urinary and anal incontinence. The Medline, Embase and Cochrane databases were searched for the relevant subjects from February 2016 to January 2021. All references obtained from the database search were screened for relevance, full text papers were obtained and reference list were used as additional source of evidence where appropriate.

The chapter covers different issues including: imaging, neurophysiological testing, and other investigations (laboratory tests, tissue analysis and pad test) in the paediatric and adult population, male and female subjects, neurogenic and non-neurogenic patients.

The following keywords were used for the difference subjects:
- Imaging: the Medline database was searched using the following keywords: imaging, urinary incontinence, continence, anal incontinence and faecal incontinence; the search has been limited to period from 2016 to 2021.
- Neurophysiology: clinical neurophysiology, conventional urodynamics, neurourology, urinary dysfunction.
- Other investigations: keywords including urinary incontinence, continence, pad test, urinalysis, urine culture, cystoscopy and tissue analysis were used.

Members of the committee were allocated the different topics of the chapter based on their specific expertise in the field. The first draft of the chapter was reviewed by all committee members, the final draft was then edited first by the Committee Chair and then by the book Editors.

Diagnostic techniques were evaulated with reference to the technique and its standardisation, intraobserver and interobserver variability, diagnostic accuracy, cost/benefit ratio and clinical benefit. The level of evidence was graded taking into consideration that imaging, neurophysiological testing and the other tests pertain to the area of “diagnosis” and the quality of the published papers was graded according to the criteria specific for this area. Areas of future research were identified.

Notwithstanding the large body of evidence, research on imaging in anal and urinary incontinence, its clinical benefit remains questionable. Test-retest, intraobserver and interobserver accuracy are often provided for diagnostic tests although diagnostic accuracy is difficult to evaluate due to a lack of a gold standard. When ultrasound is used to measure bladder volume, catheterisation can be used as a reference standard and accuracy can be easily calculated but when sphincter volume is calculated with ultrasonography, there is no solid reference standard except another imaging technique (e.g.: MRI) or the validity of an imaging measurement is tested against another weak test such as Valsalva Leak Point pressure or the maximum urethral closure pressure. Imaging can either be performed to better understand the pathophysiology of incontinence and pelvic organ prolapse and it may be of importance, although no immediate clinical benefit is evident (e.g.: calculation of sphincter volume with ultrasound). It can be performed as a diagnostic test in patients undergoing surgery so that quantification of the clinical benefit requires complex clinical trials (e.g.: MRI of pelvic organ prolapse in patient undergoing prolapse repair) in which different reference standards can be used (e.g.: physical examination or anatomic finding during surgery). Although imaging can sometimes offer a better understanding of the anatomy underlying the condition (e.g.: presence of an enterocele) the clinical benefit of this additional information may not be observed in all patients.

Although imaging is clearly a difficult area for research, the consensus regarding introduction of a diagnostic test into our daily practise must rely on the evidence of clinical benefit in terms of safety, outcome or cost-benefit ratio.

Imaging studies belong to the area of diagnostic studies, they should follow the suggestions of the STARD initiative and they differ substantially from other types of clinical trials (1). The aim of clinical studies of diagnostic tests should be to provide information regarding the diagnostic accuracy of the proposed test although, this is not always possible.

A few considerations regarding the levels of evidence in imaging studies may be instrumental in reading this chapter and are summarised herewith.

Imaging of parameters with known prognostic value (e.g. PVR)
- The first issue is to prove that imaging studies image what they are supposed to image. Although the issue may be trivial in case of PVR imaging or anal sphincter imaging, the issue is relevant in other areas (eg: enterocele imaging) and should be approached by using imaging in cadavers or other approaches such as intraoperative confirmation of the observed condition as a gold standard.
- When the imaging is quantitative, accuracy versus a quantitative gold standard technique should be provided. When the imaging is qualitative (e.g. presence or absence of vaginal vault prolapse) the diagnostic value should be provided (sensitivity, specificity, positive and negative predictive value, accuracy, interrater and intrarater variablity).
- Once validity has been proven, one can assume that the predictive value of the imaging study is equal to that observed for the parameter measured with the gold standard. The same applies to its value for patient management.

Imaging of parameters with unknown prognostic value (e.g. MRI of the pelvic floor)
- When the imaging is qualitative (eg: intact versus damaged levator ani), once validity is proven, the diagnostic value should be investigated providing sensitivity, specificity, positive and negative predictive value, accuracy, interrater and intrarater variability in cadavers or patients undergoing surgery.
- Once validity is proved, the prognostic value for patient management should be investigated.
- Confirmation of the proposed imaging study by independent groups is required ideally for both validity and prognostic value

or at least for the latter parameter (we can assume that confirmation of the prognostic value is obtained, validity of the imaging technique can be inferred).

II. IMAGING IN URINARY INCONTINENCE AND PELVIC FLOOR DYSFUNCTION

This is a broad area that often requires a multiprofessional and muldisciplinary approach. The patient population is heterogenous including children, female and male subjects suffering congenital malformation of the genital and urinary tract, neurogenic disorders, iatrogenic conditions and traumatic lesions. Clinical guidelines always refer to the so called “standard patient” but the majority of subjects referred to secondary and tertiary referral centres cannot be defined as such and their management sometimes requires deviation from guideline recommendations. The large variability and the uniqueness of the observed cases may justify the adoption of a knowledge-based management in the absence of proven clinical benefit. Research on imaging of urinary incontinence (UI) and genital prolapse remains very active. Although all guidelines recommend not to use imaging in the evaluation of the standard patient, many clinicians believe this is an ideal adjunct to physical examination in evaluating the anatomical condition of the individual subject.

1. IMAGING OF THE UPPER URINARY TRACT

Urinary incontinence is defined as the complaint of any involuntary leakage of urine, it can be urethral or extraurethral (1). This latter condition either results from congenital anomalies such as ectopic ureters (inserting in the female distal urethra or vagina), iatrogenic or traumatic conditions such as fistula. In some patients, lower urinary tract dysfunction (LUTD) causing UI, might compromise the transport of urine from the kidneys to the bladder resulting in hydronephrosis and renal failure. The relationship between high bladder storage pressure and renal deterioration was first identified in myelodysplatic children and then considered to apply in all neurogenic patients (2) and automatically transferred to male and female patients with or without neurogenic problems; the value of 40 cmH2O of bladder pressure as threshold value at which the upper urinary tract (UUT) is at risk should therefore be used with caution. In male patients, chronic retention of urine can be associated with UI and lead to chronic renal failure. Lewis et al. reported that renal function at baseline and at the time of catheterisation were significantly worse in patients with chronic retention than with acute retention (3). Therefore, UUT imaging is needed in patients with urinary retention, especially with chronic retention. In women, severe urogenital prolapse may cause angulation of the pelvic ureter by the uterine arteries leading to hydronephrosis (4)

1.1. Indications

Generally speaking, there is no need for UUT imaging in patients with UI unless any of the previously described conditions is suspected or diagnosed. In children with extraurethral incontinence imaging of the UUT helps to identify the underlying cause.

The objectives of UUT in the incontinent patient are as follows:

- Evaluation of the UUT when the presence of an ectopic ureter or ureterovaginal fistula are suspected.
- Evaluation of the kidneys whenever UI is related to bladder dysfunction with high storage pressures (e.g. in neurogenic voiding dysfunction, chronic retention with overflow or low compliance bladders)
- Exclusion of hydronephrosis in cases of UI associated with severe uterine prolapse.

1.2. Techniques

UUT imaging modalities include intravenous urography (IVU), ultrasound sonography (USS), computerized tomography (CT scan), magnetic resonance imaging (MRI), and isotope scanning. No data regarding reproducibility, specificity, sensitivity, positive and negative predictive value in relation with the diagnosis and management of UI are available. The choice of the imaging modality also depends on availability, expertise, and local management policies. Generally speaking, low cost and low risk techniques such as USS are preferred. Unless otherwise described, the following considerations regarding the different imaging modalities are based on expert opinion.

1.2.1. Ultrasonography

USS is the gold standard technique for primary imaging of the UUT because of the relatively low cost of the equipment and the examination, its wide availability, the lack of any exposure to ionizing radiation. Renal USS is independent on kidney function and provides a good evaluation of kidney morphology. Concomitant renal disorders such as urinary lithiasis and neoplasms can also be diagnosed. In patients with LUTD, the detection of hydronephrosis is of importance and it can be related to either vesico-ureteral reflux or obstruction. USS is used for the first line evaluation of the UUT conditions in neuropathic patients. Sixteen percent of chronic spinal cord injured patients with hyperreflexic bladder had UUT deterioration revealed by USS, while 17.5% of patients with areflexic bladder also had it (5). UUT deterioration more frequently occurred in hyperreflexic bladder with higher reflex detrusor contraction pressure (115 vs. 72 cm H2O) mostly accompanied by type 3 detrusor external sphincter dyssynergia, and in areflexic bladder with higher storage detrusor pressure (58 vs. 24 cm H2O). In patients adequately managed with clean intermittent catheterization annual USS monitoring without routine urodynamic testing was suggested to be an effective surveillance strategy (6). UUT deterioration was demonstrated in 70 of 193 myelodysplastic patients who underwent USS, voiding cystourethrography, DMSA scan, and urodynamics at three years old (7). The sensitivity and specificity for UUT damage were 91.4%and 22.3% in DLPP >20 cm H2O, 77.1% and 32.0% in DLPP>30 cm H2O, and 52.9% and 51.8% in DLPP >40 cm H2O, respectively. Therefore, a DLPP cut-off value of 20 cm H2O showed a higher sensitivity to predict UUT damage instead of 40 cm H2O. In the cross-sectional survey of Dutch urologists 91.5% of them performed USS at least once every 1-5 years during the follow-up of adult myelodysplastic patients (8).

USS is also used to detect hydronephrosis in prolapse patients. Hydronephrosis was revealed by USS in 5%-50% of patients with pelvic organ prolapse (POP) that reconstructive surgeries were indicated for (9). The proposed mechanisms for hydronephrosis are 1) ureteric compression between the uterine body and the urogenital hiatus, and 2) ureteral kinking caused by the cardinal ligament (9). It was reported that hydronephrosis occurred in 12.6%-22.4% of patients with severe ureterovaginal prolapse as well as 3.9%-7.1% of patients with severe vault prolapse, indicating that hydronephrosis developed after hysterectomy (10, 11). It was supposed that the ureters may be pulled down and kinked by the downward traction of prolapse upon the bladder (9). Dancz et al. reported that 30.6% of their POP patients had hydronephrosis,

and that Ba-point (OR 1.68, 95% CI, 1.22-2.12), not C-point, and maximum cystometric capacity (OR 1.50, 95% CI, 1.08-2.07) were associated with hydronephrosis on a multivariate analysis (9). On the other hand, Beverly (11) and Gemer (12) reported that 7.7% and 17.4% of patients, respectively, had hydronephrosis, and that uterine prolapse was associated with hydronephrosis on multivariate analysis (OR 3.8, 95% CI, 1.4-10.5 and OR 1.9, 95% CI, 1.1-3.2, respectively). The presence of hydronephrosis do not affect the surgical procedures for POP repair and hydronephrosis improves in 70-100% of patients after surgery (10, 13). Therefore, USS should be performed in women with advanced POP, especially when surgical intervention is not indicated or delayed (9). Although, no strict correlation exists between the degree of dilatation and the severity of obstruction, the grade of hydronephrosis is correlated with the extent of cortical damage (14). In children, kidneys with a pelvic diameter >20 mm are considered to be at risk for deterioration and require intervention (15). Measurement of the resistive index in the interlobar and arciform arteries of the kidney has been proposed for the diagnosis of urinary obstruction but this is rarely used in the evaluation of the incontinent patient (16). Whenever hydronephrosis is diagnosed on USS, other imaging modalities are often used to evaluate renal function, the degree of obstruction or vesico-ureteral re ux. USS is an ideal technique to follow the degree of hydronephrosis over time or the response to treatment.

1.2.2. Intravenous Urography

IVU is the original radiographic examination of the UUT which allows evaluation of UUT anatomy and function. Recent Canadian guidelines recommended that a serum creatinine level (SCr) should be obtained, and an estimated glomerular filtration rate (eGFR) should be calculated within 6 months as an outpatient who is stable or within 1 week for inpatients and patients who are not stable (17). Patients with an eGFR of ≥60 mL/min have an extremely low risk of contrast-induced nephropathy (CIN) (17). Fluid volume loading remains the single most important measure, and hydration regimens that use sodium bicarbonate or normal saline solution should be considered when GFR < 45 mL/min in patients who receive intravenous contrast (17). Patients are most at risk for CIN when eGFR< 30 mL/min (17). Additional preventative measures include the following: avoid dehydration, avoid contrast medium (CM) when appropriate, minimise CM volume and frequency, avoid high osmolar CM, and discontinue nephrotoxic medications 48 hours before administration of CM (17). Also, Japanese guidelines showed that chronic kidney disease (CKD, eGFR< 60 mL/min/1.73 m2) is the most important risk factor to predict the risk of CIN in patients receiving iodinated contrast media (18). In addition, aging and diabetes associated with CKD are risk factors for the development of CIN (18). Recent systematic review recognised pre-existing CKD, diabetes, age, and cardiovascular comorbidity as risk factors (19). The existing guidance documents agreed in recommending pre-hydration as the main preventive measure, but there was difference in recommended total volumes, composition, rate and duration of the infused solutions (19). There was no consensus on the use of sodium bicarbonate and none recommended N-acetylcysteine as solitary preventive measure (19). Recent guidance documents recommend avoiding hypertonic contrast media, but did not recommend preference of iso-osmolar over low-osmolar contrast media (19). During IVU successful examination is dependent upon adequate renal capacity to concentrate urine, the poor concentration capacity of an impaired kidney limits the possibility to delineate the collecting system. A number of different conditions such as renal dysfunction, obstruction, congenital anomalies, fistula, stones and tumors may be detected. IVU is the appropriate first study in cases of extraurethral incontinence. When ectopic ureter is suspected (although this condition can also be responsible for urethral incontinence), delayed films and tomography are important because the renal unit or moiety associated with an ectopic ureter is often poorly functioning. In fact, IVU is sometimes unable to detect a small, malfunctioning moiety associated with a duplication and ectopic ureter or a poorly functioning or abnormally located kidney with a single ectopic system (20-22). In such cases where the diagnosis of ectopia is still suspected after IVU, another imaging modality such as CT, MRI or isotope scanning should be considered (23- 25). IVU is the appropriate first imaging study when uretero-vaginal fistula is suspected, usually after pelvic surgery. Typically, one sees ureteropyelocaliectasis proximal to the level of the fistula. This finding has been reported in 84-92% of cases (26, 27). Sometimes extravasation can be seen. Confirmation of the presence of the fistula, its size and exact location is often obtained with retrograde ureteropyelography.

1.2.3. Computerised Tomography (CT scan)

High quality information of the UUT anatomy can be obtained using multidetector helical CT scans and 3D reconstruction software. Differently from IVU which only acquires images in the anteroposterior or oblique CT acquires images in the axial plane. Pictures can then be reconstructed in 2D along any plane or in 3D when- ever required. CT scan can be used irrespective of renal function when no iodinated contrast medium is used. Whenever hydronephrosis is present, urine can be used to delineate the collecting system reducing the need for contrast agents. In general, intravenous contrast medium is required to highlight specific anatomic characteristics. CT scan is often used after the first line evaluation with USS and it has replaced IVU almost entirely. Several authors have reported the use of CT scan to detect ectopic ureter, in cases where the diagnosis is suspected, despite a normal IVU and ultrasound (28). In these cases the small size and poor function of the ectopic moiety make diagnosis difficult by IVU.

1.2.4. Magnetic Resonance Imaging (MRI)

MRI shares some of the advantages of CT over IVU in the evaluation of the UUT. Furthermore acquisition can be performed along any plane and pictures can then be presented in a 2D or 3D fashion. The paramagnetic contrast medium is free of allergic reaction risk although its use in the UUT remains dependent upon renal function and concerns about its nephrotoxicity have been recently raised (29). Low risk gadolinium contrast agents should be the choice, and dosage should be kept to a minimum, as higher doses have been linked to the development of nephrogenic systemic fibrosis (NSF)(30). While a pre-existing pro inflammatory state in the renal impaired is a high risk factor, liver insufficiency in itself is not a contraindication; however, patients may also have coexisting renal insufficiency and thus carry a risk of NSF (30). The development of the uro-MRI technique has gained an increasing role for the technology in the evaluation of hydronephrosis and urinary tract anomalies as an alternative to IVU. The use of MRI in the diagnosis of ectopic ureter has recently been described (31-35).

1.2.5. Isotopes

Isotopes are used primarily to examine morphological and functional characteristics of the upper urinary tract. Isotope scanning can be used to identify the location of a small kidney which is otherwise difficult to image with radiological techniques. Renography is used to examine the differential function of the two kidneys, to identify disorders of urine transit and to quantify obstruction of the upper urinary tract. There are many physiological factors and technical pitfalls that can influence the outcome including the choice of radio-nucleotide, timing of diuretic injection, state of hydration and diuresis, fullness or back pressure from the bladder, variable renal function and compliance of the collecting system (36, 37). Diuresis renography with bladder drainage is recommended when obstructi-

ve uropathy is suspected (38). Renal scintigraphy may be useful in the evaluation of ectopic ureters associated with hypoplastic kidneys (39). Detection rates of dysplastic kidney in single system ectopic ureter were 95.5% on DMSA, 95.5% on CT scan, 50% on USS, and 50% on MRI (40). DMSA would be a preferred option in this setting, because of its high detection rate and not requiring contrast medium.

1.2.6. Conclusions

Imaging of the UUT is rarely required in UI unless the condition originates from a malformation, a traumatic or an iatrogenic problem of the UUT. More rarely a condition of the lower urinary tract may endanger renal function, the preservation of which is required to guarantee a normal life expectancy in patients with UI.

1.2.7. Consensus Statement

- Imaging of the UUT is NOT indicated in the evaluation of non-neurogenic stress, urgency or mixed UI. (**Level of Evidence 3, Grade of Recommendation C**)
- Imaging of the UUT is indicated in cases of:
  - neurogenic UI with high risk of renal damage (due to high storage and/or voidingdetrusor pressure, e.g. myelodysplasia, spinal cord injury) (**Level of Evidence 3, Grade of Recommendation C**)
  - chronic retention with UI (**Level of Evidence 3, Grade of Recommendation C**)
  - severe uterine prolapse, vault prolapse, or anterior vaginal wall prolapse, especially when surgical intervention is not indicated or delayed (**Level of Evidence 3, Grade of Recommendation C**)
  - suspicion of extra-urethral UI by upper tract anomaly (**Level of Evidence 3, Grade of Recommendation C**)
- The choice of the imaging techniques and their sequence depend on the clinical question and their availability. The least invasive techniques should be preferred and should precede the more invasive, also taking into consideration cost effectiveness. (**Level of Evidence 3, Grade of Recommendation C**)

1.2.8. Suggested Research Areas

Prevalence of upper tract deterioration in various UI populations

- Natural history of upper tract changes
- Relation between upper tract dilation imaging, renal damage and bladder function

2. IMAGING OF THE LOWER URINARY TRACT

The use of imaging of the LUT in patients with UI dates back 40 years more than that e.g. Jeffcoate 1950's, particularly in female patients. The techniques have changed, over the decades from static to dynamic imaging, from qualitative to quantitative information. Although some of the techniques are now more than 50 years old their clinical value remains at best, unclear.

2.1. X-Ray Imaging

Voiding cystourethrogram (VCUG) was the mainstay of x-ray imaging of the LUT but it has been replaced almost entirely by USS because of its ease of use, low cost and availability. While CT has not gained acceptance because of the exposure of ionising radiation, MRI took the lead as the most promising imaging modality because it offered a comprehensive view of the pelvis and enabled visualisation of the position of visceral organs in relation to bony reference points. 3D/ 4D USS offers volume acquisition with limitations in the depth of ultrasound wave penetration and the volume that can be imaged. Progressive technical developments in imaging technology and techniques have made this research area particularly interesting.

In males the purpose of voiding cystourethrography has been mainly to locate infravesical obstruction separating the bladder neck from benign prostatic obstruction although it may play a role in the management of post-prostatectomy incontinence (1). In children the diagnosis and classification of reflux and diagnosis of posterior urethral valves have been the primary goals (2). The severity of the vesicoureteric reflux on one side determines the development of contralateral reflux and indicates a poorer resolution rate for reflux (3).

Female urethral diverticula can be diagnosed with positive-pressure urethrography which is more sensitive than voiding cystourethrography (4-6). MRI is the gold standard for the diagnosis of diverticula and planning surgical repair (7, 8). Pelvic floor ultrasound has also been shown to demonstrate urethral diverticula as clearly as MRI (9). Ultrasound is known to be operator dependent. High frequency (5-9MHZz) transvaginal probe with 3D function can offer good visualisation of urethral diverticula.

The rationale for imaging studies of the lower urinary tract in this field derives from the hypothesis that stress UI is caused by urethral hypermobility. This was the theoretical basis of the classification of UI published by Green in 1968 and then modified by Blaivas and Olsson in 1998 (10, 11). Investigation into cohorts of continent and incontinent patients failed to provide evidence to support the hypothesis and imaging techniques aiming at measuring bladder neck displacement during straining have been abandoned. The same applies to outcome research in urinary incontinence where surgery that limits bladder neck displacement does not necessarily lead to cure of the condition. A renewed interest derived from the availability of USS which took imaging out of the radiology suites and moved it into the urological and gynaecological outpatient clinics opening new opportunities for clinical research in this field. The possibility of imaging what was usually perceived during physical examination such as bladder neck mobility or POP increased the usefulness of USS. Research in the field of MRI first assessed the possibility of fast dynamic acquisition to image the displacement of visceral organs during effort to better quantify POP and then the morphological imaging of the pelvic organs muscular support to investigate the physiopathology of genital prolapse.

2.1.1. Female Cystourethrography

X-ray imaging of the urinary bladder and urethra has been used to assess the female urinary tract in women suffering UI to evaluate urethral/bladder neck hypermobility and to assess associated conditions such as urethral obstruction, vesico-urethral reflux, diverticula, fistulae, stones and tumours. In males, the purpose of voiding cystourethrography has been mainly to locate infravesical obstruction (1, 12).

The diagnosis and classification of reflux and diagnosis of posterior urethral valves in children have been the primary goals (2). In a study comparing cystourethrography with direct radionuclide voiding cystography and voiding urosonography with contrast medium were compared. Voiding sonography and direct radionuclide voiding cystography were shown to be the most sensitive (13).

2.1.1.1. Background

History and methodology of cystourethrography in females had been reviewed by Olesen (6). The technique is now over 80 years old. Voiding cystourethrography with lateral projection was first done by Mikulicz-Radecki in 1931 (14). The use of a metallic bead chain to identify the urethra was introduced by Stevens and Smith in 1937, and in 1956 Ardran, Simmons and Stewart reported on a cinematographic technique with contrast media also in the vagina and rectum (15, 16). In an attempt to combine qualitative and quantitative information regarding the function of the lower urinary tract, the combined used of fluoroscopy and pressure-flow recordings was proposed during the nineteen sixties and seventies (17-21).

2.1.1.2. Methodology (projection, positioning and exposures)

Bladder neck displacement is best viewed and quantified in true lateral projection although image quality is sometimes poor because of the increased body mass and the overlap of bony structures with the bladder neck area. Consequently, oblique projections are sometimes used notwithstanding the lack of quantitative information. Achieving a quasi-physiological voiding in a radiology suite is difficult because of the inevitable impact of the environment. The use of a sitting position is recommended for micturition studies as voiding while standing or lying will increase the embarrassment and therefore many impair the quality of the examination (14). Especially in patients with large body mass index, imaging of female urethra in a true lateral projection is difficult, it necessitates high radiation doses as the central x-ray beam must penetrate the trocanteric regions and further because the urethrovesical junction is sometimes overshadowed by the lateral parts of the bladder. A significant improvement in this area has been brought about by digital imaging which allows the subtraction of the bony structures. The position and mobility of the urethrovesical junction as well as urine leakage are supposed to be influenced by the filling volume as has been demonstrated on ultrasonography and leak point pressure measurements (22, 23). However, in VCUG the bladder is filled to capacity. Addition of a urethral bead chain or catheter and vaginal contrast to improve the visualisation of the urethra, bladder neck and trigone has been abandoned. Contrast in the rectum is not necessary for urinary incontinence purposes. Exposures at rest should be supplemented with provocative manoeuvres to test bladder neck mobility by contracting and relaxing the pelvic floor (e.g. coughing, straining, and squeezing). Whenever possible, pictures while the patient is voiding should be obtained. It is important to consider that coughing and straining result in a different effect on the pelvic floor. Straining might be associated with relaxation or contraction of the pelvic floor, and the imaging can change accordingly.

During coughing there is a reflex contraction of the pelvic floor, but coughs are of a short duration and difficult to capture on spot films. Bladder suspension defects were diagnosed at rest in 49% of 420 examinations, while coughing and micturition disclosed a further number of 20% and 4% respectively (14). Squeezing can demonstrate pelvic floor awareness and contraction (24).

2.1.1.3. Combined imaging and urodynamics

Videourodynamics has been regarded by some as the “gold standard” in the evaluation of LUTD (24). Reproducibility of the combined examination has not been assessed and further the radiation dose has to be considered (16, 21, 25-27). One study has attempted to compare videourodynamics with saline cystometry (24). Independent observers carried out the two procedures with 75 women having the saline cystometry first and a further 75 women had videourodynamics first. The degree of bladder descent noted on screening was greater than on clinical examination. Nineteen women had trabeculation and a further 11 women had bladder or urethral diverticula, urethral stenosis and vesicoureteric reflux (1, 12, 15). Only seven of the eleven women could have been predicted by a selective imaging policy based on history alone which would image 43% of the 150 women. This suggests that a selective policy of screening will unnecessarily expose patients to radiation while not using the optimal technique for investigation for all patients who need the test. Nevertheless simultaneous videomonitoring along with tracings of pressure and urine flow rate are important to ensure that the exposures are made at appropriate moments so that the radiographs can be representative of the various functional states (14, 19, 28, 29).

Patients with Parkinson’s disease and multiple system atrophy are best evaluated by videourodynamics with sphincter motor unit potential analyses to identify the characteristic features of these conditions including: external sphincter denervation, neurogenic sphincter motor unit potentials, open bladder neck at rest and detrusor-external sphincter dyssinergia (30). Neurogenic patients show severe bladder trabeculation with diverticula and pseudodiverticula, pelviureteric reflux, widening bladder neck and proximal urethra, and narrowing at the level of the membranous urethra can suggest, the presence of neurogenic dysfunction of the lower urinary tract (occult spinal dysraphism, non-neurogenic neurogenic bladder (Hinman syndrome)) even in the absence of neurogenic symptoms and signs (31-33). Urodynamic parameters in children do not discriminate between those with or without vesicoureteral reflux thus videourodynamics has been considered essential. Additionally children with non-neurogenic voiding dysfunction are found to have a number of abnormalities with videourodynamics (34, 35). Indications for videourodynamics include previous continence and vaginal surgery, neurological disorders and suspicion of urethral diverticula.

2.1.1.4. Normal and defective bladder support

The whole issue about the clinical value of VCUG is about the pathophysiology of defective bladder support in the pathophysiology of SUI in female patients and the relation between the surgical correction of such a defect and cure. The concept of urethral hypermobility was central to the classification of SUI and the concept that impaired transmission of abdominal pressure to female urethra could be responsible for the observed leakage. Little remains regarding the concept of urethral hypermobility in a modern view of female SUI and this contributed to the decreasing use of VCUG in the evaluation of a standard female patient.

The normal resting bladder has a smooth surface although bladder trabeculation is often seen in elderly women and not necessarily related to any pathological condition. The internal urethral orifice is located just above a horizontal line through the lowermost part of the symphysis in a coronal projection. The urethra is straight and runs anteriorly and caudally toward the external meatus.

On coughing and straining, relaxation of the pelvic floor results in downward movement of the bladder neck, which can be associated with a backward movement of the bladder neck resulting in a change in urethral axis. Squeezing (and sometimes also straining) results in contraction of the pelvic floor muscle with a cranial movement of the bladder neck. During voiding the bladder base is usually lowered about 1 cm, the angle between the urethra and the trigone is straightened, making a funnelled appearance of the proximal urethra and the bladder base, the bladder contour is rounded and a fine sawtooth irregularity of the mucosa becomes visible above the trigone. Angles and distances between the urethra, bladder base and symphysis pubis have been assessed radiologically. The following parameters have been assessed for reliability:

1. The posterior urethrovesical angle (PUV) is defined by lines along the posterior urethra and the trigone (36). Cut off values were usually 115° or more (37, 38);
2. The urethral inclination is between the proximal urethral axis and the vertical plane, which is a plane outside the patient and, therefore, the angle also varies with pelvic inclination. In Green type I and type II descent the angle is less or more than 45° respectively (38);
3. The urethropelvic (UP) angle is measured during voiding as the anterior angle between a line through the middle of the internal urethral orifice and the urethral knee and a line through the posterior surface of the symphysis through the lowermost part of the obturator foramen closest to the film. In normal subjects the mean UP is about 95° and the cut off point for bladder descent are values below 70° (14);
4. Symphysis orifice (SO) distance is measured at rest as the distance on a horizontal line from the symphysis to the internal urethral orifice. Normal values are 31 ± 6 mm (mean ± SD) and values less than 20 mm are the cut off points for descent (14);
5. The urethral axis at rest (UAR) and during straining (UAS)

Funnelling of the proximal urethra and flatness of the bladder base (both anterior and posterior to the internal urethral orifice) and the most dependent portion of the bladder base (the urethrovesical junction or a point posterior to that) are important qualitative parameters estimated on straining films (37).

Anterior bladder suspension defects or bladder base insufficiency (BBI) is defined as SO < 20 mm with a normally positioned vagina at rest, during coughing or micturition and/or funnelling of the bladder base at rest or with coughing. BBI can be graded 1-3, which corresponds to Green's type I descent (14, 39). The supportive defect is supposed to be in the fascial and ligamentous system and their abnormal detachments (eg., paravaginal defects).

Posterior bladder suspension defects are defined as a posterior-inferior bladder displacement and a UP of less than 70° (14). It corresponds to Green's type II (40). Sometimes only the trigone and posterior part of the bladder is involved. The supportive defect is supposed to be in the muscular pelvic floor, that is, the pubo-vesical part of the pubococcygeus muscle or in paravaginal detachment.

Interestingly, when UAR and UAS were examined in a group of 76 continent women and correlated with age, a perfect linear regression was noted between UAR and age (R^2= 0.28). Patients with stress urinary incontinence were found to have an average UAR value of 25° with a mean UAS of 43° leading to a threshold value of hypermobility of about 20°. When standing cystourethrograms were repeated 3 to 6 months after surgery for SUI, UAR and UAS values were found to be close to normal suggesting a relation between the correction of the defective bladder support and cure (40). A more structured definition of cystocele (ranked by height in centimetres) was also obtained, adding to the emerging data that the reliability of the pelvic organ prolapse quantification (POP-Q) system increases when measurements are performed in a more upright position (40).

2.1.1.5. Reproducibility

The observer variation has been evaluated in four university uro-gynecological units (Table 1) (24, 37, 41, 42). The inter-observer agreement was 43-79% and the intra-observer agreement was 53-99%. These figures are in the same range as has been found for other diagnostic tests (43).

2.1.1.6. Accuracy for the diagnosis of SUI and post-operative results

Evaluation of accuracy is the mainstay in the evaluation of a diagnostic technique. The sensitivity and specificity of a diagnostic technique depend on intrinsic factors such as reproducibility (as measured by intraobserver and interobserver variation) and extrinsic factors such as the characteristic of the patient cohort used to assess accuracy.

The accuracy of the previously mentioned radiological criteria have been measured by comparing imaging data with the 'so called' index-test which in this case was a clinical diagnosis of urodynamic stress incontinence and expressed as specificity and sensitivity or as predictive values. Unfortunately, the diagnosis of SUI is controversial and might be based on subjective criteria, urodynamic tests, or measurement of leakage. Even radiological criteria have been included in the diagnosis.

Reproducibility (e.g. test-re-test agreement) has not been measured, but intra- and inter-observer variation has been calculated and adjusted for expected chance agreement (kappa coefficient). The predictive values and the kappa coefficient are supposed to depend on the prevalence, and therefore, comparison between different materials are difficult (43).

No consensus has been reached in the peer-review literature as to the lack of discriminant value of VCUG between SUI and continence, the majority of published papers are consistently negative although new promising data have been published (38, 40, 44-46).

The specificity of 5 radiological parameters on static bead chain VCUG was 44-76% and the sensitivity 53-100% (46, 47). Neither was the degree of SUI correlated with the type or degree of suspension defects (24, 41, 48). The positive and negative predictive values for a bladder suspension defect were 0.70 (95% C.I.: 0.62-0.78) and 0.52 (95% C.I. 0.41-0.63) respectively on voiding colpo-cystourethrography (39, 49). In a later publication on 159 women, positive and negative predictive values of 0.56 and 0.74 were obtained (46). Evaluation of the urethral angle at rest and during stress in controls and in patients with SUI and various grades of anterior vaginal prolapse show a significant relationship between UAR and aging (from 2.4° ± 14.9° in the third decade to 29° ± 9.2° in the 9th decade; r^2= 0.28). In patients with SUI, UAR and UAS decreased from 25.7° ± 13.6 ° and 42.6° ± 15.9° to 16.6° ± 14.7° and 23.8° ± 17.5°, respectively; the observed changes were found to be statistically significant. A similarly significant difference was found in patients with moderate to grade 3 cystocele and urethral hypermobility (at least 5 cm descent of the bladder base below the inferior ramus of the pubic symphysis on the lateral view of a standing VCUG): UAR and UAS decreased from 48.1° ± 16.5 ° and 64.4° ± 16.8° to 22.3° ± 26.9° and 29.8° ± 22.8°, respectively.

Comparison of a randomly selected control cohort (aged-matched) with patients suffering SUI showed a significant difference of UAR and UAS at diagnosis while similar values were found after surgery. This was similar to patients with grade 3 cystocele in whom both UAR and UAS were significantly different from controls at baseline while showed similar values in the postoperative follow-up.

Measurement of the cystocele height obtained as the distance between the inferior border of the pubic symphysis and the inferior edge of the cystocele in controls and patients with mild and severe cystocele showed a significant difference between the two cohorts (16.63 ± 10.9 versus 27.4 ± 12.3 mm versus 73.4 ± 15.6 mm, respectively). Following formal cystocele repair, a significant change

Table 1: Inter- and intra-observer variation (agreement) on cystourethrography in females with urinary incontinence

Type of examination, patients and observers	Inter-observer variation	Intra-observer variation
Bead-chain [1] stress & urgency incontinence n°92 3 observers on 5 landmarks	45.8-80.7 %	
VCCU [2] stress incontinence n° 52 1 observer on type of descent	79% 95% c.l. 65-89	
VCCU [3] stress incontinence n° 29 2 observers on type of descent	70% 95% c.l. 75-89	53% 95% c.l. 27-78
VCCU [4] n° 93 stress & urgency incontinence 6 observers on type of descent	43-60% kappa 20-39%	72-99% kappa 57-98%
VCUG [5] Stress incontinence n° 11 2 observers on urethral angle shift from rest to straining	r = 0.83 (p=0.001) for UAR r = 0.82 (p=0.002) for UAS	

[1] static bead-chain cystourethrography with straining (37). The 5 landmarks were the posterior urethrovesical angle, urethral inclination, funnelling of the proximal urethra, flatness of the bladder base and most dependent position of the bladder base;
[2] voiding colpo-cystourethrography (VCCU) at rest and with coughing, straining, micturition and squeezing; one observer against original diagnosis (that is, normal appearance or anterior, posterior or combined suspension defects) made by a few senior radiologists (23);
[3] voiding colpo-cystourethrography at rest and with coughing, straining, squeezing and micturition. Possible diagnoses were: normal appearance or anterior, posterior or combined descent respectively (42).
[4] voiding colpo-cystourethrography at rest, coughing, with holding and voiding. Possible diagnoses were: normal appearance and anterior or posterior descent respectively (41);
[5] standing voiding cystourethrography, urethral angle was measured at rest (UAR) and during straining (UAS) (40).

of cystocele height values was found in patient with mild and severe cystocele (from 27.4 ± 12.3 mm to 13.9 ± 18.0 mm and from 73.4 ± 15.6 mm to 25.4 ± 24.6 mm, respectively (p<0.001).

These are the first data supporting the use of standing VCUG as an outcome measured, previous peer-review papers suggested the inability of its technique to distinguish postoperative failures from success (14, 24, 43, 45, 47, 50-53).

2.1.1.7. Comparison of cystourethrography and ultrasonography

The development of USS techniques for the evaluation of the lower urinary tract raised the question of the relationship between X-ray and USS imaging. Static bead chain cystourethrography has been compared with transrectal and perineal USS and voiding colpo-cystourethrography has been compared with perineal USS (47, 48, 54, 55). The findings correlated well regarding bladder neck position and mobility, PUV, urethral inclination, SO distance and rotation angle.

Specificity, sensitivity and interobserver agreement were also comparable for the two methods. All the authors seem to prefer the sonographic modality because imaging can be performed at the same time as the physical examination. This has also been the case in men with neuromuscular dysfunction (12). Simple and extensive funnelling is more easily imaged in upright patients during cystourethrography than in the supine position frequently used for ultrasound studies (31).

2.1.1.8. Comparison of cystourethrography and MRI

The introduction of MRI in the assessment of the LUT required adequate comparison of this technique with standard X-ray imaging. The comparison of cystourethrography and colpocystourethrography with dynamic MRI showed comparable data on bladder neck position and cystocele extension (56, 57). Although there is an obvious concern about the fact that dynamic MRI imaging is usually performed with the patient lying in a dorsal lithotomy position, comparison of standing and lying colpocystourethrography did not show any significant difference (57).

2.1.1.9. Conclusions

VCUG does not have a major role in the evaluation of the standard female patient with UI confirmatory results on the clinical utility of measuring urethral angle and cystocele height in patients with UI and POP who are scheduled for surgery still missing. Defective bladder support can be diagnosed on VCUG with a reliability comparable with other diagnostic tests.

Dependent on local facilities the method might be considered if the choice of a surgical procedure is based on type and degree of supporting tissue deficiencies and possibly if new procedures are evaluated for the ability to restore this deficiency.

2.1.1.10. Consensus statement

Cystourethrography is NOT indicated in primary uncomplicated stress, urgency or mixed female urinary incontinence (***Level of Evidence 3, Grade of Recommendation C***).

Cystourethrography may be a reasonable option in the preoperative evaluation of complicated or recurrent female urinary incontinence (***Level of Evidence 3, Grade of Recommendation C***).

2.1.1.11. Suggested Research Areas

Variation of VCUG parameters in patients with USI +/- ISD and prognostic value for surgical repair.

VCUG parameters in re-do surgery for USI compared with controls

2.2. Ultrasonography

The pelvic floor structures that can be visualused include the urethral sphincter, anal sphincter and perineal body. Ultrasonography has been used in the evaluation of urinary incontinence as early as 1980 (58). Over the past three decades the quality of the ultrasound image and its processing has improved beyond what could have been imagined during the 70's. Various new developments, such as the use of contrast medium, colour Doppler, 360° degree transducers and 3D and 4D imaging have been introduced and have led to the more widespread use of ultrasonography in the evaluation of the lower urinary tract and pelvic floor disorders.

There is a good correlation between ultrasound and x-ray evaluation of urinary incontinence (59-68). In particular, the position of the bladder neck at rest and during Valsalva manoeuvre has frequently been compared (67, 69), and all authors agree on a good correlation. Some authors even found better accuracy for ultrasound (62), especially in obese women (59). Ultrasonography is cheaper than X-ray imaging, it is often preferred by physicians because the imaging studies can be performed in their own office as part of the physical examination. Ultrasound requires the probe to be in direct contact with the patient at all times for the images to be acquired including during dynamic manoeuvres. Overall, ultrasound is highly acceptable to patients, because it does not involve radiation, particularly when compared to comparable imaging modalities for the posterior compartment.

2.2.1. Types of Ultrasonography

Different imaging approaches have been used for pelvic floor ultrasound, such as transabdominal, transvaginal, transrectal, transperineal and transurethral. Synonyms for the transperineal approach are perineal, introital, labial or translabial access, all use a similar method and there does not appear to be a substantive difference between these terms, a common agreed term needs to be decided upon. See Figure 1 for an example of an image from a 2D mid-sagittal trasnperineal scan in a healthy asymptomatic nulliparous woman.

Abdominal ultrasonography is not helpful in pelvic floo imaging because of the acoustic shadow caused by the pubic bones particularly in the obese patient (58). All approaches in ultrasound have a problem of distorting the tissue being imaged due to compression. With vaginal ultrasonography this risk is highest (70). Perineal ultrasonography allows the visualisation of all three compartments in one image. A study comparing endovaginal, transperineal with fluoroscopic and MRI proctograms, showed that endovaginal ultrasound is the most likely to underdiagnose prolapse, as it may act as a pessary, followed by transperineal ultrasound (71). Fluoroscopic proctography done sitting on a commode was the most physiological and was the most likely to demonstrate the pathology present.

Three-dimensional ultrasonographic systems has increased accuracy in measuring volumes of irregular structures as well as reconstructed images from novel directions and allowing pelvic floor imaging. Three-dimensional ultrasonography was first described for the female urethra in 1999 (72); the three-dimensional image can either be evaluated as a separate entity on the screen, or in combination with each of the two-dimensional planes from which it is derived (**Figure 1**). These three two dimensional planes are orthogonal to each other: the sagittal, coronal and axial planes. Three-dimensional images are built up as a rendered image of a self defined region of interest, major advantages over 2D imaging include the possibility of reviewing the acquired images from any investigator and the ability to analyse the acquired volume through any plane (similar to CT scans or MRI) (**Figure 2**). The disadvantage is that it is time consuming and requires specialist software analysis that is not practical in clinical practice.

The levator ani muscle can be visualised in 3D and 4D ultrasound (73).

The pelvic floor includes the vaginal walls, bladder, urethra, anal canal, perineal body, rectum and puboviscerales muscle (also known as levator ani muscles). The pelvic floor can be visualised with ultrasound and other imaging techniques (non-ultrasound) including X- ray cystourethrograms (74-76), magnetic resonance imaging (56, 77) and defaecation proctography (78). Computer tomography (CT) is not the modality of choice to visualise the pelvic floor. Pelvic

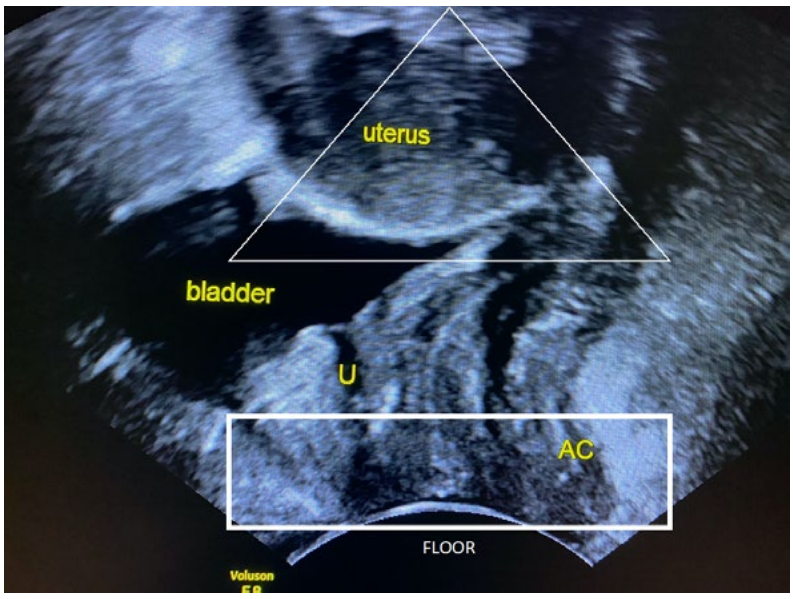


Figure 1. Transperineal ultrasound panoramic view with 2D midsagittal ultrasound. U - urethra. AC -anal sphincter complex.

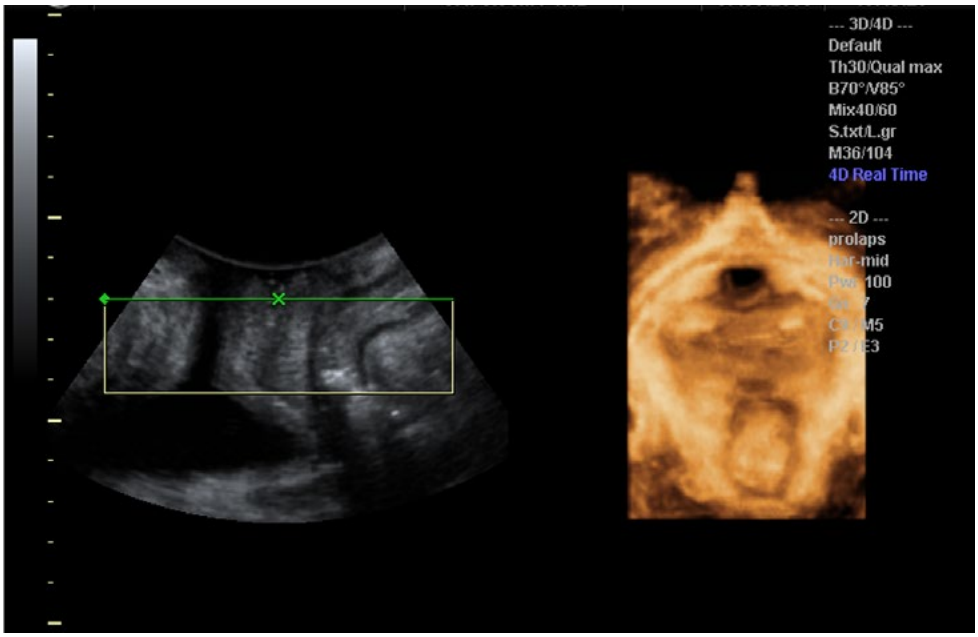


Figure 2a: Perineal midsagittal two-dimensional view and three-dimensional rendered image. Normal anatomy.

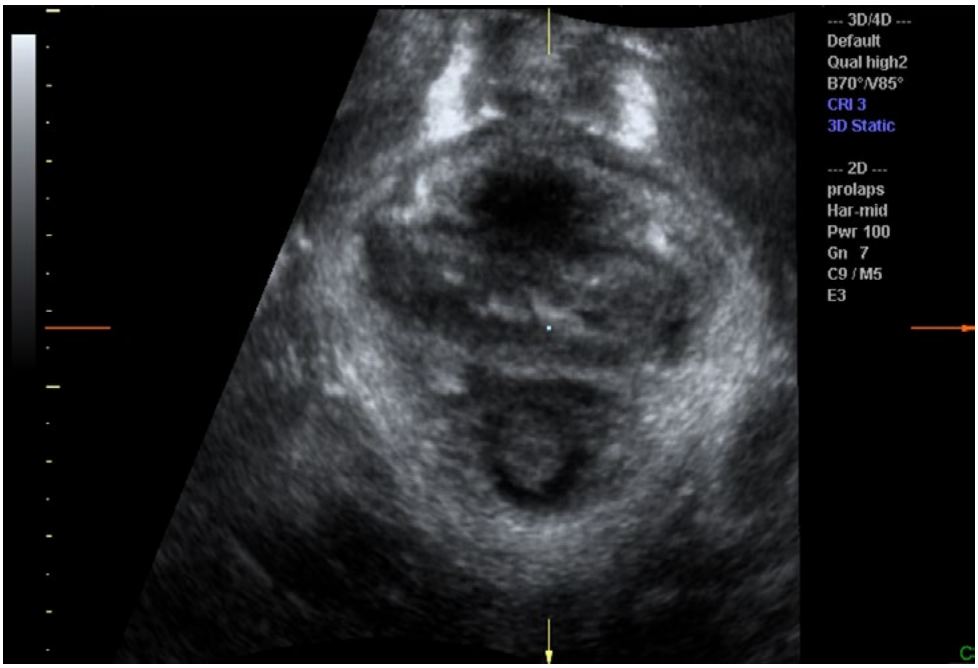


Figure 2b Perineal midsagittal two-dimensional view. Normal anatomy of the levator ani muscle.

floor imaging, including ultrasound, seeks to diagnose and assess conditions including urethral diverticulum, fistula, surgical and mesh complications. Pelvic floor ultrasound includes transperineal, endovaginal and endoanal techniques (79). A wide variety of techniques have been described for the measurement of different structures on the pelvic floor since the 1980s. Consequently, a wide variety of probes and ultrasound machines have been used. The frequency of the scanning probe can affect the image quality and measurements acquired (80). The detail in the method of measurement and route of scanning (transabdominal, transvaginal or transperineal) can change the data acquired (81). These observations highlight the importance of these considerations when reviewing the literature.

Some techniques require offline analysis with specialist software on a computer away from the scanner. Offline analysis requiring techniques lend themselves mainly for research as this is cumbersome and time-consuming, therefore suitable for use in out-patient clinics. Techniques that can provide bedside data have greater

potential to be applied in clinical practice widely for the benefit of patient care. In clinical practice, the pelvic floor is assessed by the POP-Q score, which has been shown to correlate well with pelvic floor ultrasound assessment (82-84).

Pelvic floor imaging is challenging because of the dynamic pelvic floor organ movement. The dynamic nature of the pelvic floor during Valsalva manoeuvre and pelvic floor contraction, change the measurements acquired during scanning. Maximal Valsalva manoeuvre can produce increasing values on each attempt. An MRI study of repeated maximal Valsalva manoeuvres showed that 95% of women pushed the prolapse further on the second and third attempts (85) with the difference of first and third attempt being more than 2cm (85). Prolapse grade severity appearance has been shown to change on a supine versus a sitting position on MRI (86). The levator hiatus on 3D ultrasound is worse on standing (87). The positional differences are more marked for the posterior compartment (88).

2.2.2. Standardisation

No consensus has been reached as to the standardisation of image orientation. Some prefer orientation with cranial structures below (**Figure 3a**) (72) whereas others prefer presentation of the cranial parts above (**Figure 3b**) (89, 90). All authors agree that the symphysis pubis, and its inferior border in particular, is a well recognisable and fixed reference point. This point can be used in the evaluation of the various aspects of relevant structures at rest and during dynamic imaging. In general, ultrasonographic studies are performed in the supine position, with the knees flexed and comfortably apart (**Figure 4**). Small differences between the supine and standing position of the patient have been documented, although these differences disappeared during a Valsalva manoeuvre (91). Only a few studies have been performed in the standing position (92). There is no clear consensus on the amount of bladder filling, some authors prefer significant bladder filling, others prefer a nearly empty bladder because an empty bladder seems to descend more on Valsalva manoeuvre compared with a full bladder (93). Attempts to standardise Valsalva manoeuvre, ideally with intra-abdominal pressure measurements, has not been widely accepted (94). In one study a peak flow meter has been used where women were asked to “huff” maximally and to reach the same force during a number of “huffs” (92). It has been shown that the mobility of the bladder neck differs between coughing and Valsalva manoeuvre (95). Co-activation of the pelvic floor muscles during Valsalva manoeuvre has been documented and is one of the reasons for the lack of standardisation (95, 96).

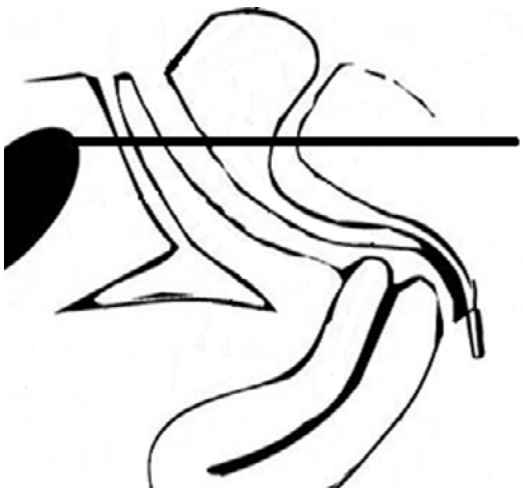


Figure 3a: Perineal midsagittal two-dimensional ultrasound view on three compartments and horizontal reference line according to Dietz.

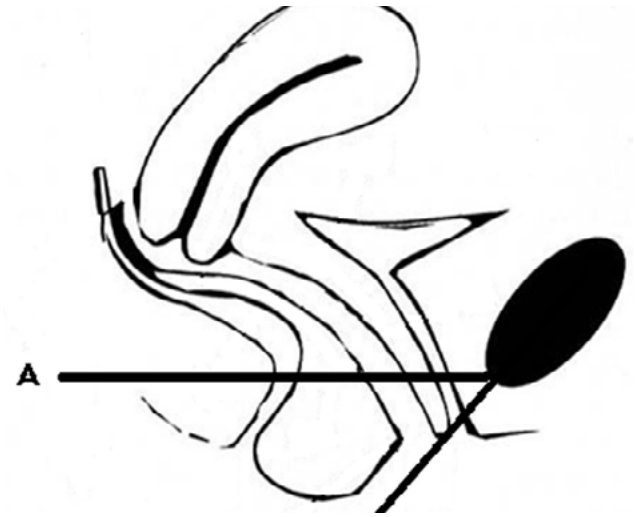


Figure 3b Perineal midsagittal two-dimensional ultrasound view on three compartments and reference lines according to Tunn and Schaer (61, 89).
A= horizontal reference line.
B= central line of the symphysis as reference line for bladder neck descent.

2.2.3. The Urethra and Bladder Neck

When collagen fibres and muscle fibres are located parallel to the ultrasound beam, the structure becomes hypoechoic. These same structures will become hyperechoic, however, when the fibres are located perpendicular to the beam. Ultrasonography may result in variable images of the urethra, since the echogeneity of the structures depends on the position of the transducer in relation to the urethra. This may produce confusing images, especially in the dynamic process of pelvic floor contraction and Valsalva manoeuvre. In the midsagittal plane on perineal ultrasonography, and with normal anatomical position of the urethra at rest, the internal sphincter and inner urothelial layer of the urethra will appear hypoechoic (Figure 1), thus making these structures indistinguishable on ultrasonography. In the midsagittal plane and with normal anatomical position of the urethra at rest, the striated external sphincter or rhabdosphincter will appear hyperechoic, and can hardly be distinguished from the surrounding structures. It will, however, be easily visible as a hyperechoic circular structure in the axial plane as seen on three-dimensional ultrasonography (97, 98). The rhabdosphincter has been found to be thinner dorsally (72), and both ventrally and dorsally (98) by various authors and more difficult to distinguish from the internal sphincter ventrally and dorsally compared with laterally (99). These differences may be due to the approach used to image the structures as well as types of probes applied but this has not been addressed in any study to date.

With the use of ultrasonography, thickness and length of the urethral sphincter muscle can be measured and urethral volume calculated (90, 99, 100).

Intra-urethral ultrasonography has been used for this purpose although complete imaging of the lateral parts of the sphincter are difficult due to the higher frequencies emitted by these probes (101),

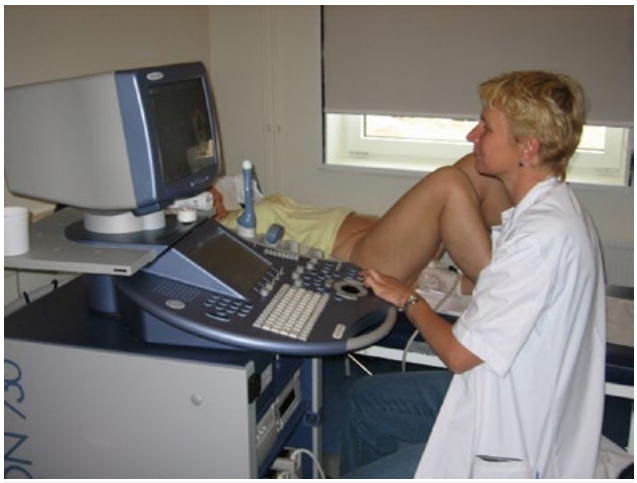


Figure 4 Perineal ultrasound examination in the supine position.

others have used two- or three-dimensional ultrasonography of the urethra (72, 97, 98, 102).

Comparison of transvaginal and transrectal approach showed a lower degree of urethral compression with the latter approach (100, 103). Ultrasound measurement of the female urethra has been found to be reproducible (72, 97, 103). Sphincter volume may differ significantly when 2D or 3D imaging is used (97). Urethral volumes, measured by 3D ultrasonography, were positively correlated with the actual volumes in cadavers (99). A significant and positive correlation between rhabdosphincter volumes and symptoms and signs of urinary incontinence has been reported (104); correlation with the urethral pressure profile (UPP) measures has also been found (101, 102) but these data could not be reproduced (105). Ultrasonography imaging during micturition has been explored with the aid of a remote control systems (106). The use of intra-urethral ultrasonography with rotating probes (360°) has been proposed by various authors although no advantages over perineal US could be identified and incomplete imaging appears to be a problem due to the high ultrasound frequency emitted (104, 106-110).

The advantage of preoperative and intraoperative three-dimensional ultrasound scanning in women with urethral diverticula has been outlined by Yang et al (111, 112).

2.2.4. Bladder Neck

The bladder neck and proximal urethra are easily visible on all types of ultrasonography without the need for catheterisation (Figure 1). The terms urethral descent and bladder neck descent are interchangeable. Measurements are usually taken at rest, during straining (Valsalva manoeuvre), and sometimes during a cough and squeeze. The position and movements are measured in relation to the lower margin of the symphysis pubis. The difference between rest and strain is referred to as the bladder neck descent (the distance between the bladder neck and a horizontal line through the lower end of the symphysis pubis) (**Figure 5**). On Valsalva manoeuvre the bladder neck rotates in a posterior and inferior direction away from the symphysis pubis. The axis of the urethra in relation to a vertical or horizontal line can be measured in degrees and provide the degrees of urethral rotation or bladder neck mobility. Other parameters are the posterior urethrovesical angle and the anterior urethrovesical angle.

The first 2D technique for the assessment of urethral descent was described by Schaer in 1995. The Pubis was used as the reference line for assessing the descent of the bladder neck (proximal urethra)(61). Schaer measured the retro-vesical angle in the context of assessing for urethral funnelling seen in stress urinary incontinence (61). The Schaer method should be performed with a bladder volume of 300ml supine, standing, coughing, with pelvic floor contractions and the Valsalva manoeuvre (61). Later, the technique was developed to assess urethral movement in two planes (113, 114). Transperineal ultrasound has been shown to correlate well with lateral chain ultrasonography (60). The disadvantage of this technique is that it generates negative vectors when the bladder neck descends below the Pubis. This was followed by a 2D technique based n the Pythagorean theorem: $V= \sqrt{[(Vx-Rx)2 + (Ry-Vy)2]}$ (113, 114). Detailed analysis of urethral descent at 6 points along the urthral length in 3D/4D ultrasound based on the Pythogorean theorem formula, showed that the distal urethra is the most stable part of the urethral anatomy (115). Using this as a given, the bladder neck descent can be assessed during dynamic 2D scanning, where the bladder neck descent can be assessed relative to the position of the urethra at rest, by using the properties of parallel lines (116).

Urethral descent validated the use of ultrasonography in the assessment of the position and mobility of the bladder neck and proximal urethra. Good results for this validity testing have been reported (61, 94, 116-118). See Table 2.

Bladder neck descent is associated with stress incontinence (42, 44, 119, 120). Clinical techniques for the assessment of bladder neck descent include the Q-tip test (121, 122). Assessment of bladder neck descent is of relevance in clinical practice because patients with greater bladder neck mobility are more likely to benefit from stress incontinence surgery (121).

Multiparous women demonstrate a greater bladder neck mobility compared with nulliparous women (123-125). Bladder neck hypermobility is considered to be related to stress urinary incontinence (90, 105, 126). Ultrasonographic findings are correlated with urodynamic parameters (68, 127-134). Specificity and sensitivity of ultrasonography for the diagnosis of stress incontinence were 83% and 68% in one study (128) and 92% and 96% in another study (135). Other studies have demonstrated that ultrasonographic findings of bladder neck descent and rotation of the retro-vesical angle increase the odds for SUI by 2.5, however they concluded that ultrasonography's low diagnostic value does not allow it to replace urodynamics (136).

Table 2. Bladder neck descent in asymptomatic women. (from VA thesis) (submitted to Imperial college for VA thesis)

Technique	N	Cohort characteristics	Mean (mm)	Reference:
$V= \sqrt{[(V_x-R_x)^2 + (R_y-V_y)^2]}$	25	Antenatal (AN) third trimester vs post-natal (PN)	Bladder neck descent on Valsalva **Primips**: AN 15.6 +/- 6.9 vs PN 22.2 +/- 8.7 (p<0.001) **Muptips**: AN 11.4 +/- 5.5 vs PN 19.9 +/- 7.8 (p<0.001) **Elective Caesareans**: AN 9.5 +/- 2.5 vs PN 10.4 +/- 3.1 (p=0.3)	Peschers et al (114)
Schaer et al, 1995 (61)	46	Pregnant vs Non-pregnant controls	Pregnant (P) vs Control (C) **Supine Rest:** P Dx 1.7 +/- 2.5 vs C 0.4 +/- 0.8 (p=0.006) P Dy 30 +/- 5 vs 32 +/- 5 (p=0.09) **Supine Valsalva** P Dx 7 +/- 4 vs C 7 +/- 4 (p=0.2) P Dy 9 +/- 6 vs C 7 +/- 4 (p=0.3) **Standing Rest** P 4 +/- 4 vs C 1.2 +/- 2.2 (p=0.04) P 27 +/- 5 vs C 27 +/- 5 (p=0.3) **Standing Valsalva** P 8 +/- 5 vs C 10 +/-6 (p=0.09) P 7+/-4 vs C 8 +/- 4 (p=0.3)	Meyer Bachelard & De Grandi, 1998 (137)
Meyer et al, 1998 (137)	40	10-15 vs 16 – 26 years old Asymptomatic	Mean bladder neck descent (p=0.9) **10-15 years old**: 5.3mm **16 – 26 years ol**d: 5.4mm	Brandt et al (138)
Pirpiris et al, 2010 (115)		Urodynamic Stress incontinence (USI) vs other urogynaecology complaints 90% parous	Bladder neck descent (p=0.001): **USI** 3.1 +/- 0.9 vs **other** 2.6 +/-1.1	Pirpiris et al, 2010 (115)
Dietz, 2004 (90)	15	Bladder neck descent in asymptomatic young women during Gymnastics exercises (Pilates Clam, shoulder bridge, abdominal press, tiptoe). No vaginal births.	Bladder neck descent **without** pelvic floor pre-contraction: 2.3-4.4mm descent **with** pre-contraction, and elevation: 2.3-4.4mm was observed (p=ns)	Baessler & Junginger, 2017 (139)
Asfour et al, 2020 (116)	21	Healthy nulliparous non-pregnant volunteers	Bladder neck descent **Controls**: 6.2mm, SD 3.1, 95%CI +/- 1.5, (range 2.2 -14.9)	Asfour et al, 2020 (116)

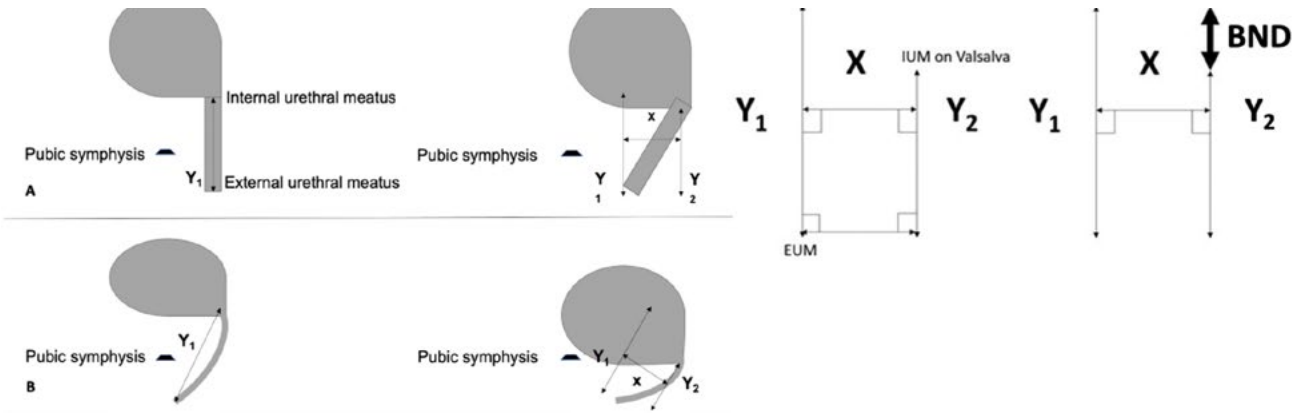


Figure 5. Diagram representation of urethral descent assessment technique. (A) The urethral at rest is uncurved and upright. (B) The urethra at rest is curved and tilted. Y1 is the length of the urethra when the urethra is straight. IUM: Internal urethral meatus; EUM: External urethral meatus; BND: bladder neck descent (116).

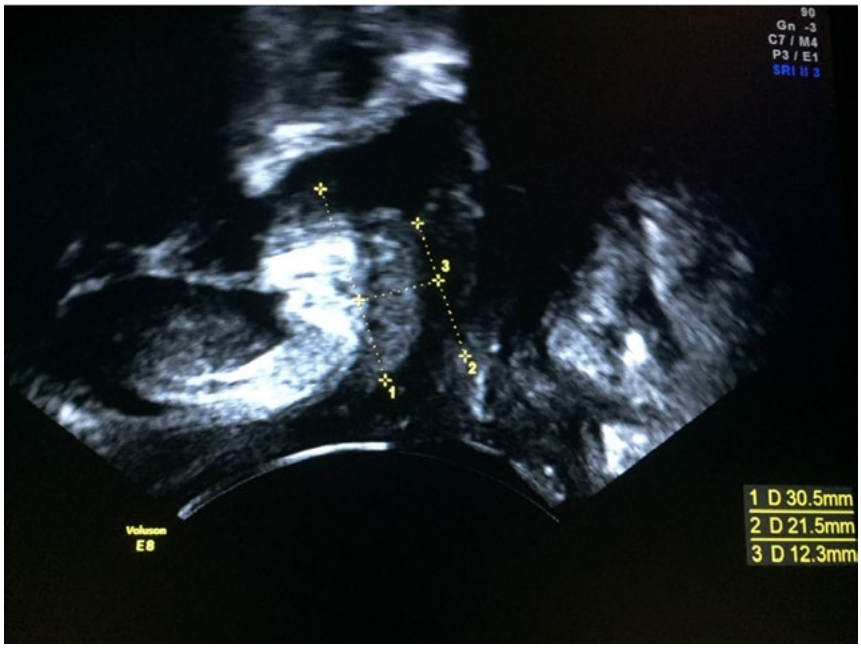


Figure 6. Urethral descent assessment in a healthy nulliparous volunteer without prolapse. The urethral length at rest was 30.5mm, the bladder neck moved forward 12.3mm. The bladder neck descent was 9mm (30.5-21.5 = 9).

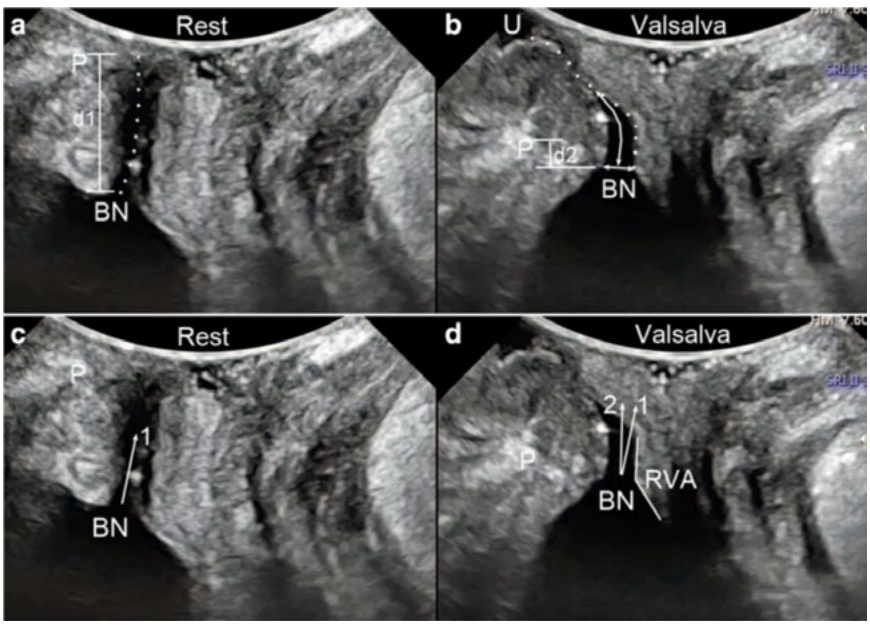


Figure 7. Transperineal ultrasound images in the mid-sagittal plane during real-time leaking. A and C were taken at rest, B and D during the Valsalva manoeuvre. A and b Urethral movement during the Valsalva manoeuvre; the dotted line in A shows the urethra at rest while in B it shows the urethra during the Valsalva manoeuvre. The length of the dotted line is equal to the urethral length. B Funnelling measurements (the long arrow shows the funnelling length and the short arrow shows the funnelling width) and urine leakage, seen as fluid (urine) between the external urethral orifice and the probe surface. A and b Measurement of the position of the bladder neck relative to the posterior inferior margin of the pubic symphysis (P); the difference between these measurements during the peak of the Valsalva manoeuvre and at rest (d1–d2) produces the value for bladder neck descent (BND). C and d Measurement of the urethral rotation angle (URA), which is the angle between the proximal urethra at rest (arrow 1) and during the Valsalva manoeuvre (arrow 2). D The retrovesical angle (RVA) during the Valsalva manoeuvre, which is measured between the proximal urethra and the trigone. P: symphysis pubis, BN: bladder neck, URA: urethral rotation angle, RVA: retrovesical angle, U: urine. (140)

A randomised controlled trial in primigravidae suggested that PFMT can play a preventative role in reducing the risk for SUI despite not conveying a significant change in bladder neck descent (141).

One research group has specifically investigated simultaneous perineal ultrasonography and urethrometry. They demonstrated that the variations in urethral pressure were caused by the activity of the urethral sphincter as well the pelvic floor muscles (142). The contractions from the urethral sphincter during acute stress events such as coughing are thought to be due to fast contractions. Some studies have used ultrasonography to optimise patient management, but despite the abundant literature on the use of ultrasonography in the investigation of women with urinary incontinence, disappointedly, a clinical advantage in terms of patient outcome has not been reported until now (143, 144).

Urethral funnelling can be observed on ultrasonography (**Figure 7**) particularly with the use of contrast agents. It is a typical finding in women with stress urinary incontinence but can be seen in asymptomatic women as well (145, 146). In a study on stress incontinent women, funnelling was found to be present in nearly all women (147). Urinary incontinence can be demonstrated by the use of colour Doppler of the urethra (148, 149). Colour Doppler has, furthermore, been used to visualise the periurethral vasculature in nulliparous women (150) and differences have been described between continent and incontinent women (151, 152) and before and after oestrogen supplementation in postmenopausal women. Data with the use of high frequency endovaginal ultrasonography have highlighted differences in urethral vascularity amongst continent women with parity (153). Doppler velocimetry has been used in a study on the vascularisation of the levator ani musculature and a correlation has been found between the absence of an end-diastolic flow and the presence of stress urinary incontinence (154). The blood flow around the urethra and bladder has been studied with Doppler before and after insertion of tension free vaginal tape and the transobturator tape. The blood flow decreases only after insertion of the tensional free vaginal tape whereas the blood flow was unchanged after insertion of the transobturator tape which may relate to the direction of urethral compression (155). Data showed no difference in urethral vascular indices measured by endovaginal ultrasound between women with SUI who were managed surgically or conservatively (156).

2.2.5. Determination of the Post Void Residual Urine and Bladder Wall Thickness

Ultrasonography is the gold standard technique for measuring bladder volume and post-void residual urine (157-161). Ultrasonographic data have been compared with residual volumes obtained by in and out catheterisation under ultrasound control and were found satisfactory. Although there is no universally accepted definition of high urine residual volume, there is consensus on the need for a short interval between voiding and post-void residual (PVR) measurement and the preference of ultrasound bladder volume measurement over urethral catheterization (162). However, Khan et al. have challenged the methodology of some studies and found deficiencies in all reports on the topic (163). A simple formula often used is (Height * Width* Depth cm) * 0.7= Volume (ml) in which the factor 0.7 is the correction for the non-spherical shape of the bladder. Automated ultrasound systems for measuring bladder volume and post-void residual have been developed and found to be more accurate than standard ultrasound measurements, furthermore they can be used by health care providers with no training in ultrasound imaging (164). However, measurement of bladder volume can easily and accurately be facilitated by use of cheap, standard 2D ultrasound machines, irrespective of the calculation formula used, even in women with severe pelvic organ prolapse (165). Automated bladder scanners are widely used and are, in general, experienced as reliable enough for clinical use, however, in the case of ascites (166) or an ovarian cyst (167) for example, the estimated urinary volumes can be incorrect, and in post partum women.

Normal values for the post void residual urinary volumes in asymptomatic women have been presented; in 60 year-old women, the median residual volume was 19 ml, and 95% of women had a post void residual volume of less than 100 ml (158). The ICS Urodynamics Committee has published its Good Urodynamic Practice recommendations regarding PVR measurement suggesting that for clinical practice a PVR <30 ml can be considered insignificant, while residual volumes persistently >50 ml could be regarded as important. They also suggested that large PVR (>200–300 ml) often indicates LUTD, acknowledging however that no level of residual urine, of itself, mandates invasive therapy and no PVR threshold is yet established for decision-making (162).

Ultrasound measurement of bladder wall thickness (BWT). Ultrasound measurement of BWT was first proposed as a non-invasive method for diagnosing infravesical obstruction in children (168). BWT was validated by measuring the thickness of the bladder by ultrasound and with microcalipers (80). Higher frequency ultrasound yielded measurements the closest to the microcliper measurements. BWT has been used to predict the outcome of children with primary nocturnal enuresis (168-170). BWT has also been proposed as a risk factor for upper urinary tract deterioration in children with myelodysplasia (171). Measurement of BWT was also proposed to diagnose bladder dysfunction (detrusor overactivity and detrusor hypocontractility versus normal detrusor function) in children with urinary tract infections (172, 173). Additional parameters such as the bladder wall thickness index (length x width x depth of the bladder at full bladder/average BWT) were proposed and a nomogram for the paediatric population provided (174).

In the adult population, higher BWT values have been measured in men than in women. Thickness may certainly differ depending the measurement technique; values of 3.3 +/- 1.1 mm and 3.0 +/- 1.0 mm, respectively were reported by Hackenberg and co-workers (175). Oelke confirmed a significant difference between male and female detrusor thickness (1.4 versus 1.2 mm, respectively) (176). A small increase of detrusor hypertrophy with age has been reported in both genders (174). In men, measurement of bladder wall thickness proved to be the most sensitive parameter (outperforming uroflowmetry) to diagnose BOO in patients suffering LUTS (177, 178). These findings were corroborated by the results of more ultrasonographic studies by use of automated bladder scanners (179).

Transvaginal ultrasound was first proposed in 1994 for the measurement of BWT in women with bladder volume of less than 20 ml. A large review of all studies on BWT with all three modes of imaging (transvaginal, transperineal and transabdominal) showed that the measurement is best measured by the transvaginal route (180). See Figure BWT. A significant difference was shown in patients with DO and USI (6.7 +/- 0.6 versus 3.5 +/- 0.6 mm, respectively). Low intraobserver and interobserver variability were measured: 0.02 mm in both with a 95% confidence interval of -0.22 to 0.18 and -0.32 to 0.35 mm, respectively (181). In 1996, Khullar and co-workers showed how ultrasound measurement of BWT is a sensitive method for diagnosing DO in symptomatic women without bladder outlet obstruction with 94% of women with BWT greater than 5 mm having involuntary detrusor contractions on videocystourethrography or ambulatory urodynamics (182). In 2002, the same group showed no overlap in the 95% confidence intervals of BWT between pa-

tients with DO and USI in women with storage symptoms, confirming the potential of this parameter for diagnosing DO (183). More data on the diagnostic value of transvaginal ultrasound in patients with overactive bladder symptoms confirmed a sensitivity of 90 % and specificity of 78 % for predicting OAB, when a cut off value of 4.78 mm was used (AUC = 0.905) (184). Conversely, a large UK-based cross-sectional test accuracy study found no evidence that BWT had any relationship with DO, regardless of the cut-off point, nor any relationship to symptoms as measured by the ICIQ-OAB; the authors concluded that despite patients' wide acceptability of the method BWT measurement was not sufficiently reliable or reproducible to predict DO (185).

In 2003, a study on ultrasound cystourethrography in women confirmed a significant association between age and intravesical pressure at maximum flow with BWT (186). Researchers have also demonstrated reduction in BWT following urethrolysis in women with bladder outlet obstruction resulting form anti-incontinence surgery (81). Methodological and technical issues in the ultrasound measurement of bladder wall thickness and weight remain open and constitute a major limitation for a more widespread use of these parameters. In 2005 Chalana and co-workers published an early report on automatic measurement of the ultrasound estimated bladder weight from three-dimensional ultrasound (187). An average value of 42 +/- 6 g was measured in healthy male subjects. A standard deviation of 4 g was seen among measurements performed in the same subject at different bladder volumes (200 to 400 ml). Normative values for UEBW and BWT in healthy female volunteers were calculated by another group by use of an automated bladder scan device showing mean values of 32.23g (SD +/- 4.9) and 1.62 (SD +/- 0.34), respectively (188). Further research in this area is certainly needed and further improvement in the accuracy of automated systems is eagerly awaited.

Although data published in the peer review literature on this subject are quite consistent, two discordant papers were published from Australia. Blatt and co-worker showed uniform values of BWT measured using an abdominal approach among men and women with non-neurogenic voiding dysfunction suggesting this parameter cannot be used to diagnose storage or voiding dysfunction; this may reflect the thinning of the bladder wall with increasing bladder volume (176, 189, 190). A retrospective study on women undergoing translabial ultrasonography suggests a significant association between BWT and DO although a low diagnostic accuracy was shown for the diagnosis of DO (191), which could be due to translabial ultrasound being a less reliable technique (192).

The association between detrusor hypertrophy and bladder dysfunction (DO and BOO) is a well established fact in Urology. Reduction in bladder wall thickness is observed after the relief of bladder outlet obstruction (81). The development of automated ultrasound systems for measuring UEBW is instrumental to foster further research in this area, particularly in the management of patients with LUTS (193) and in the evaluation of bladder response to pharmacological treatment (177).

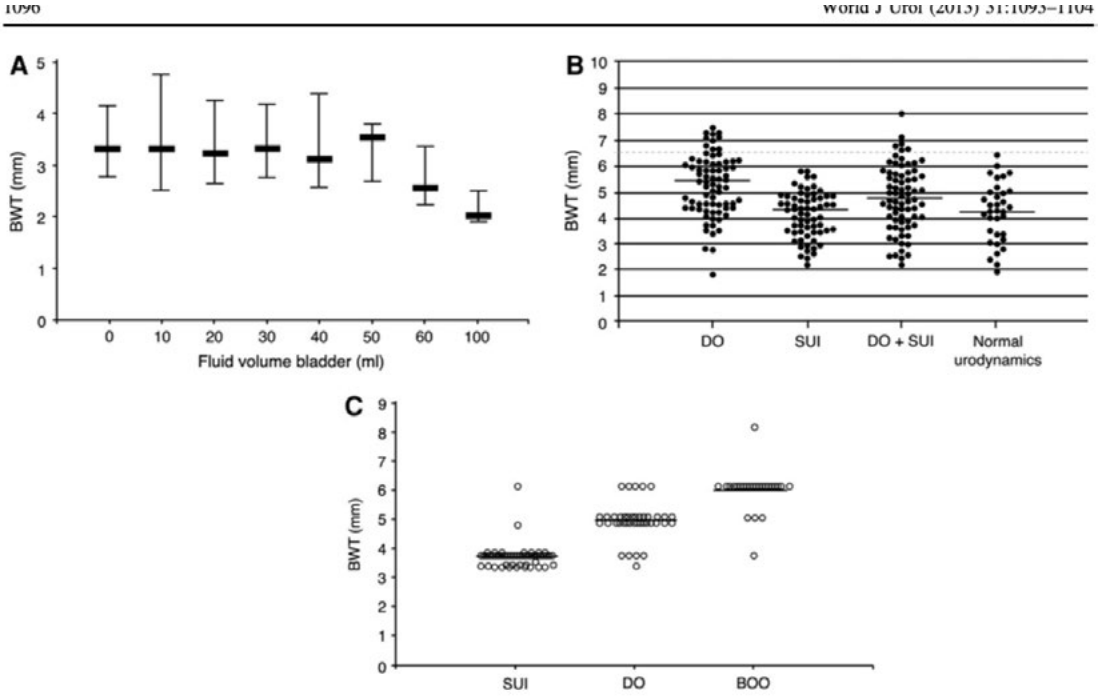


Fig. 2 **a** Mean BWT changes with increasing bladder volume in women with genuine stress urinary incontinence. A decrease in BWT was observed only when bladder-fluid volume exceeded 50 ml. *Black bars* indicate the median, *error bars* indicate the range. Source: Khullar et al., Ultrasound Obstet Gynecol 1994 [11]. **b** *Scatter plot* illustrating the BWTs of females with different urodynamic diagnoses from Serati et al. (2010). The *dotted line* represents a BWT threshold of 6.5 mm. Source: Serati et al., Int Urogynecol J 2010 [15]. **c** Correlation between BWT and urodynamic diagnoses from Kuhn et al. (2011). Mean BWT values are significantly different between urodynamically diagnosed groups ($p < 0.0001$). Source: Kuhn et al. Neurourol Urodyn 2011 [16]. *BWT* bladder wall thickness, *DO* detrusor overactivity, *SUI* stress urinary incontinence, *BOO* bladder outlet obstruction

Figure 8: Graphs showing ultrasound female bladder wall thickness changes with bladder volume and difference in ultrasound female bladder wall thickness with different urodynamic diagnoses (180)

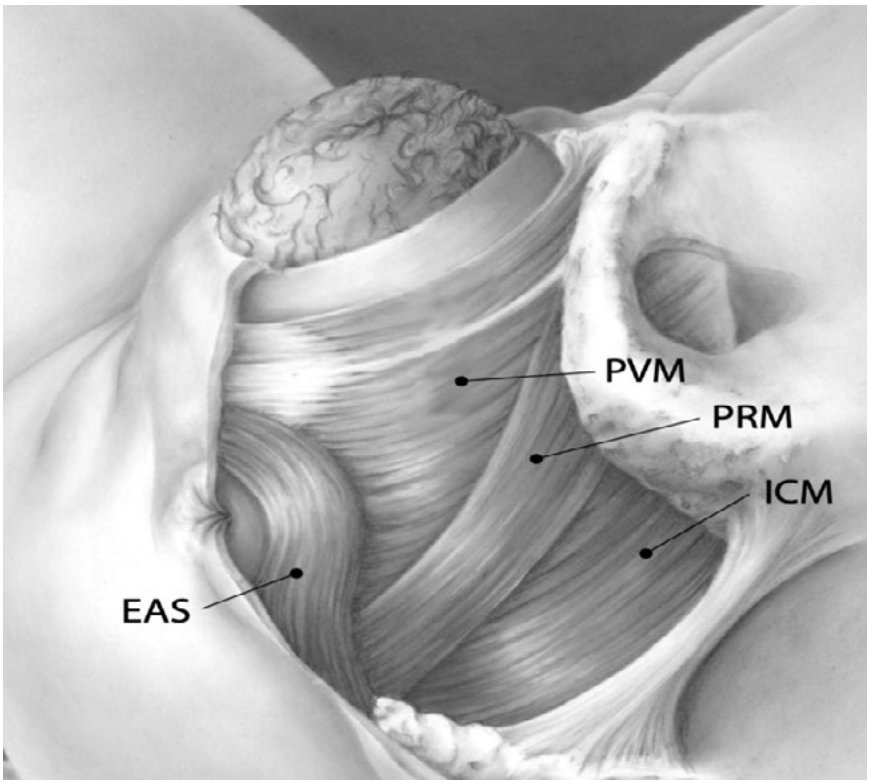


Figure 9: A left inferior view illustrating the pubovisceral muscle (PVM), which originates behind the pubic bone and forms the most distal portion of the levator ani muscle. It is particularly stretched late in the second stage of labor as the fetal head is driven by stron 2-maternal pushes, at 3-minute intervals, through the birth canal to crown. EAS: external anal sphincter, ICM: iliococcygeal muscle, PRM: puborectal muscle. (194) © DeLancey

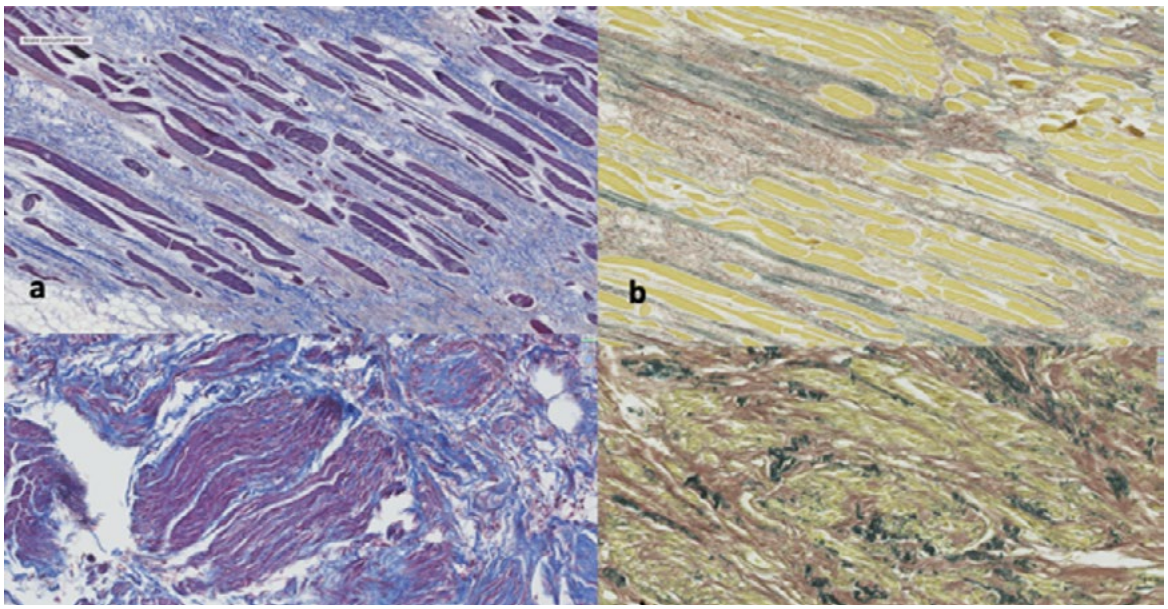


Figure 10. Pubovisceral enthesis muscle in cadavers; a. Masson Trichrome stain in normal enthesis; b. Van Gieson stain in intact enthesis; c. Masson Trichrome in cadavers with appearance of avulsion on ultrasound; d. Van Gieson stain in cadavers with appearance of avulsion on ultrasound. (195)

2.3. Ultrasound techniques for assessing the pelvic floor

A wide range of techniques that may be clinically applied have been described. The pelvic floor has been assessed with a wide variety of ultrasound machines and probes. The technology used is important because it can change the appearance of the image obtained. See Figure 11 for an example of the same image taken in 2D with three different ultrasound probes on a Voluson E8. See Table 3 for a summary of different pelvic floor techniques that have been described for the assessment of the pelvic floor.

The most established technique in clinical practice is endoanal ultrasound for the assessment of obstetric anal sphincter injuries (OASI). The clinical application

of these ultrasound techniques peri-operatively is not fully established (153). Ultrasound in not routinely recommended in current clinical guidelines for neither the assessment or the management of incontinence or prolapse.

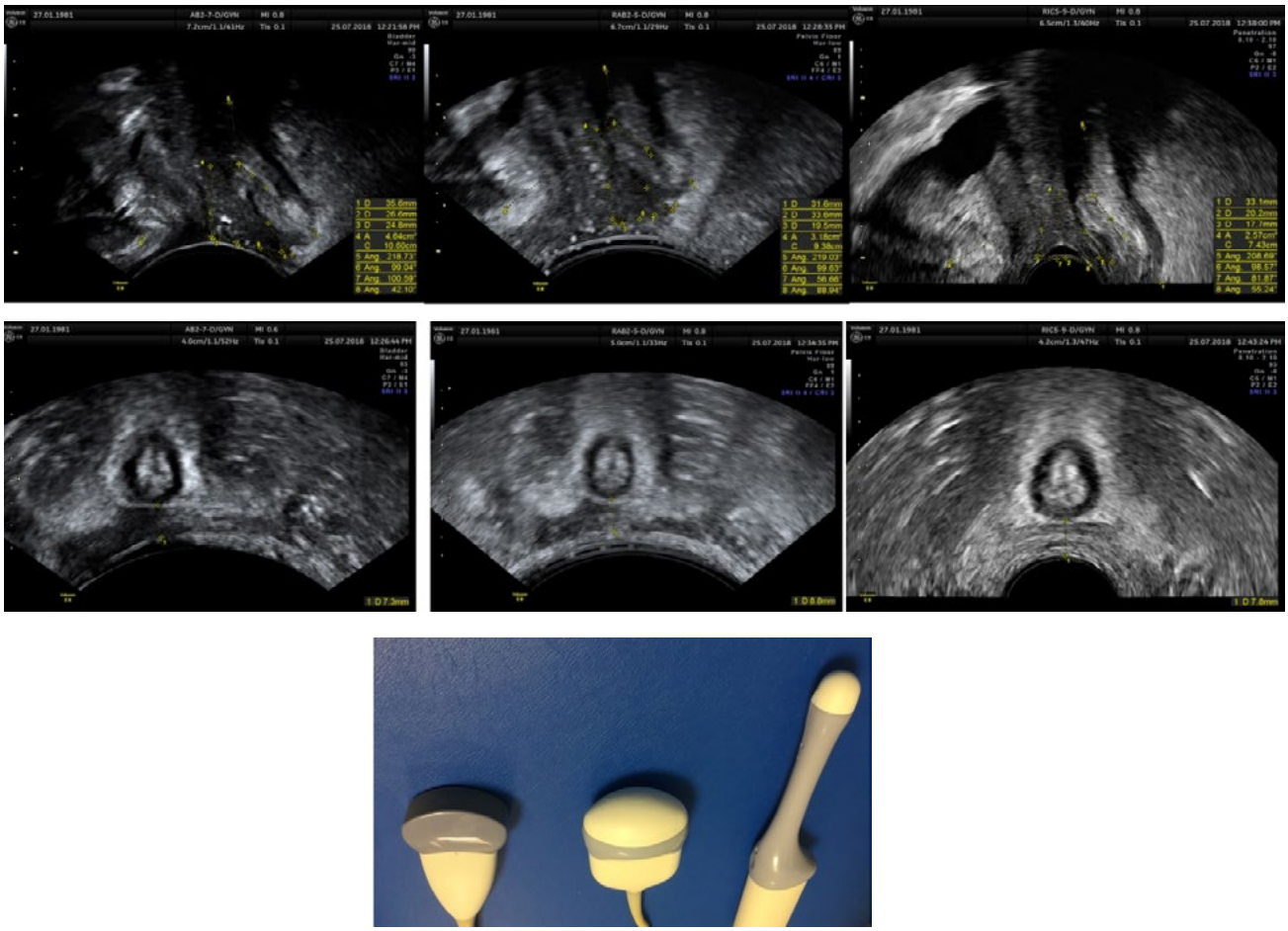


Figure 11. Pelvic floor ultrasound in 2D. The top row of images are mid-sagittal, the 2nd row of images are coronal angled downwards towards the anal canal. The second image shows in order the probes with which these images were acquired: 7 MHz (AB27D); 5 MHz (RAB25D); 9 MHz (RIC50D)

2.4. Perineal body

The perineal body fuses with the anal sphincter, anterior to the anal canal. The perineal body is where the muscles of the pelvic floor from both sides fuse together (puborectalis, transverse peronei and the bulbospongiosus muscles). The perineal body used to be called the 'central tendon' of the perineum (196). Histological studies have shown that the perineal body is entirely made out of striated muscle (197). Therefore, it may be more appropriate to refer to it as the central confluence of the pelvic floor muscles (not a tendon). The perineal body size can be evaluated in the mid-sagittal plane on 2D transperineal ultrasound (198). Prolapse is associated with a smaller perineal body. Perineal body mobility can be assessed with 3D transperineal ultrasound (199). Increased perineal body mobility has been demonstrated after vaginal birth (199).

The perineal body can be visualised and accurately measured in the midsagittal plane by transperineal 2D ultrasound (198). The legth, width (height), perimeter and area can be measured. The area is the most representative measurement as this measurement is less likely to be skewed by an irregular shape. The perineal body area in nulliparous women is 2.8+/-0.38cm2, compared with 2.1+/-0.5cm2 in women with prolapse (paired t-test, p<0.0001) (198). The prolapse patients were also observed to have a wider POP-Q GH (paired t-test, p=0.0003). Interestingly the POP-Q PB was not different (198).

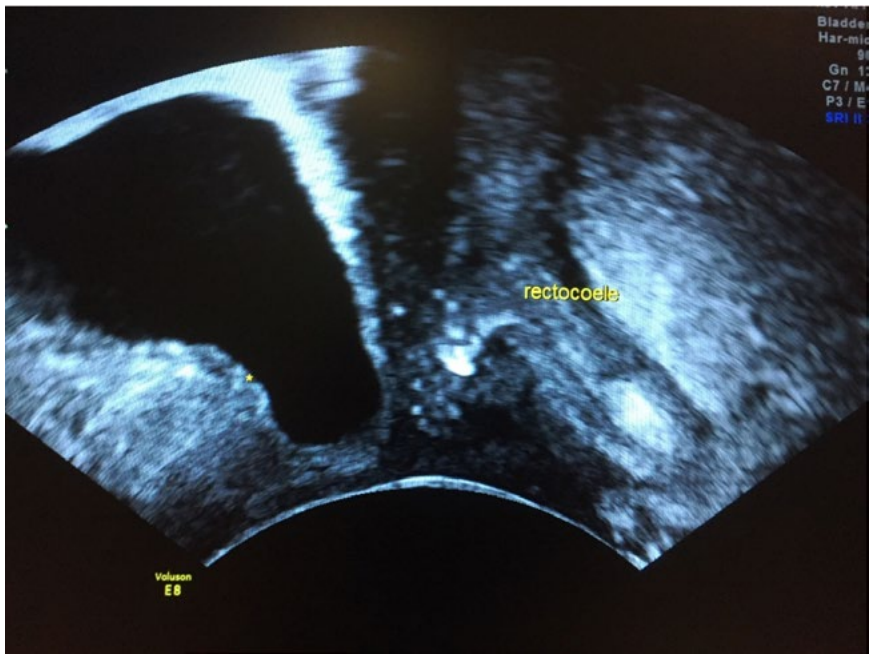


Figure 12. Midsagittal 2D image of a large cystocoele and rectocoele at maximal Valsalva.

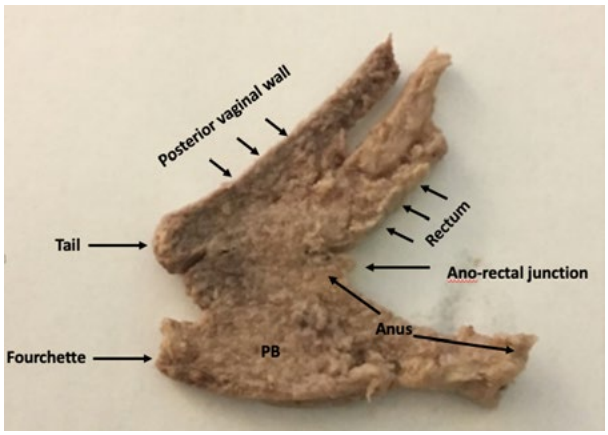


Figure 13a. Cadaver midsagittal section of the Perineal body. The perineal body is fused with the anal sphincter in the midline. The pointy part on the posterior vaginal wall is at the same level as the anorectal junction.

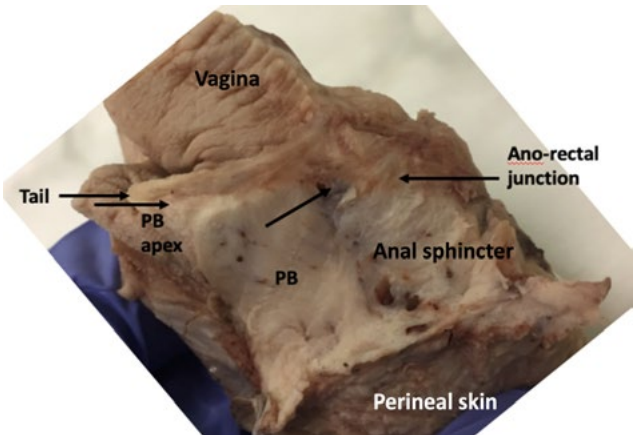


Figure 13b. Cadaver parasagittal section of the perineal body and anal sphincter.

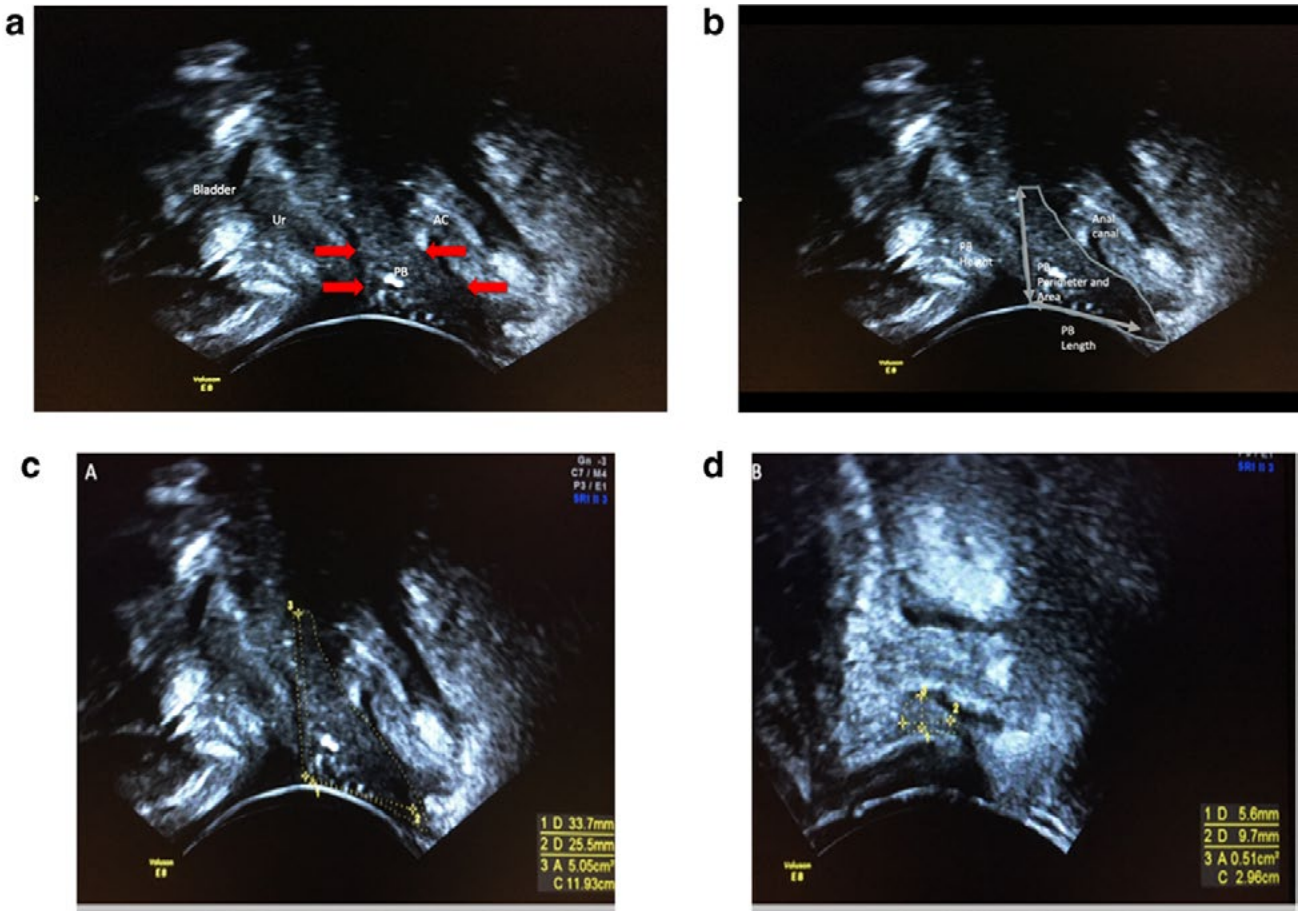


Figure 14. Perineal body on 2D midsagittal ultrasound. A. perineal body shown by the red arrows. B. perineal body width, legth and perimeter demonstrated. C. perineal body measurements done on Voluson E8, showing area 11.93cm2 that is derived from tracing the perimeter with the roller ball. D. small perineal body in the presence of a large rectocoele showing area 2.96cm2. (198)

2.5. Anal Axis (Anal Canal to Pubis Angle)

The anal axis can be assessed in the mid-sagittal plane with 2D ultrasound by measuring the angle between the anal canal and the Pubis, by pivoting on the ano-rectal junction (200). The angle is wider in prolapse patients 122.9° (SD 15.6°) compared to 98.2° (SD 15.9°) (two-sample t-test, $p<0.001$)(200). In children with congenital anomalies of the anorectal region, the anorectal axis has been assessed with MRI, as it is associated with obstructive defaecation (201).

Further work should be focused on assessing the clinical usefulness of the wide variety of ultrasound techniques described.

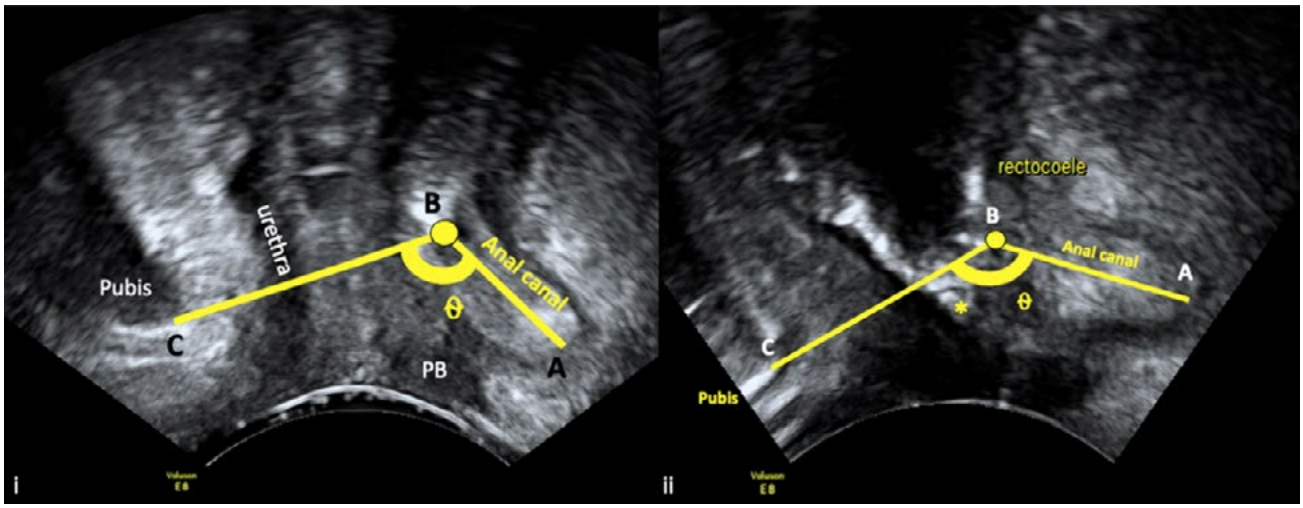


Figure 15. Anal axis in control and prolapse patients (200).

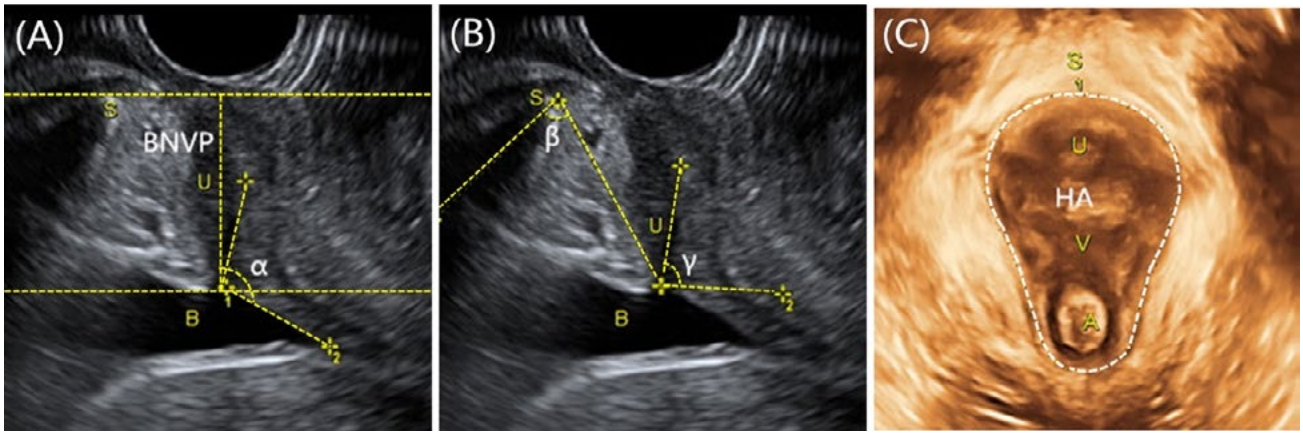


Figure 16. Transperineal ultrasound measurement of pregnant women. (A) the measurment of BNVP and α angle; (B) the measurment of β angle and γ angle; (C) the measurment of HA. B, bladder; S, symph- ysis pubis; U, urethra; V, vagina; A, anus; BNVP, bladder neck vertical position; HA, hiatal area. (202)

Table 3. Pelvic floor ultrasound techniques.

Technique	Clinical application	Offline analysis needed	Scanner & Probe	Method	Results	Ref
Anterior						
Bladder voume	Measure bladder volume	No	N/A	Bladder volume= 0.7(h x d x w)	0.7 reduces the error of the measurement adjusting for the bladder shape	Pederson et al, 1975 (203)
Postmictrition residual	Post-void residual	No	Static B Scanner (technicare model EDP 1000) TA 5MHz	Assess accuracy Combined Pedersen method and void volume measurements	Post-void residual 0.7[pre-void (h x d x w) – post-void (h x d x w)]	Poston et al, 1983 (204)
Bladder wall thickness (BWT)	Marker for over-active bladder	No	Acuson 128XP-10 and Ultramark 9, ALT TVS 5-9MHz	Bladder empty. 1cm lateral to the midsagittal plane Maximum magnification Measurements perpendicular to the bladder at the thickest parts of the trigone, dome and anterior bladder wall	DO Mean 6.7mm, SD 0.6 USI Mean 3.5mm, SD 0.6 Mann-Whitney U test p<0.001	Khullar et al, 1994 (181)
Bladder neck descent	Mobility following vaginal birth	No	Siemens SI 400 convex scanner TP 3.5MHz	V= Ö[(Vx-Rx)2 + (Ry-Vy)2] 32-36 weeks pregnant 6-10 weeks PN	Increased mobility after vaginal birth. See table 2.	Peschers et al, 1996 (114)
Urethral descent	Stress incontinence	No	Linear probes TP 3.5- 5MHz	Bladder full (300ml). Midsagittal, pubis is the line of reference. Distance of bladder neck from the reference line at rest at on Valsalva.	Ultrasound was better at detecting BND. Lateral chain cystourethrography was better are detecting funnelling.	Schaer et al, 1995 (61), Schaer et al, 1998 (205)
Urethral angles	Stress incontinence	No	Kranzbuhler mod. Sonofritz microconvex array 180° TP 6.5MHz	Lithotomy, midsagittal Before and after void BN-S: Bladder neck to lowest point of symphysis Alpha angle: midline of symphysis and BN-S Beta angle: midline of symphysis and urethral knee	Beta angle is inversely proportional to urethrovesical mobility. Urethral angle was more sensitive and specific than BND for SUI (sensitivity 96% vs 87%; specificity 92% vs 68%; PPV 85% vs 55%).	Pregazzi et al, 2002 (135)

Technique	Clinical application	Offline analysis needed	Scanner & Probe	Method	Results	Ref
Urethral descent	Stress incontinence	Yes 4D Sonoview, v5 GE Medical systems	GE Voluson 730 Expert system curved array 85° acquisition angle TP 4-8MHz	Urethral length at rest traced and divided into 5 segments. Point 1 (Bladder neck) Point 6 (External urethral meatus). Semi-automated method of bitmap from 4D view to Excel for automatic division of the urethra and distance calculations. Urethra mobility vectors= (xvalsalva -xrest)2 + (yvalsalva – yrest)2	Urethra at the external urethra meatus is a stable point in all patients.	Pirpiris et al, 2010 (115)
Urethral descent	Stress incontinence and prolapse	No	Voluson E8 (GE systems) Curved linear probe TP AB27D (2-7MHz)	Urethral descent assessment technique (UDAT method) Proximal urethra is the point of reference. Urethral length at rest (Y1) during live scanning (do not freeze the image). Valsalva and freeze image at maximum descent. Draw a parallel line from the new location of the bladder neck down to the urethral meatus (Y2). Urethral descent = Y1 – Y2	In healthy volunteers, BND was mean 6.2mm (95% CI +/- 1.47).	Asfour et al, 2020 (116)
Retrovesical angle	Incontinence and prolapse	No	GE Voluson 730 Expert system curved array 85° acquisition angle TP 4-8MHz	Midsagittal supine Measurement is taken at maximum Valsalva.	A significant cystocoele is defined as one that descends 10mm below the pubis. RVA> 140° - Green II (intact RVA) RVA< 140° - Green III	Chantarasorn et al, 2012 (199)
Bladder neck rotation				BND and rotation at baseline and after 4 months of physio	Physio elevated the BN voluntarily but did not change the stiffness with Valsalva in SUI/MUI	Hung et al, 2011 (206)
Urethral levator gap	Marker of severe prolapse	Yes 4D View v5	Voluson E8 GE scanner Probe not stated	Lithotomy Midsagittal 3D TP volumes Probe on introitus and external urethral meatus	Association between levator-urethra gap, avulsion severity and multi-compartment prolapse.	Kozma et al, 2018 (207)

Technique	Clinical application	Offline analysis needed	Scanner & Probe	Method	Results	Ref
Urethral funneling	Marker for stress incontinence	No	Scanner not stated TVS 6.5MHz	Lithotomy Bladder full (250-350ml) Cough test Probe against external urethral ostium	Positive cough test positive: funnelling of >50% of urethra on Valsalva. No SUI + No funnelling = 83% Funnelling less than 50% = asymptomatic Funnelling more than 50% = SUI	Wlazlak et al, 2018 (208)
Urethral muscle volume	Urine incontinence	No	Kretz Combison 530 140° acquisition angle TVS 7.5MHz	Bladder full. Pubic symphysis used as line of reference. Cross sectional area of the urethral sphincter was manually traced.	Bladder neck is more mobile at 6 weeks and at 6 months after vaginal delivery compared to Caesarean section.	Tooz-Hobson et al, 2008 (209)
Urethral vascularity	Stress incontinence	Yes Pixel Flux software (Chameleon software, Munster, Germany)	EVUS BK Medical 9-12MHz biplane electronic transducer Type 8848 Colour Doppler	Supine, bladder comfortably full Transducer placed in vagina and 10 seconds video recorded for later analysis. Assessed flow velocity, area of the vessels, intensity of vascularity	Continent nulliparous have higher vascularity than continent parous women. No difference in any treatment modality at 1-year.	Lone et al, 2016 (156)
Bladder neck	Mesh	No	Flex Focus 500 BK TP 4.3-6MHz 2D Convex transducer Type 8802 EVUS 12MHz Type 8838 3D Radial array 360° rotational probe	2D TP: Midsagittal panoramic, wide angle to include urethra, bladder, vagina, rectum and anal canal. Probe is turned 90° to visualise coronal and axial views of the mesh. 3D endovaginal: transducer is placed in a neutral position in the vagina for image volume acquisition.	TOT: 'sea-gull shape' TVT: U-shape Visualise mesh pre- and intra-operatively in mesh removal surgery.	Taithongchai et al, 2019 (210)
Vaginal wall thickness (VWT)	Prolapse	No	N/A	Bladder empty. VWT measured thickness between the vaginal lumen and prolapsed organ at: Bladder neck, Anterior and posterior fornix, anorectal junction.	Higher grades of prolapse have significantly thinner VWT.	Bray et al, 2017 (211)

Technique	Clinical application	Offline analysis needed	Scanner & Probe	Method	Results	Ref
Periurethral lesions	Urethral diverticulum	Yes 4DView & Resona 8	Voluson E8, E10 system (GE systems, USA) & Resona 8 system (Mindray Medical International, China) TP 4 – 8MHz curved array volume transducer 85° acquisition angle	Bladder empty. Midsagittal on urethra tomographic ultrasound imaging (TUI) mode with 'C plane' from main menu. Slice spacing 1-3mm.	It is possible to differentiate periurethral cyst from diverticulum on TUI.	Liu et al, 2020 (212)
Pre-operative for Burch colposuspension Pre-operative planning	Predict outcomes	No	Kretz Combison 530 scanner TVS 7.5MHz	Post-void (<20ml in bladder) Probe on external urethra meatus. Urethral volume measured pre-op Burch colposuspension for USI	Larger sphincter volume pre-op were dry post-op 4.2 vs 1.9cm3 Mann Whitney U- test p<0.001	Digesu et al, 2009 (213)
Posterior						
Anal sphincter	Anal incontinence and OASI care	No	BK Medical (Bracknell, UK) type 1846 7MHz rotating 360° rectal probe Focal length 2-5cm, 1.1mm minimal beam width	Probe is inserted in the anal canal and a volume acquisition is obtained.	Anal sphincter injuries were observed after vaginal delivery.	Sultan et al, 1993 (214, 215)
Anal sphincter	OASI assessment	No	EAUS Profocus 2202 or Flex-focus 500 BK Medical 12-16MHz rectal probe Type 2052 (focal point up to 20mm, focal range 5-45mm) with 360° acquisition. GE Voluson Introital (IUS): TVS 3D 5-9MHz TP 3D 4-8.5MHz curved array	EAUS: Left lateral Endoanal volume acquisition of the full anal sphincter length TP/IUS: Supine IUS: probe placed gently on posterior fourchette TP: transverse on perineum to visualise the puborectalis and angulated for visualisation of the anal sphincter	IUS and TP can identify intact anal sphincters but EAUS is superior for detailed defect assessment	Taithongchai et al, 2019 (216)
Anovaginal distance	OASI	No	Voluson TVS 5-9MHz type E8C	Lithotomy Probe placed inside the fourchette pointed vertically down to visualise the anal sphincter complex. The distance between the vaginal skin to the anal inner boundary of the internal sphincter was measured.	OASI had smaller ano-vaginal distance with a mean difference of 6.2mm (95% CI 4.1-8.4, p<0.001). OASI 11.6mm (95% CI 9.3-13.8) vs 2nd degree tear 17.8mm (95% CI 16.9-18.7). PPV 0.23 NPV 0.97	Pihl et al, 2019 (217)

Technique	Clinical application	Offline analysis needed	Scanner & Probe	Method	Results	Ref
Perineal mobility	Yes	4DView v5 & v7 GE Kretz Medical systems	Voluson 730 expert system (GE) TP 3D 4-8MHz acquisition angle 85°	Midsagittal TP Volume datasets were obtained at rest and maximum Valsalva for later analysis. Hiatal biometry. Pubis used as line of reference to determine perineal and anorectal junction (ARJ) mobility antenatally (AN) and 3 months postnatal (PN).	Validated method Perineal mobility: AN mean 18.4mm (1.3-40.7) vs PN mean 21mm (p<0.001) ARJ mobility: AN mean 17.1mm (1.6-44.4) vs PN mean 20.6 (p<0.001). VD vs CS no difference	Chantarasorn et al, 2012 (199)
Perineal body	Anatomical study	Yes 3DViewer	BK Medical EVUS 3D 9-16MHz 360° acquisition Type 2052	Cadaver scans + histology, Patient scans Probe was inserted in the vagina in a neutral supine position and held in place 60 seconds for volume acquisition for later offline analysis. Evaluated perineal body as 'visible' or 'not visible'. Perineal body (PB) Height, Depth, Width were measured.	PB Height 7.5mm PB Depth 14.5mm PB Width 13.3mm K=0.6 (good agreement)	Santoro et al, 2016 (218)
Anal sphincter and pubovisceral muscles	New Scoring system for fecal incontinence	Yes	Pro-Focus 2052 BK scanner EVUS, EAUS 3D 12-16MHz	Probe placed in the vagina in a neutral position EVUS: Complete or partial pubovisceral avulsion (LAM) was examine EAUS: OASI assessment Anal manometry	N=84 of Vaginal delivery + faecal incontinence: 25% normal scan 41% OASI only 11% LAM only 23% both	Murud Regadas et al, 2017 (219)
Perineal body	Prolapse	No	GE Voluson E8 scanner TP 7MHz curved Type AB27D	Image zoomed and optimised on the perineal body. Measured (mm) Height, Length, Perimeter and Area.	Women with prolapse have a significantly smaller perineal body. PB Height N 22.5mm vs POP 16mm. PB Length N 17.4mm vs POP 16mm. PB Perimeter N 7.5mm vs POP 6.5mm. PB Area N 2.8cm2 vs POP 2.1cm2 (p<0.0001).	Asfour et al, 2020 (198)
Panoramic						
Pubovisceral avulsion (LAM)	Levator ani injury	Yes 4DView v2.1 GE Kretz	Philips HDI 4000 (Philips Electronics Australia) TP 3D 4-7MHz	At least 3 sets of rest, contractions and Valsalva volumes for later analysis after 3 months.	Appearance of pubovisceral muscle avulsions were observed only after vaginal childbirth.	Dietz et al, 2005 (220); van Delft et al, 2014 (221)

Technique	Clinical application	Offline analysis needed	Scanner & Probe	Method	Results	Ref
Pubovisceral avulsion (LAM)	Levator ani injury	Yes 4DView v5 GE Kretz	Voluson 730 Expert, GE TP 3D	Dietz 2005 protocol TUI and rendered volumes Digital palpation with dominant hand in parallel to urethra, with fingertip at the bladder neck.	Agreement of: Palpation vs rendered volume 86% (k=0.43) Rendered volume vs TUI 80% (k=0.35) Palpation vs TUI 87% (k=0.56)	Dietz et al, 2012 (222)
Levator hiatus	Perineal ballooning	Yes 4DView v2.1-5 GE Kretz	Voluson 730 Expert, GE TP 3D	Dietz 2005 protocol	Ballooning: Hiatal area of >25cm2	Dietz et al, 2008 (223)
Pelvic floor contractility	LAM squeeze Prolapse evaluation	Yes 4DView v10.2 GE Medical systems	Voluson 730 system TP 4-8MHz curved array 3D/4D acquisition angle 85°	3 volume sets obtained and the best one analysed 2 months later. Modified Oxford score to assess pelvic floor contractility	Correlation between Modified Oxford score to TP rho=0.47 for hiatal area ($p<0.001$) and rho=0.51 for hiatal anteroposterior diameter ($p<0.001$).	Van Delft et al, 2015 (224)
Paravaginal defects	Prolapse	Yes GE 4D View	Voluson E8 GE scanner TP 3D RAB 2-8MHz	Midsagittal perpendicular to the long axis of the vagina 3D volume acquisition 2mm intervals TUI 3 months after delivery	The paravaginal supports were visible in more slices in nulliparous than post vaginal birth (11 vs 7 slices; $p<0.05$) No difference of CS vs nulliparous	Dou et al, 2018 (225)
Rectovaginal septum	Assess the rectovaginal septum	Yes	BK Pro focus system TP 4.3-6MHz 8802 convex array TVS 3D 6.5MHz 8848S integrates 6.5cm linear transducer and convex array for transverse views. Magnetic clip-on collar acquisition angle up to 179°	3D volumes were assessed rectovaginal fascia (RVA): layer between hypoechoic vagina and anorectal muscularis	RVA mean 1.1mm (range 0.2-2.9). Gaps identified in 22%. Moderate repeatability k=0.5. No associations with clinical findings. 1 patient with no RVS identifiable had no rectocoele.	Dietz et al, 2011 (226)

Technique	Clinical application	Offline analysis needed	Scanner & Probe	Method	Results	Ref
Posterior compartment diagnosis	Rectocoele Intussusception Enterocoele Anismus	Yes	Profocus scanner TP 3.5-6MHz, focal range 10-135mm EVUS 6-12MHz high resolution linear array, focal range 3-60mm, contact surface 65mm	3 Valsalva volume datasets were acquired for later analysis. MRI, Evacuation proctogram (EP), TP, EVUS Measured rectocoele depth VAS score of acceptability of the methods used.	Ultrasound was more acceptable to patients. Best interobserver agreement (Cohen's k) for rectocoele depth was best for TP and MRI (0.7). Enterocoele diagnostic accuracy was best for EVUS (AUC 0.87) vs TP (0.73). Intussusception highest diagnostic accuracy was EP (AUC 0.76), EVUS (0.77), with fair to poor agreement MRI (k=0.37), TP (k=0.22), EVUS (k=0.1), EP (k=0.03). No optimal scan.	Van Gruting et al, 2017 (71)
Peri-operative	Plan surgery	Yes MRI 3D computerised model	MRI 3D USS	EVUS Not state but likely BK	Translevator hernia identified pre-operatively allowing for surgical planning	Rostaminia et al, 2018 (227)
Total pelvic floor ultrasound	Defaecatory dysfunction	No	EVUS 12MHz linear array No bowel prep TP 6MHz 70° acquisition angle	Compared EVUS to defaecatory proctography for accuracy of findings, correlation with symptoms and management ODS score	Defaecatory imaging could be avoided	Hainsworth et al, 2017 (228)

Acronyms used in this table: BWT: bladder wall thickness, VWT: vaginal wall thickness, OASI: Obstetric anal sphincter injury, LAM: Levator ani muscle injury, TA: transabdominal, TVS: transvaginal, TP: transperineal, EVUS: endovaginal, EAUS: endoanal, TUI: tomographic ultrasound imaging

2.5.1. Pelvic Floor Muscles

Ultrasonography can be used to assess pelvic floor muscles and their function. Contraction of the pelvic floor results in displacement of pelvic structures that can easily be imaged on ultrasound (**Figure 17**) such as the cranial lift of the urethra in relation to the symphysis pubis during a maximal squeeze (91, 229) but also the dimensions of the genital hiatus or the posterior ano-rectal angle can serve this purpose (230). Comparison with traditional measurements of pelvic floor muscle strength has been performed (229), and good correlations with palpation and perineometry have been found (231, 232). Ultrasonography has been used to evaluate the effects of pelvic floor muscle training. A higher resting position of the bladder neck and a reduction in the rotational excursion of the urethra during Valsalva manoeuvre have been found with pelvic floor training (233). Another research group has reported that the thickness of pelvic floor muscles increased after training (234). A number of studies have assessed healthy female volunteers to establish normal values (126, 234) and one study has specifically compared elite athletes with normal volunteers (235). One study has compared three-dimensional ultrasound of the levator ani hiatus at rest and during contraction in a number of different groups of women with prolapse, urodynamic stress incontinence and asymptomatic women suggesting that these measurements are not sensitive enough to discriminate between different groups (236).

Almost half of women are unable to perform an optimal contraction of the pelvic floor muscles. Ultrasonography can be used in pelvic floor training to provide women with a visual feedback of their exercise (91, 237). In one study, 57% of the women who were not able to perform a proper pelvic floor contraction, were able to do so with the help of visual biofeedback of ultrasonography to observe bladder neck movement (91). This does not appear to produce better outcomes of changes with pelvic floor physiotherapy (206). Another prospective study in women receiving physiotherapist-guided PFMT due to pelvic floor dysfunction, however, did demonstrate that the vast majority of patients would improve muscle contractility after the programme; amongst the non responders (“non-contractors”) almost 67% were found to have levator ani defects on transperineal ultrasound (238). The contraction of the pelvic floor muscle just before and during a cough, “the knack”, can also be visualised (239). It has been demonstrated that the knack can significantly reduce urethral mobility during a cough.

Direct measurement of the pelvic floor muscles is possible with the use of two and three-dimensional perineal ultrasonography. An alternative technique makes use of a 360 degree rectal probe intravaginally (**Figure 18**) (240). Most studies, however, have used three-dimensional perineal ultrasonography for this purpose (92, 230, 235, 241, 242). The thickness of the pelvic floor muscles as well as the hiatal area can be measured. Hiatal dimensions and pelvic floor muscle thickness have been extensively validated and have good test retest and inter observer characteristics (92). There is a learning curve to measurement of the levator ani hiatus needing over ten sets of scans to perform the measurement. However, measurements of the pubic arch were not accurate suggesting that measurements of levator avulsion may require more training (243).

The pelvic floor muscles were thinner in women with pelvic organ prolapse (90, 240, 244) and with urinary incontinence (245), whereas their genital hiatus was larger (73); interestingly this finding does not produce a significantly reduced maximal voluntary contraction even with pubovisceral muscle defects (246). Well trained women have thicker pelvic floor muscles compared with controls (234), and Chinese women had thinner muscles compared with Caucasian women (136). In nulliparous Chinese women, the anterior/posterior hiatal diameter was significantly increased in women with a higher body mass index (242).

A RCT in 140 incontinent women demonstrated that TAUS was accurate in detecting even minor differences in pelvic floor muscle strength between the PFMT and non-intervention groups and this correlated very well with assessment by digital palpation (247). By using this imaging modality as biofeedback, another research group from Japan established that women with postpartum SUI were less successful in achieving good pelvic floor muscle strength following an intensive PFMT in comparison to their continent counterparts, despite no morphological differences in the LAM between the groups before and after intervention (248).

Pelvic floor biomechanics were investigated with ultrasound using the position of the bladder neck in combination with continuous vaginal pressure measurements (249, 250). A novel biosensor was used to measure the force as well as the displacement of the pelvic floor during contraction (251). Another research group has inserted a water filled plastic bag to study the shape of the vagina during contraction (252). Others have assessed elasticity by means of the correlation of the dynamic dimensions of the hiatal circumferences and direct palpation of the muscles (253). Real time biomechanics of the pelvic floor have been compared between women with and without pelvic organ prolapse with the use of translabial 3D ultrasound and standardised Valsalva effort; significant pelvic organ prolapse was associated with a less compliant levator ani muscle close to its origin from the pubic ramus (median maximum strain 26% vs 32%, respectively, P=0.03) (254).

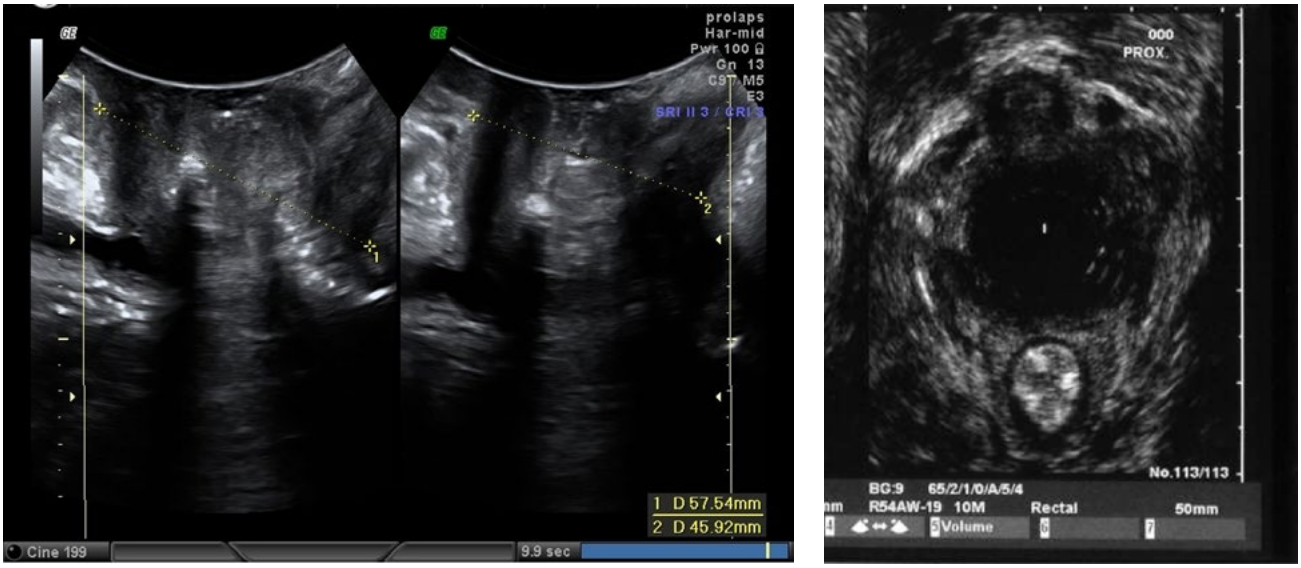


Figure 17: Perineal midsagittal two-dimensional view at rest and on contraction. Levator contraction with ventro-cranial displacement of the urethra. Measurement of minimal dimension of genital hiatus (from symphysis pubis to levator ani muscle)

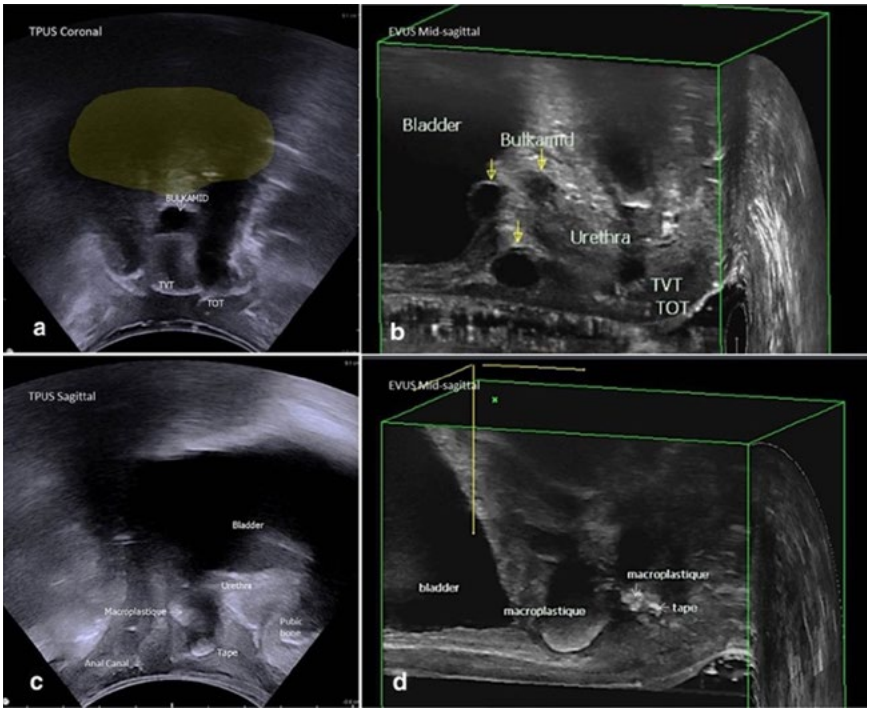


Figure 18: Urethral bulking agents. a Perineal pelvic floor ultrasound coronal view showing Bulkamid® as a hypoechoic area by the bladder neck as labelled (bladder highlighted in yellow). This patient presented with de novo urgency and reported to have undergone a transobturator tape (TOT) insertion that was partially excised owing to voiding dysfunction, followed by a tension-free vaginal tape (TVT) insertion (as labelled). Evidence of material used for Bulkamid® injections was also seen (unknown to the patient). b Mid-sagittal view on endovaginal ultrasound of the anterior compartment demonstrating the bulking agent (arrows) bulg- ing into the bladder and bladder neck. The two MUSs can also be seen the distal urethra. c Mid-sagittal view on perineal ultrasound. Macroplastique® is seen with higher echogenicity compared with Bulkamid® injections allowing differentiation, but may obscure sur- rounding pelvic structures. This patient presented with a history of having had three MUSs inserted; on ultrasound it was discovered that she in fact had Macroplastique® with only one MUS, which is seen very close to the urethral lumen (labelled tape). d Mid-sagittal view on endovaginal ultra- sound of the anterior compartment demonstrating the high echogenicity of the Macroplastique® compared with Bulkamid® . (210)

3. ENDOVAGINAL ULTRASOUND (EBUS) THE EMERGENCE OF HIGH FREQUENCY, HIGH DEFINITION POINT OF CARE ULTRASOUND

3.1. Introduction

Based on the practice parameters published by the American Institute of Ultrasound in Medicine (AIUM), in collaboration with the American College of Radiology (ACR), the American Urogynecologic Society (AUGS), the American Urological Association (AUA), the International Urogynecologic Association (IUGA), and the Society of Radiologists in Ultrasound (SRU),

Endovaginal Ultrasonography ultrasonography (EVUS), Perineal Pelvic Floor Ultrasound (pPFUS) and Introital Pelvic Floor Ultrasound (iPFUS) indications include but are not limited to the following:

Urinary incontinence;
- Recurrent urinary tract infections;
- Persistent dysuria;
- Symptoms of voiding dysfunction;
- Symptoms of pelvic organ prolapse;
- Obstructed defecation;
- Anal incontinence;
- Vaginal discharge or bleeding after pelvic floor surgery;
- Pelvic or vaginal pain after pelvic floor surgery;
- Dyspareunia;
- Vaginal cyst or mass;
- Synthetic implant visualizations (slings, meshes, and bulking agents);
- Levator ani muscle assessment after childbirth;
- Obstetric perineal injury;
- Obstetric Anal Sphincter Injury (OASIs);
- Perineal cyst or mass.

There are no contraindications except where patients are unable to consent to the procedure and in situations that would breach infection control guidelines, such as the presence of an open wound or severe vulvovaginal pain and discomfort.

3.2. Anterior and Posterior Endovaginal Ultrasonography

Anterior and posterior dynamic imaging may be performed using EVUS. In a study of nullipara correlated with the histology of the anterior and posterior compartment, the following measurements were found: urethral length 36 mm (±5); striated urogenital sphincter area 0.6 cm^2 (±0.16); longitudinal and circular smooth muscle area 1.1 cm^2 (±0.4); urethral complex width 14 mm (±2); urethral complex area 1.3 cm^2 (±0.4); internal anal sphincter length 26 mm (±4); internal anal sphincter thickness 3.2 mm (±0.8); and rectovaginal septum length 31 mm (±5). The agreement for visualization of structures was as follows: vesical trigone 96% ($\kappa = 0.65$), trigonal ring 94% ($\kappa = 0.8$), trigonal plate 84% ($\kappa = 0.6$); longitudinal and circular smooth muscle 100%; compressor urethra 97% ($\kappa = 0.85$); striated urogenital sphincter 97% ($\kappa = 0.85$); rectovaginal septum 100%; internal anal sphincter 100%; external anal sphincter subdivisions 100% (2).

To visualize the anterior compartment, introduce the transducer into the vagina until the vesicourethral junction is visualized. During anterior compartment imaging, the details of the urethral anatomy along with any sling or mesh present can be visualized (3-7). Levator ani deficiency (LAD) and urethral sphincter complex status, as visualized on 3D ultrasonography, are independent factors. Moderate to severe LAD is more prevalent in patients with SUI (8). Smaller rhabdomyosphincter length and area on 3D EVUS are associated with x-ray funneling. Ultrasound urethral volume of 3.5 cm^3 as a cutoff provides the same reliability as x-ray funneling for the diagnosis of ISD (4). During posterior compartment imaging, any mesh present can be visualized (5). Cough, Valsalva and

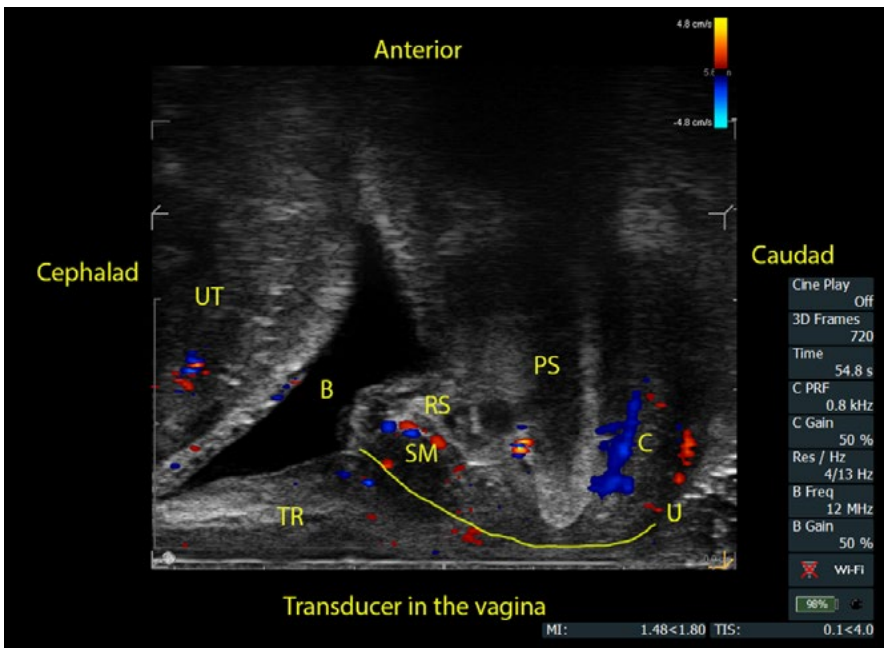


Figure 19: Anterior compartment with doppler flow view of the urethra and the bladder. B= bladder, C= Clitoris, PS= pubic symphysis, RS= rhabdomyosphincter, SM=Smooth muscle, TR= trigone, U=Urethra delineated by the yellow line, UT=Uterus (anterior edge of the uterus is seen cephalad to the bladder).

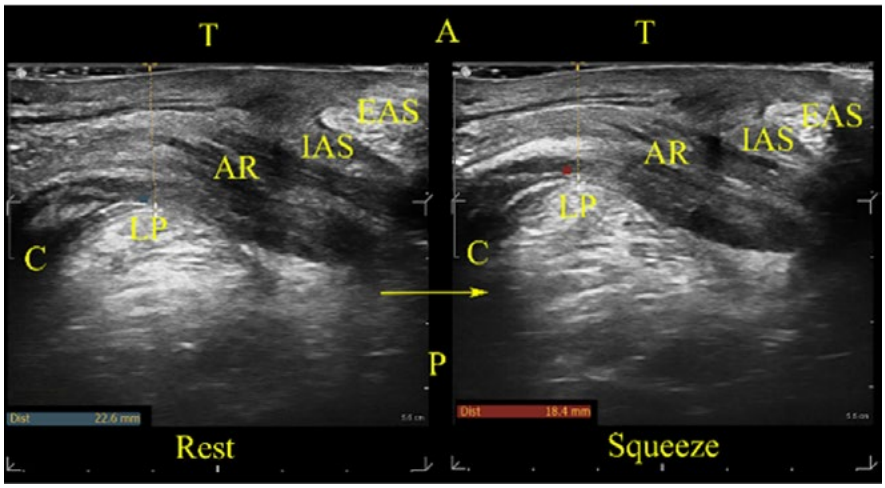


Figure 20: Posterior imaging of the anorectum using a side-fire transducer at rest and contraction. A= anterior, AR = anorectum; C= cranial, IAS = internal anal sphincter; LP= levator plate, P= posterior; T= transducer.

contraction maneuvers can be performed by the patient to improve visualization of high rectocele, enterocele, sigmoidocele, or intussusception. Visualization of a low rectocele may be impeded by the presence of the transducer in the vagina. Pelvic floor dyssynergia can also be noted during the maneuvers. Measure the distance from the transducer to the levator plate with the patient at rest. Then direct the patient to contract her pelvic floor muscles, and measure the distance at maximal contraction of pelvic floor muscles (9, 10) (*Figure 20*).

The visualization of correct pelvic floor lift is an important clue to the patient's pelvic floor function. This measurement has a good correlation with the Oxford scale in measuring pelvic floor lift. If the patient has defecatory dysfunction, she may, at this time, be asked to perform the Valsalva maneuver. Women with obstructive defecatory symptoms have wider rectum and descendent levator plate regardless of the prolapse stage as measured by POPQ or the severity of rectocele (11).

3.3. 3D Endovaginal Ultrasonography (3D EVUS)

Once the transducer is advanced to visualize the anterior compartment as in Figure 19, the 3D volume is obtained. The scan starts from the vesicourethral junction and will continue 6 cm caudal to include the perineal body (12). The 3D volume clearly demonstrates the levator ani muscle subdivisions and defects, vaginal masses and cysts, slings, and mesh. The levator ani muscle integrity, minimal levator hiatus area, anteroposterior diameter, urethral length, and sling and mesh position and dimensions, along with the levator plate descent angle, should be documented (*Fig 21).*

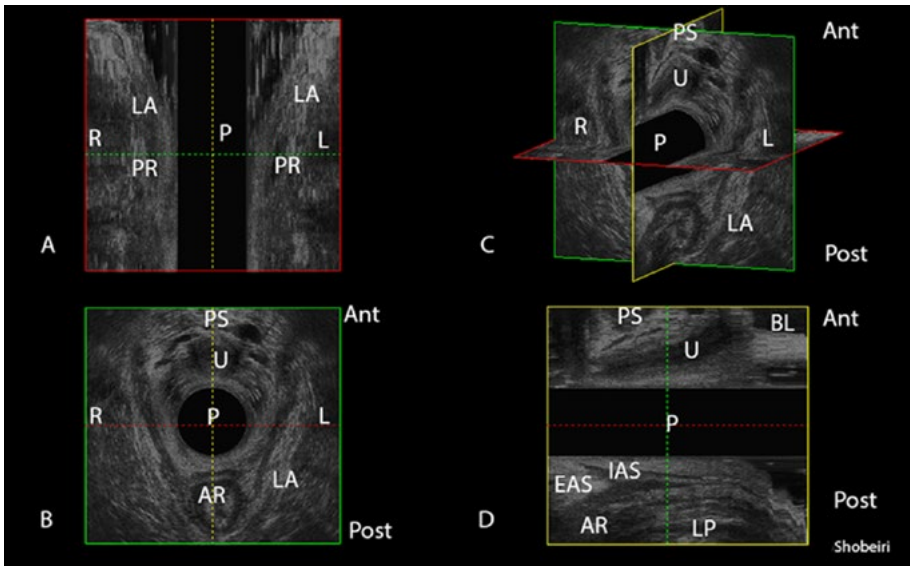


Figure 21: Endovaginal 3D volume as seen on workstation.
A in red frame is 2 D coronal view of the pelvic floor.
B in green frame is the axial view of the minimal levator hiatus.
D in yellow frame is the right midsagittal view of the pelvic floor.
C is the 3D volume with all three planes in yellow, red and green colors

3.3.1. 3D Endovaginal Ultrasonography: Levator Ani

The location of the puboperinealis, puboanalis, puborectalis, pubococcygeus and iliococcygeus as seen by three-dimensional endovaginal ultrasonography has been confirmed through anatomic dissection of fresh-frozen pelves. Subdivisions of the levator ani muscle can be visualized reliably with three-dimensional ultrasonography due to a high frequency of the probe placed directly adjacent to the muscles in the vagina (13, 14). In nulliparous women, Anterior and lateral borders of the minimal levator hiatus are formed mostly by pubococcygeus (Fig 22). The puborectalis, pubococcygeus, and iliococcygeus form the bulk of the levator plate (Fig 23). The mean of minimal levator hiatus and puborectalis hiatus areas are 13.4 cm^2 (±1.89 cm^2 SD) and 14.8 cm^2 (±2.16 cm^2 SD). The mean levator plate descent angles is -15.9° (±8.28° SD) (Fig 22) (1).

The levator ani subdivisions can be individually scored (0=no defect, 1=50% or less defect, 2=more than 50% defect, 3=total absence of the muscle) on each side. A levator ani deficiency score is categorized as mild (score 0–6), moderate (score 7–12), and severe (score more than 13). Score distribution significantly differs by prolapse stage (*P*<.001). No patients with stage 3 prolapse had a levator ani score less than 6, and no patients with stage 4 prolapse had a levator ani score less than 9. In patients with prolapse, those with moderate levator ani deficiency have 3.2 times the odds of POP compared with patients with a minimal defect; those with severe levator ani deficiency have 6.4 times the odds of prolapse than those with minimal deficiency (15). Furthermore, Worsening LAD score is associated with levator plate descensus and decreasing levator plate descent angle (10).

Childbirth causes overstretching of the levator ani muscle (LAM), predisposing to avulsion. 24% of women after delivery have well-delineated, hypoechoic areas consistent with hematomas. Hematomas away from the attachment zone of the LAM to the pubic bone resolve. Hematomas at the site of LAM attachment to the pubic bone always result in avulsion diagnosed three months postpartum. However, 1/3 of avulsions are not preceded by a hematoma at the site of LAM attachment to the pubic bone (16). Although the prevalence of pelvic floor hematoma is higher in vaginal-primiparous women than vaginal-multiparous women after vaginal delivery, hematomas are present in both groups, pointing to the fact that the cycle of LAM overdistention, injury, and recovery is persistent with each additional pregnancy and vaginal birth (17). From the time of injury to the LAM that goes unrecognized to the development of prolapse may

take up to 18 years (18). Aging is also a strong risk factors for pelvic floor prolapse, and urinary incontinence. Levator ani muscle hiatus changes to a more oval form in older nulliparous postmenopausal women, and this change in shape is associated with increased pelvic floor symptoms (19).

3.3.2. 3D Endovaginal Ultrasonography: Mesh and sling imaging

Three-dimensional endovaginal sonography allows for more detailed imaging compared to computed tomography and magnetic resonance imaging of the female pelvic floor, in that each plane can be manipulated to show unique images of synthetic implanted materials (20). The EVUS easily distinguishes any type of sling with mesh.

tomography and magnetic resonance imaging of the female pelvic floor, in that each plane can be manipulated to show unique images of synthetic implanted materials (20). The EVUS easily distinguishes any type of sling with mesh.

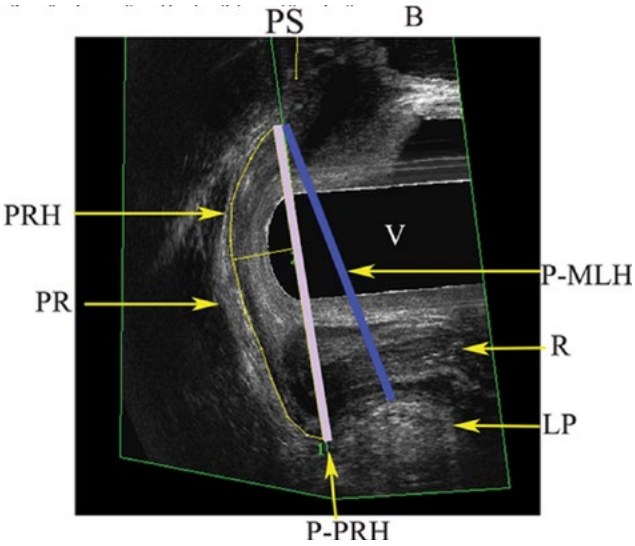


Figure 22. Ultrasound showing plane of MLH and PRH in the right sagittal view. Abbreviations: B, bladder; LP, levator plate; P–MLH, plane of MLH (blue line); P–PRH, plane of puborectalis hiatus (purple line); PR, puborectalis; PS, pubic symphysis; R, rectum; V, vagina (1).

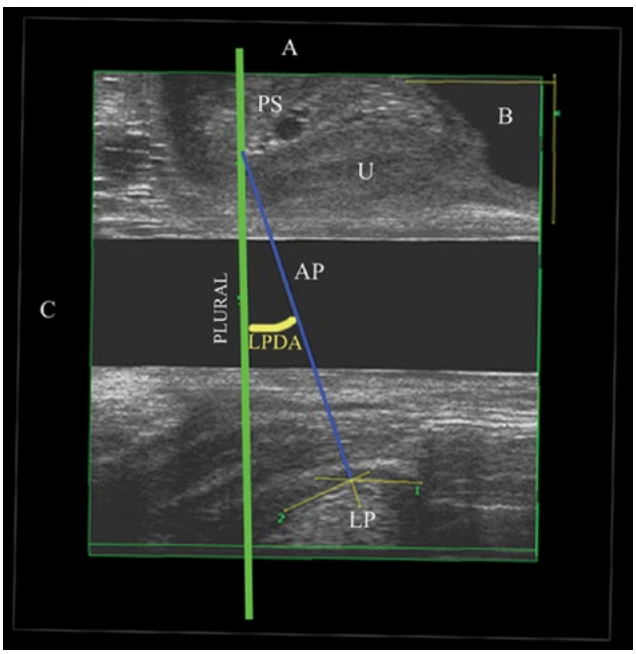


Figure 23: Levator plate descent angle (LPDA) in mid-sagittal view by transvaginal 360° ultrasound. Abbreviations: A, anterior; B, bladder; C, caudad; LP, levator plate; LPDA, levator plate descent angle; PLURAL, pubic levator ultrasound reference assessment line (green line); PS, pubic symphysis; U, urethra (1).

The most common complaints of vaginal mesh complications are pain and dyspareunia. EVUS helps assess mesh presence, location, and extent, including planning for surgical intervention (7). Anterior and posterior vaginal mesh have distinct patterns on 3D EVUS. In patients presenting with mesh complications, the posterior meshes are more often visualized as a "flat" pattern with a higher frequency of pain. Mesh complications of the anterior compartment have a higher frequency of folding and shrinkage (5).

3.3.3. 3D Endovaginal Ultrasonography: Urethral bulking agents

The ultrasound signal produced by the bulking agents varies depending on the makeup of the agent. Collagen-based bulking agents vary between hypoechoic, isoechoic, and hyperechoic. The signal from a calcium-based agent will produce a hyperechoic structure on the image near the urethra (Fig 24). Bulking deposits vary in size and shape. A well-placed bulking agent should appear round or oval in shape, whereas a poorly distributed bulking agent may track along the urethra. An agent tracking along the urethra will have the same echotexture but will appear elongated (21). Although the bulking agent is most often found at 3- and 9-o'clock positions as intended, the distance from the UVJ is highly variable after an uncomplicated office-based transurethral injection. The bulking material does not form the distinct spheres in 41% of cases and tracks toward the bladder neck or the distal urethra (22).

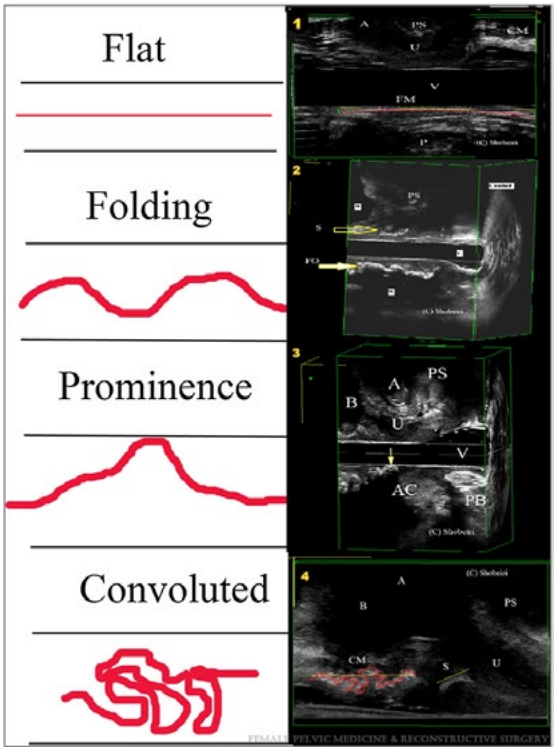


Fig 24b: Three-dimensional ultrasound images depicting vaginal mesh location and patterns based on their US manifestation: (1) flat posterior mesh in the same patient as convoluted anterior mesh, (2) left lateral view of folded mesh and anterior sling, (3) mesh prominence posterior mesh, and (4) convoluted anterior vagina mesh and sling. Arrows indicate mesh location. A, anterior; AC, anal canal; B, bladder; CM, convoluted mesh; FM, flat mesh; FO, folded mesh; P, posterior; PS, pubic symphysis; PB, pubic bone; R, rectum; S, sling; U, urethra; V, vagina.

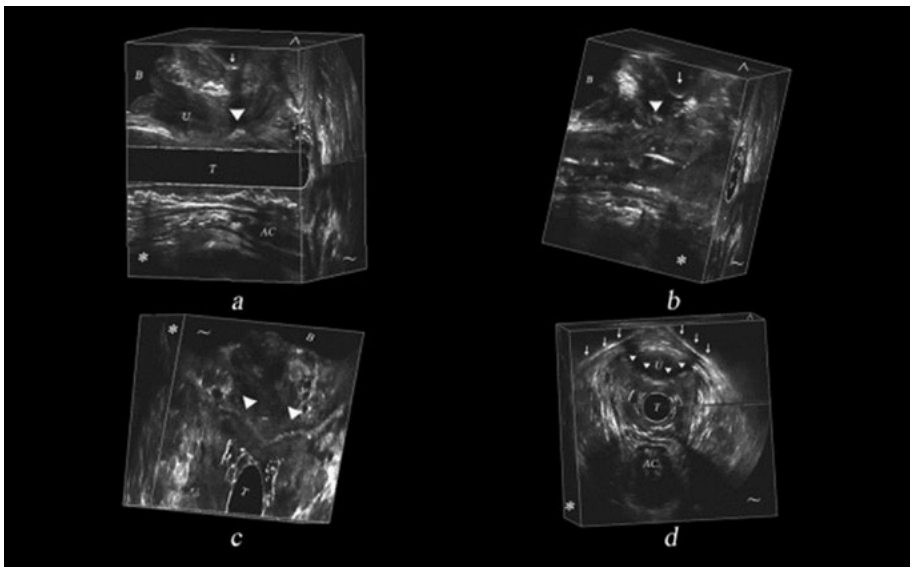


Fig 24a: Polypropylene tension-free vaginal tape retropubic midurethral sling (arrowheads).
A: Patient's left sagittal view; b: coronal view; c: axial view; d: axial view. Arrows indicate pubic bone.. AC shows anal canal; B, bladder; S, sling; T, transducer; U, urethra; *, sagittal plane; ^, coronal plane; and ~, axial plane.

3.3.4. 3D Endovaginal Ultrasonography: Cysts and Masses

The utility of 3D EVUS in evaluating Gartner duct cysts, solid masses, urethral diverticula, and Bartholin glands is well established. Most urethral diverticula are located in the middle of the urethra and involve the posterolateral wall facing the vagina. Sonography shows a relatively anechoic cavity adjacent to the urethra and may show an orifice that communicates with the urethral lumen; it also may show inflammatory debris or surrounding inflammatory edema (Fig 26) (23).

3.4. Consensus Statement

3D EVUS has been shown to be in correlation with tissue characterstics as validated by histologic and cadaveric studies and has been shown to have good intra and interobserver reproduceability. **[Level of evidence 2, Grade of Recommendation B].**

3D EVUS enables imaging of the levator ani muscle subdivisions and allows for quantification of muscle injury. **[Level of evidence 2, Grade of Recommendation B].**

3D EVUS enables direct visualization implanted mesh, slings, implanted urethral bulking agents, vaginal cysts and masses including the urethral diverticulum and should be considered as first line of investigation where the technology is available. **[Level of evidence 2, Grade of Recommendation B]**

3.5. Future Research Areas

- Examining the utility of 3D EVUS during surgery to assess surgery outcomes.
- Examining the utility of 3D EVUS to assess surgery outcomes and correlate with recurrence rates.
- Comparing 3D EVUS pre and post surgical to assess surgical outcomes
- Evaluate advance ultrasound technologies such as shear wave elastography (SWE) for the assessment of tissue characteristics.
- In general there is a lack of core competency in EVUS and there is a need for widespread education for full adaptation of point of care ultrasound.

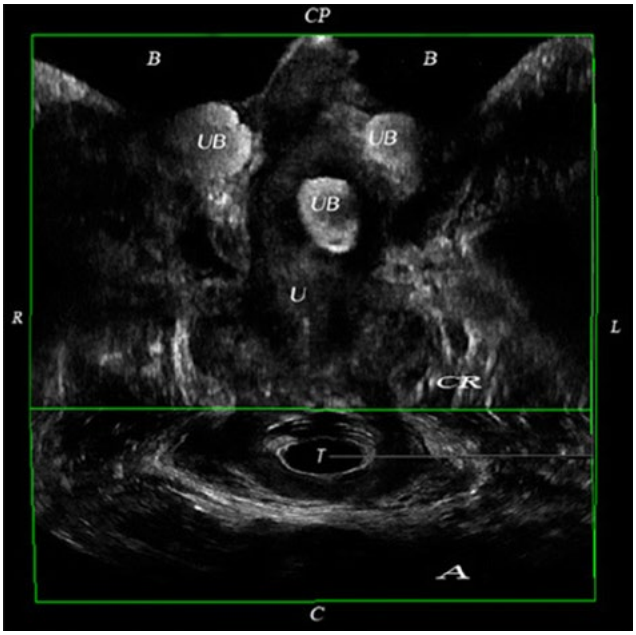


Fig 25: Coronal view obtained using an endovaginal transducer of a 3D volume demonstrating a urethral bulking agent. B, bladder; UB, urethral bulking agent; U, urethra; T, transducer; C, caudad; CP, cephalad; R, right; L, left; CR, coronal view; A, axial view.

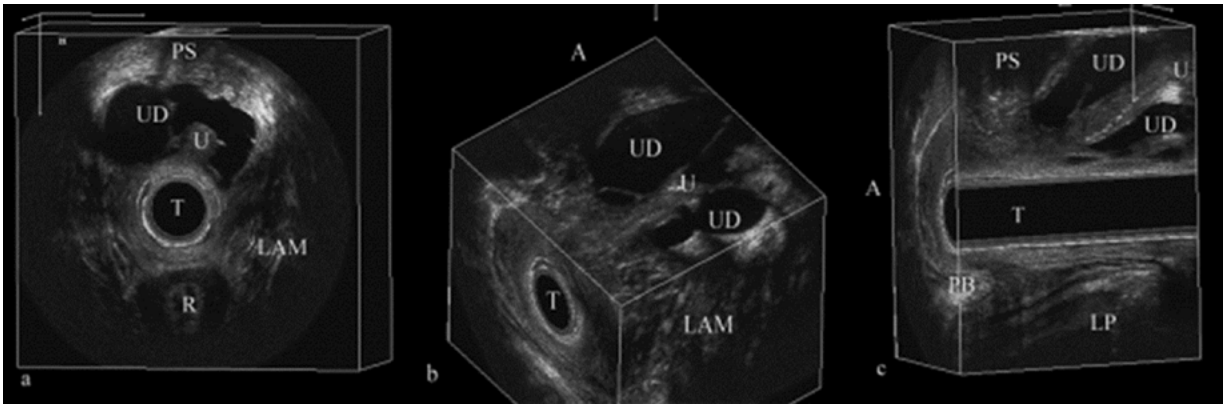


Fig 26. A: Axial view of the urethral diverticulum. The urethra is surrounded by the diverticulum. Anatomic landmarks are the pubic symphysis and pubic ramus superiorly, urethra medially, and vagina inferiorly.
B: Coronal view showing the diverticulum along both sides of the middle and proximal parts of the urethra. Cephalad extension of the diverticulum can be evaluated in this view.
C: Midsagittal view confirming the diagnosis, with an anechoic cavity adjacent to the urethra that starts in the middle third of the urethra and extends near to the bladder. A indicates anterior; LAM, levator ani muscle; LP, levator plate; PB, perineal body; PS, pubic symphysis; R, rectum; T, transducer; U, urethra; and UD, urethral diverticulum.

4. THE ROLE OF MRI IN THE ASSESSMENT OF THE FEMALE PELVIC FLOOR

4.1. Introduction

The role of magnetic resonance imaging (1) in evaluating pelvic floor disorders has been established in recent years and continues to evolve. This technique provides unparalleled images of pelvic floor muscles, connective tissue, and organs. In addition to the detailed static picture of the pelvic organ support system anatomy, MR can also reveal the downward movement of each pelvic compartment during increases in abdominal pressure. Advances in MR imaging, equipment and software have significantly improved image quality and now MRI provides ever more detailed pictures of anatomy and function. At present active investigation is ongoing to see how this imaging might result in a better understanding of these diseases and improve their diagnosis and management.

Although women might present with symptoms isolated to one of the pelvic compartments, they often have concomitant defects in other compartments or pelvic structures. In these women, imaging can provide information to extend what can be determined on physical examination (2). Furthermore, surgical failures could result from lack of a thorough preoperative evaluation of the female pelvis and inadequate diagnosis and staging of pelvic floor deformation and dysfunction (3). Accurate diagnosis of coexisting abnormalities is therefore essential in planning reconstructive and anti-incontinence procedures. Although most diagnoses of pelvic floor prolapse are made on detailed physical exam, the sensitivity and specificity of the pelvic exam in diagnosing various forms of pelvic floor prolapse is low (4-6) . Ultrasound and fluoroscopy have been used to improve diagnosis (7, 8) and the role of MRI in pelvic floor dysfunction is rapidly developing. A systematic review suggests that prolapse assessment on dynamic MR imaging may be useful in the posterior compartment, although clinical assessment and dynamic MR imaging seem interchangeable in the anterior and central compartment (9).

MRI provides detailed images of bladder neck and urethral mobility, rectocele, cystocele, enterocele and uterine prolapse, in a single non-invasive study without exposing the patient to ionizing radiation (10-20). MRI also provides a multiplanar thorough evaluation of pelvic organs including the uterus, ovaries, ureters, kidneys, and levator muscles, as well as the urethra, that is unavailable by any other imaging modality (12, 14-18, 21, 22). MRI can identify ureteral obstruction, hydronephrosis, and uterine and ovarian pathology. In addition, MRI remains the study of choice for the evaluation of urethral diverticula.

The following measurements using MRI in urogynecology and female urology have been highlighted in the IUGA/ICS Joint Report on the Terminology for Female Pelvic Floor Dysfunction (23):

a) Bladder neck and cervical descent/mobility:

   1. Position of bladder neck and cervix at rest and on Valsalva.
   2. Pubo-coccygeal line: A line extending from the inferior border of the pubic symphysis to the last joint of the coccyx. Bladder neck or cervical descent >2 cm below this line with straining indicates weakness of the pelvic floor. If alternative landmarks are used in scientific papers they should be clearly described.

b) Intercurrent pelvic pathology: For example, fibroids, ovarian pathology.
c) Uterine version: Anteverted or retroverted; flexion at the isthmus.
d) Bladder abnormalities: For example, tumor; foreign body.
e) Urethral abnormality: For example, diverticulum.
f) Postoperative findings: For example, bladder neck mobility.
g) Pelvic floor measurements/levator defects: Assessment of the configuration of pelvic floor muscles, in particular, the levator ani.
h) Descent of pelvic organs.

This article is an update to the ICI article on the role of MRI in assessing the female pelvic floor (2012) and provides a current review of the role of MRI in understanding the causes and treatment of pelvic floor disorders.

4.2. Technique

4.2.1. Conventional MRI

Standard MRI consists of two-dimensional image acquisitions. In contrast to tumor diagnostics, MRI for urogynecological investigations can be performed without contrast media. The examination parameters are chosen organ- and examination-specific (T1, T2, proton density weighting)(24). The T2-weighted multiplanar slices are particularly suitable for visualizing the fine anatomical layers and structures, which allows, for example, the assessment of the layering of the vagina (mucosa, musculature and adventitia), urethra and its sphincters, different uterine structures, but also for the assessment of levator ani muscle fibers or ligaments **(Figure 27).** The T1 weighted sequences are ideal for the detection of fat, blood (for example hematocolpos/-metra in malformations), gas in infectious disease or metal (25). With technological advances, dynamic examinations of Valsalva maneuvers lasting 14 to 16 seconds can be recorded, which is reasonable in terms of time for the patient. Thus, MRI may become more widely used for functional assessment in the future, especially due to advances in technology and lower costs of the MRI examination. Contraindications for the use of MRI are non-MRI capable pacemakers and implants as well as severe claustrophobia. History of brain or heart surgery might also be a contraindication due to the use of potentially non-MRI-suitable clips or prostheses.

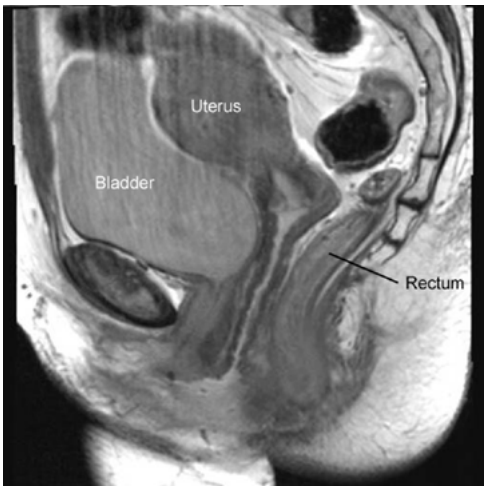


Figure 27: Sagittal mid pelvic section showing anatomical detail visible in static images made with Proton Density sequence.

4.2.2. Ultra fast image acquisition and MR sequences

Pelvic organ movement during Valsalva is identifiable using very fast single-shot MR sequences and the technical aspects have been summarized in a previous report **(Figure 28)** (ICI 2016) (16, 17, 26, 27). These sequential images are obtained approximately once per second, either as a series of images covering the entire pelvis (static imaging) or repetitively in one plane while the patient is straining (dynamic imaging). The patients are placed in the supine position with legs slightly spread apart, and knees bent and supported by a pillow. Most pelvic floor details can be seen without the need for bowel preparation, premedication, instrumentation or contrast medium but often, especially with MR defecography, ultrasound gel or other suitable agents are used to enhance visibility of the rectum and vagina. The MRI torso coil is centered at the symphysis pubis. Images are acquired in the sagittal plane using single-shot fast spin echo (SSFSE) or half Fourier acquisition, single shot turbo spin echo (HASTE) sequences. Single, mid sagittal views are obtained during 3 seconds of apnea with the patient relaxed and during various degrees of progressive abdominal straining.

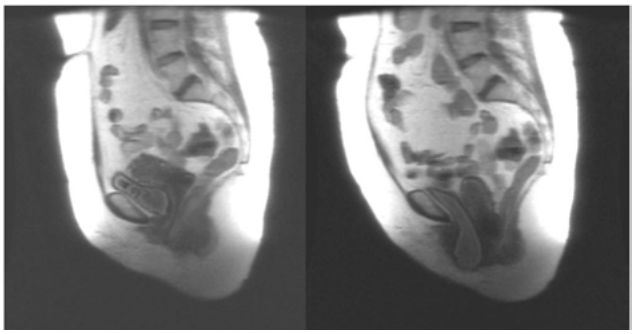


Figure 28: The rest and strain image taken from a mid-sagittal dynamic MR sequence revealing cystocele and uterine descent using SSFSE sequence.

Steady-state free precession gradient-echo imaging provides an alternative T2-like imaging contrast (T2- and T1-weighted imaging) with robust signal and a rapid acquisition time of less than 1 second, thereby permitting near real-time continuous imaging. This is an improvement on the HASTE approach that requires 1–2 seconds between acquisitions to allow T1 recovery; therefore, real-time imaging is not possible. Comparisons of the degree of POP shown on dynamic true fast imaging with steady-state precession (FISP) versus HASTE sequences in symptomatic patients reveal a greater degree of prolapse in all three compartments with a dynamic true FISP sequence. Near real-time continuous imaging with a dynamic true FISP sequence may therefore be useful to evaluate pelvic floor dysfunction in addition to dynamic multiplanar HASTE sequences (28).

During a typical study of pelvic organ movement two sets of images are obtained. The first set consists of static sagittal and para-sagittal images covering the pelvis from left to right sidewall. These images are used to select the mid-sagittal plane for the dynamic second set of images. This static sequence also allows for anatomic delineation of the pelvic sidewalls and muscular and fascial components of the pelvic floor (16, 17, 26, 27). The perineal membrane and the levator ani musculature, as well as the anal sphincter anatomy, are also clearly demonstrated (29, 30). The static set consists of 17-20 sequential images independently acquired in a total of about 18 seconds.

The second set of images consists of relaxed and straining mid-sagittal images used to assess the degree of pelvic floor relaxation and organ prolapse. Images can then be looped for viewing on a digital station as a cine stack.

Dynamic MRI allows detection of POP that may not be evident on conventional static sequences, as it permits both structural and functional evaluation. For example, in women with lower urinary tract symptoms, evaluation of the urethra may be of added value (31).

The first time a woman performs a Valsalva maneuver, she may not get the prolapse to protrude to its maximal extent. Forty per cent of women have a greater than 2cm increase in prolapse size from their first to third Valsalva attempt and 95% of women extend their prolapse further with a third Valsalva (32). As with clinical examination, several attempts may therefore be required to have maximal anterior compartment prolapse present during dynamic MRI of the pelvic floor. Delaney et al evaluated whether the use of a speculum blade modifies the evaluation of pelvic organ prolapse (POP) as assessed by dynamic MRI. Twenty-seven women with POP Quantification (POPQ) stage II or greater, scheduled for POP surgery, were evaluated using MRI. The procedure was repeated using the posterior blade of a standard plastic Grave's speculum to successively retract the anterior and posterior vaginal walls. Standard POPQ was 15% stage II (n =4), 59% stage III (n =16) and 26% stage IV (n =7). The use of a blade evidenced hidden pelvic prolapsed compartments in 59% (n =16) of cases. For 48% of patients (n =13), the variation of the leading edge of at least one additional prolapsed compartment was diagnosed as more than 20 mm. In this series, the use of a speculum blade during dynamic MRI modified the POP evaluation in a large proportion of patients with POP stage > or =II (33).

More recently, open magnetic resonance imaging (MRO) with vertical magnets, has allowed imaging in a variety of upright postures (34). A pilot study compared distances between the lowest point of the bladder to the pubococcygeal (35) and pubopromontoreal (PP) lines as well as the ratio of bladder area under the PC and PP lines to the total bladder area. Significant elongation between the PC line and lowest point of the bladder was evident in women with POP comparing supine and standing images ($p = 0.03$), but not controls ($p = 0.07$). Similarly, this axis was significantly longer in women with cystocele versus controls only in the standing position. Bladder area under the PC line was significantly increased between supine and standing positions only among women with cystocele ($p < 0.01$), and significantly larger among the study group in the standing position ($p < 0.005$), less significant in the supine position ($p = 0.015$), and not significant in the sitting position ($p = 0.3$) (36).

4.2.3. Three dimensional MRI

Three dimensional (3-D) MRI provides precise detail of the bony and muscular pelvic structures **(Figure 29)** so that 3D models can be constructed based on these detailed images. In this technique, static or dynamic images are reconstructed using consecutive planes in the axial, sagittal and coronal dimensions. Anatomic variations of the insertion and path of the pubococcygeus and iliococcygeus muscles can be seen. Fielding et al. made 3D models of the pelvic viscera and supporting muscles and bones with the marching-cubes algorithm and a surface-rendering method in nulliparous continent female volunteers and found that the muscle morphology, signal intensity and volume are relatively uniform (29). They described an average volume of the levator ani of 46.6 cc, width of the levator hiatus of 41.7 mm and an average posterior urethrovesical angle of 143.5°. In addition, these 3D models made

from multi-slice scans during a maximal Valsalva have allowed direct measurements of changes in the relationship between the vagina and pelvic walls.

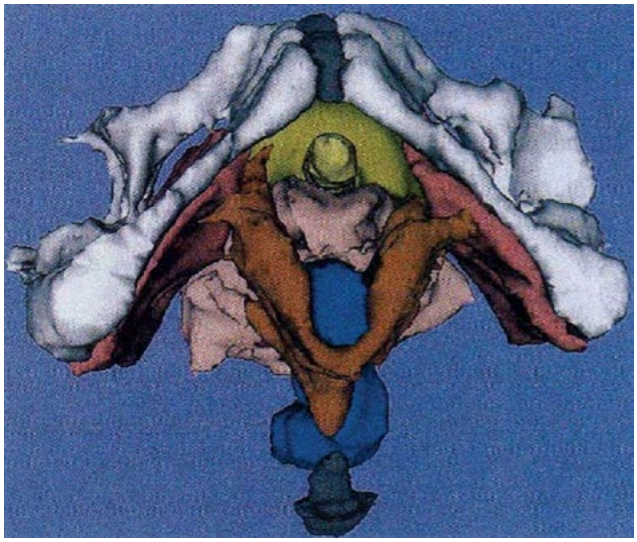


Figure 29: Pelvic Organs as seen from caudal on a three-dimensional reconstruction from Magnetic resonance images. Copyright Mosby Inc.

3D MRI enables evaluation of paravaginal defects, apical descent and vaginal widening. Larson et al (37) studied the relative contributions of "midline defects" (widening of the vagina) and "paravaginal defects" (separation of the lateral vagina from the pelvic sidewall) in women with anterior prolapse using 3D MRI models of the anterior vaginal wall and found that changes in lateral anterior vaginal wall were considerably greater than changes in vaginal width in cases vs controls. These "paravaginal defects" were also highly correlated with apical descent.

The geometry of the arcus tendineus fascia pelvis (ATFP) and arcus tendineus levator ani (38) in women with unilateral levator ani muscle defects and associated "architectural distortion" has been studied using 3D MRI. In those women, the ventral arcus anatomy is significantly altered in the presence of levator defects as well as architectural distortion, resulting in change of the supportive force direction along the lateral anterior vaginal wall, thus increasing the risk for anterior vaginal wall prolapse (39).

Luo et al (40) developed a method to evaluate changes in apical ligament lengths and lines of action from rest to maximal Valsalva using 3D stress magnetic resonance imaging (MRI). In a case-control study, 3D reconstructions of the uterus and vagina, cardinal ligament (CL), deep uterosacral ligament (USL(d)), and pelvic bones were created using 3D Slicer software. At maximal Valsalva, CL elongation was greater in cases than controls, whereas USL(d) was not; CL also exhibited greater changes in ligament length, and USL(d) exhibited greater changes in ligament inclination angle.

Following studies that reported diffusion tensor imaging (DTI) as a method for detecting alterations in tissue organisation of injured striated skeletal muscles, the clinical application of DTI and fibre tractography in pelvic floor imaging was assessed by Zijta et al (41). A two-dimensional (2D) spin-echo (SE) echo-planar imaging (EPI) sequence of the pelvic floor was acquired. Offline fibre tractography and morphological analysis of pelvic magnetic resonance imaging (MRI) were performed. Inter-rater agreement for quality assessment of fibre tracking results was evaluated. DTI with fibre tractography seems to enable 3D visualisation and quantification of elements of the female pelvic floor.

The first models of the pelvis, pelvic muscles and ligaments reconstructed in 3D from tracing a magnetic resonance imaging (MRI) were built from a female pelvis from a cadaver (42) and from a 45-year-old multiparous woman. The models were obtained with the aid of the Slicer® software an open source software platform for medical image informatics, image processing, and three-dimensional visualization (43).

4.2.4. Reference Lines and quantification of POP

As POP is a downward movement, quantification of this movement is of major importance to classify the descent in imaging. A number of studies have described reference values for grading POP (16, 17, 19). Traditional reference lines are drawn in the midsagittal plane and are based on certain anatomic landmarks. The pubococcygeal line (PCL) marks the distance from the pubis to the coccyx and serves as a fixed anatomical reference. In the nomenclature used by Comiter et al. (16), Gousse et al. (17), and Barbaric (27), the width of the levator hiatus is measured as the distance from the pubis to the pubococcygeus muscle (H-line). The hiatus is formed by the puborectalis muscle and encompasses urethra, vagina, and rectum. The M-line depicts the relaxation of the muscular pelvic floor by measuring the descent of the levator plate from the PCL. Using these three simple measurements, an MRI classification of the degree of POP has been described (16, 27). In the normal population, during straining, the hiatus (H-line) is less than 6 cm long and does not descend (M-line) more than 2 cm below the PCL. The upper urethra, urethrovesical junction, bladder, upper vagina, uterus, small bowel, sigmoid colon, mesenteric fat and rectum are all above the H-line. A combination of hiatal enlargement and pelvic floor descent constitutes relaxation. As the pelvic floor descends, so do the organs above it. The grading system for prolapse of any pelvic organ is based on 2 cm increments below the H-line. By determining the degree of visceral prolapse beyond the H-line, the degree of rectocele, enterocele, cystocele, and uterine descent can be graded in a 0 to 3 scale as follows: 0=none, 1=minimal, 2=moderate, and 3=severe. Other similar systems have been described (19) highlighting the need for standardization of nomenclature and grading of organ prolapse using MRI. In a small study, Ginath et al showed that MRI measurements of pelvic landmark angles can differentiate between women with and without uterine prolapse and correlate best with POPQ point C (44).

Novellas and colleagues evaluated two classification systems using the PCL and the midpubic line, (MPL) in 30 patients with symptoms of POP. For prolapse detection, the correlation between clinical examination and MRI ranged between 74 and 89%. For prolapse staging, the correlation was poor to moderate. Inter-observer agreement was good to very good (kappa between 0.67 and 0.95). It was slightly better at the mid stage, with both systems (kappa between 0.83 and 0.97). Comparison of the inter-observer agreement between both MRI classification systems showed better results for the system using the pubococcygeal line ($p<0.005$). The classification system based on the pubococcygeal line appeared more reliable and simple for the evaluation of pelvic prolapse on MRI (45). In another study, agreement between clinical and PCL staging was fair in the anterior (kappa = 0.29) and poor in the apical (kappa = 0.03) and posterior (kappa = 0.08) compartments. Agreement between clinical and MPL staging was fair in the anterior (kappa = 0.37), apical (kappa = 0.31), and posterior (kappa = 0.25) compartments. The MPL had higher agreement with clinical staging than the PCL

in this study. However, neither reference line had good agreement with clinical staging (46). The intra- and interobserver reliability of dynamic MR staging in POP patients has also been evaluated using various anatomical landmarks in relation to the PCL, H-line, and MPL. Clinical measurement points were assessed in relation to the mid-pubic line. Overall, the intra- and interobserver reliability of MR imaging measurements was excellent to good. The PCL showed superior reliability (intraclass correlation coefficients-ICC range 0.70-0.99). The reliability of clinical measurement points, however, were only moderate (ICC range 0.20-0.96). The intra- and interobserver reliability of quantitative prolapse staging on dynamic MR imaging were good to excellent. The PCL appeared the most reliable to use (47).

The sacrococcygeal-sacrospinous inferior pubic point (SCIPP) line is another widely used reference line, first introduced for measurements in the lateral cystourethrogram later applied in MRI (48). In pelvic floor imaging there have been used several reference lines, however there is no consensus yet, which reference line should be used in the clinical practice.

Singh et al (49) compared a new technique of grading POP by using dynamic MRI with the clinical staging proposed by the POP-Q system (50). A new reference line, the mid-pubic line, was drawn on the MR image to correspond to the hymenal ring marker used in the clinical staging. The proposed staging by MRI showed good correlation with the clinical staging (kappa = 0.61). Torricelli (51) also used MRI to evaluate functional disorders of female pelvic floor. In symptomatic women MRI confirmed the pelvic examination findings in all cases; MRI also detected additional alterations (4 cases of uterine prolapse and 3 of enterocele) that had been missed at clinical evaluation. Deval (52) compared dynamic MR imaging with physical examination as an alternative to dynamic cystoproctography for the evaluation of POP. PCL and puborectalis muscle were the reference points. The grading system is based on degree of organ prolapse through the hiatus and the degree of puborectalis descent and hiatal enlargement. They also used, the mid pubic line, which was drawn on the MR image to correspond to the hymenal ring marker used in clinical staging. Intra-operative findings were considered the gold standard against which physical examination, dynamic colpocystodefecography and MRI were compared. The sensitivity, specificity and positive predictive value of MRI were 70%, 100%, 100% for cystocele; 42%, 81%, 60% for vaginal vault or uterine prolapse; 100%, 83%, 75% for enterocele; 87%, 72% and 66% for rectocele. More recently Etlik (53) found physical examination and MR findings to be very concordant in the diagnosis of pelvic prolapse. Statistical correlations in the stages of prolapse between both of the methods were significant for anterior and middle compartment ($P<0.01$), as well as for posterior compartment ($P<0.05$).

Rosenkrantz et al evaluated the prevalence of pelvic organ prolapse as an incidental finding on dynamic magnetic resonance imaging (MRI) using the pubococcygeal line (PCL) and mid-pubic line (MPL) to diagnose and grade prolapse in all three pelvic compartments. Sixty women with symptoms unrelated to pelvic floor dysfunction who underwent dynamic MRI were included. In asymptomatic women, dynamic MRI identified the greatest degrees of prolapse in the posterior compartment. The MPL consistently yielded greater frequency of prolapse than the PCL. These findings however are of uncertain significance, requiring correlation with clinical examination (54).

Semiautomated pelvic floor measurement algorithmic models on dynamic MRI images have been developed and compared with manual pelvic floor measurements for pelvic organ prolapse (POP) evaluation. These models were shown to provide highly consistent and accurate locations for all reference points on MRI. The reference points can also be identified faster compared to manual-point identification (55). A fully automated localization method for multiple pelvic bone structures on magnetic resonance images (MRI) has been developed by the same group. Identifying structures of interest such as the pubic bone, sacral promontory, and coccyx correctly, by a fully automated identification method may result in improved diagnosis of female pelvic organ prolapse according to the authors (56).

Many different reference lines in relation to a wide variety of reference points have been used in different kind of studies. The definition of reference lines can be imprecise and interchangeable, such as the PCL and the SCIPP line. In 2013 Tunn and Rizk stated in an Editorial comment that a proper validation system for interpreting MRI measurements of POP is lacking and we urgently need to reach a consensus on a more standardized and scientifically robust MRI protocol for examination of the pelvis (57).

As a further advancement the Pelvic Inclination Correction System (PICS) line was introduced in 2013 by Betschart et al. It allowed the determination of descent of any pelvic organ in a standardized way, independent of the location of the pelvis in the scanner, whether it is tilted, flexed or extended, independent of the size or shape of the pelvis, and the orientation between different examinations or individuals (58). As the structures involved in prolapse, like the

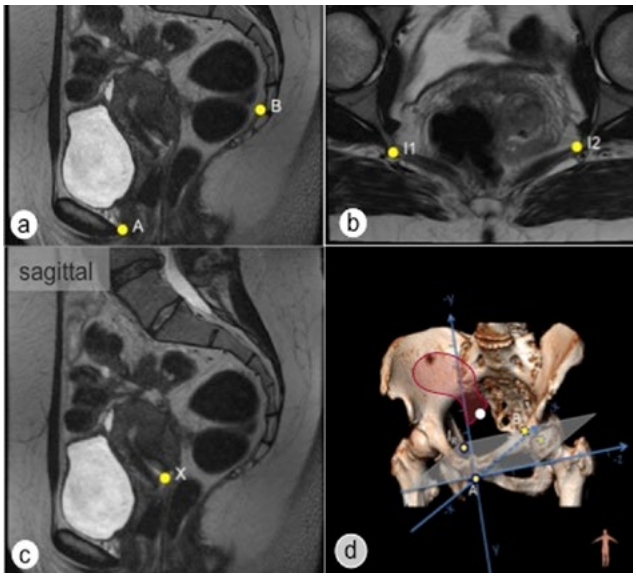


Figure 30: 3D PICS system to localize the cervix. To establish the 3D PICS coordinate system four bony landymark points are needed: a) symphysis (A), sacrococcygeal joint (B) in the midsagittal plane, b) ischial spines on the left and right side in the axial plane. c) localization of the cervix (x). d) Vector geometry can now be used to calculate the position of the cervix that is expressed with three coordinates (x/y/z, x=47, y=-54 and z=-9mm). The coordinates x means that the cervix is located 47mm from the symphysis on the antero-posterior x-axis, -54mm (y-value) means that the point lies cranially in the standardized PICS plane about 5cm above the introitus in the middle of the pelvis, and -9mm in the z-axis equals in a right-handed coordinate system 9mm to the left from the midline (59).

levator ani muscle and pelvic floor ligaments, are dispersed in the 3D space, a universally applicable 3D coordinate system was proposed that allows the measurement of any point, attachment or organ in the pelvis independent of the patient's position in the scanner, at rest or strain (59) **(Figure 30)**. Within this 3D measurement system defect localization of any point within the 3D space of the pelvis can be done. As it is based on bony landmarks in two perpendicular planes it not only allows spatial localization but also the comparison of outcomes between different surgical collectives independent of the actual position or time of the recording in the scanner and allows longitudinal studies before and after an event like a prolapse surgery or a delivery.

4.3. Normal Pelvic Floor Functional Anatomy

4.3.1. MR imaging of normal pelvic support structures

MRI studies of normal subjects have improved our understanding of normal pelvic anatomy, its variations (29) (30, 60) as well as anatomic changes in pelvic floor dysfunction (22, 61, 62).

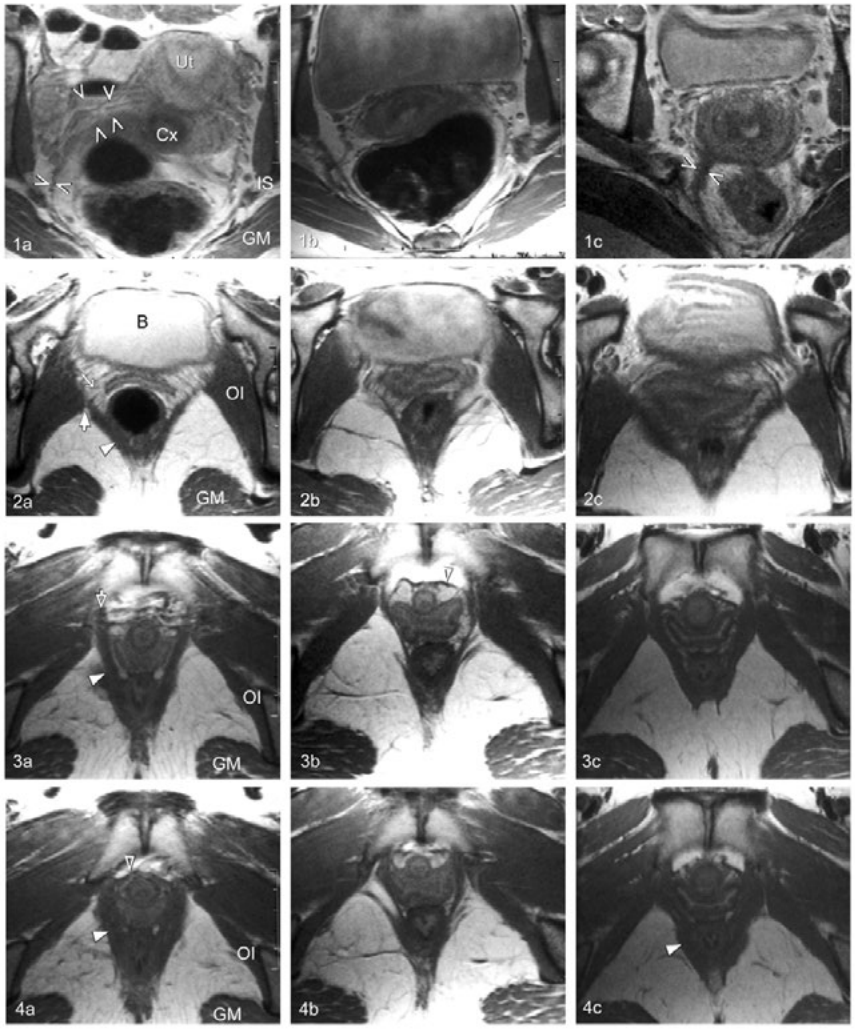


Figure 31: Axial images according , in 22-year-old (A, D, G, and J), 24-year-old (B, E, H, and K), and 34- year-old (C, F, I, and L) nulliparous women without urogynecologic problems. A-C, Level of cervix (Cx) and ischial spine (IS); uterus (Ut) with bright endometrium is also seen. Paracolpium and parametrium suspend (open tips) vagina and cervix from lateral and posterior pelvic sidewall. Smooth muscle of uterosacral ligament (open tips) is best seen in C. GM, Gluteus maximus muscle. D-F, Level of bladder (B) base. Upper vagina between bladder and rectum (R) and its attachment to pelvic sidewall by vascular and connective tissue mesentery (small arrow) are seen. Levator ani muscle (iliococcygeal part, filled arrowhead) arises from arcus tendineus of levator ani muscle (filled arrow). OI, Obturator internus muscle. G-I, At level of proximal urethra, levator ani muscle (pubovisceralis part, filled arrowhead) arises from pubic bone (open arrow). Pubovesicalis muscle (open arrowhead) is clearly seen in H. Vessels (white gap) are visualized between smooth muscle layer of lateral vaginal wall and levator ani muscle at this level. J-L, At level of middle urethra, pubovesicalis muscle is seen as shown in J (open arrowhead). Vessel layer (white gap) between lateral vaginal wall and levator ani muscle (filled arrowhead) has disappeared; direct connection between vagina and levator ani muscle is seen at this level. Small white gap in levator ani suggests fascia between puborectalis and pubococcygeal muscles (especially in J and L)(179).

In the supine position the female pelvic floor is dome-shaped at rest (62, 63). During voluntary pelvic floor contractions, the levator musculature straightens and becomes more horizontal. With bearing down the muscle descends, the pelvic floor becomes basin-shaped, and the width of the genital hiatus widens.

With MRI the specific structures are identified and their normal variations described (**Figure 31**). Tan (61) demonstrated the anatomy of the female pelvic floor with MRI. The pelvic and the urogenital diaphragm were well depicted as were urethral supporting structures—the peri-urethral and paraurethral ligaments, the pubovesical muscle, the lateral vesical ligament and the zonal anatomy of the urethra (64). The MRI findings in volunteers correlated with the endovaginal MR findings and gross anatomy in cadavers. Chou (65) studied the urethral support structures relative to the arcuate pubic ligament including the arcus tendineus fasciae pelvis, the perineal membrane, the pubococcygeal levator ani muscle and its vaginal and bony attachments, and the pubovesical muscle. Tunn et al (66) showed that 2- to 3-fold differences occur in distance, area, or volume measures of continence system morphologic features in continent nulliparous women with normal pelvic organ support and urodynamics. Sekhar et al described female urethral pathology including benign lesions, malignancy and post-intervention appearance (67).

The uterosacral ligaments also exhibit greater anatomic variation than their name would imply (68). A first quantitative analysis of uterosacral ligament origin and insertion points was done by Umek et al. This study remains unsurpassed to date in its morphometric accuracy and size of study collective (68).

Three dimensional simplified biomechanical models constructed from MRI scans showed that the CL is parallel to the body axis. The US ligament is dorsally directed. The tensions on these ligaments seem to be affected by their orientations according to this study (69). Luo et al performed stress MRI to analyze the 3D changes in apical ligament geometry within the uterosacral – cardinal ligament complex. At maximal Valsalva the CL elongation was greater in women with prolapse then in controls, whereas the USL exhibited a greater change in the ligament inclination angle downwards (40).

Kaniewska et al described the female pelvic anatomy with special focus on the suspensory ligaments of the female genital organs as depicted with MRI. They also proposed a checklist for structured reporting of the MRI findings in the female pelvis (70).

Characteristic anatomic features of the posterior compartment and perineal body have been studied with MR cross-sectional anatomy and can be further elucidated and integrated with 3-D anatomy. In nulliparous asymptomatic women the posterior compartment's upper, mid, and lower segments are best visualized in MRI in the axial plane. It is bounded inferiorly by the perineal body, ventrally by the posterior vaginal wall, and dorsally by the levator ani muscles and coccyx. In the upper portion, the compartment is bordered laterally by the uterosacral ligaments, whereas in the middle portion, there is more direct contact with the lateral levator ani muscles. In the lower portion, the contact becomes obliterated because the vagina and levator ani muscles become fused to each another and to the perineal body (71) (**Figure 32**). The perineal body anatomy has been possible to study using 2mm MR images. Visualization of perineal body anatomy in living women and development of 3-D models enhanced our understanding of its 3 different regions: superficial, mid, and deep (72). The three distinct perineal body regions (73) are a superficial region at the level of the vestibular bulb, a midregion at the proximal end of the superficial transverse perineal muscle, and a deep region at the level of the midurethra and puborectalis muscle. Structures are best visualized on axial scans, whereas craniocaudal relationships are appreciated on sagittal scans. In the superficial portion at the level of the vestibular bulb (VB), the bulbospongiosus (BS) inserts into the lateral margins of the perineal body, whereas the superficial transverse perineal muscle (STP) and external anal sphincter (EAS) traverse the region. In the perineal body's midregion at the proximal end of the superficial transverse perineal muscle, the puboperinealis muscle inserts into the lateral margins of the perineal body and in some individuals can be seen to cross the midline. This region also contains the distal internal anal sphincter. The puboanalis muscle is also visible as it inserts in the intersphincteric groove between internal and external anal sphincters. The puboanalis muscle and internal anal sphincter extend into the perineal body's most deep region at the level of the midurethra. Here the pubovaginalis muscle also becomes visible as it fuses with

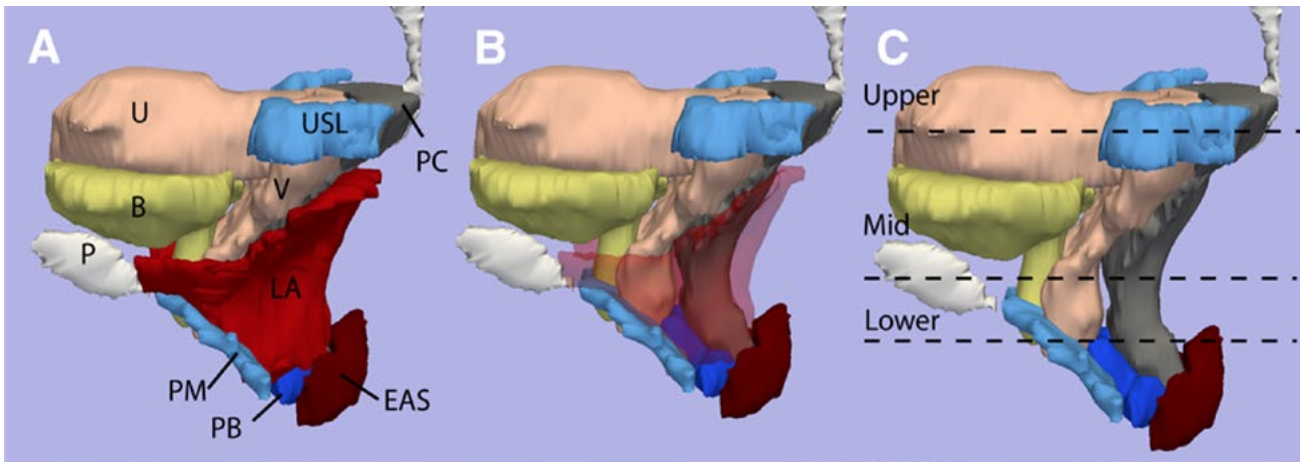


Figure 32: The outline of the midsagittal pubic bone (P) is shown. The bladder (B) is yellow; the uterus (U) and vagina (V) are pink; the uterosacral ligament (USL) and perineal membrane (PM) are turquoise blue; the levator ani muscle (LA) is red; the perineal body (PB) is royal blue; the external anal sphincter (EAS) is dark red; and the posterior compartment (35) is gray. Image A, All organs are shown. B, Levator ani muscles have been faded to show the underlying structures. C, Levator ani muscles have been removed. The locations of the upper, mid, and lower axial cross-sections are shown.(71) Reprinted with permission from John O. L. DeLancey.

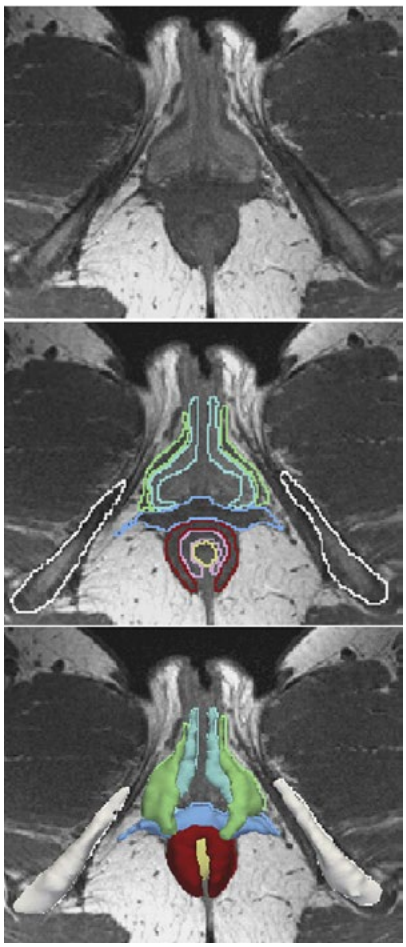


Figure 33: 3D Model of the perineal body (72).

the vaginal side wall, sending fibers posteriorly to the perineal body. In this location, the longitudinal muscle of the rectum may be visible in the midline. The puborectalis muscle forms a loop behind the rectum at this level but does not contribute fibers to the perineal body (**Figures 33 & 34**).

One of the key anatomical contributions MRI has made to the understanding of normal pelvic floor structure, regards the ability to make images of a wide variety of normal living women. The pelvic floor is greatly distorted in cadavers due to loss of muscle tone and pressures during embalming. Otcenasek et al have used MR images of a normal nulliparous woman to establish geometry and then added details from dissection to produce an anatomically based topographically normal 3-D model that displays the features of pelvic floor anatomy (**Figure 35**)(74).

Nardos et al (75) compared levator hiatus measurements between pelvic magnetic resonance imaging (MRI) and 3-dimensional pelvic ultrasound (US) in 37 asymptomatic nulliparous women. They found that the MRI measurements obtained from the sagittal images were consistently greater than the ones obtained by US. However, there was no such difference between MRI and US for the axial images. The authors attributed this observation to acquisition planes for axial images or interpretation of landmarks for the sagittal images.

4.3.2. Levator Ani Muscle Functional Anatomy

Evidence from MR and CT images in volunteers and cadavers shows that the anterior transverse portion of the levator muscle is basin-shaped; the middle transverse portion funnel-shaped, while the posterior transverse portion dome-shaped. The puborectalis appears u-shaped outside the vertical portion (76). On MR images of the five Terminologia Anatomica-listed levator ani components: pubovisceral (pubovaginal, puboperineal, and puboanal), puborectal and iliococcygeal portions of the levator ani muscle muscles in women with normal pelvic support., the puborectal muscle can be seen lateral to the pubovisceral muscle and decussating dorsal to the rectum in the axial plane. The course of the puboperineal mus-

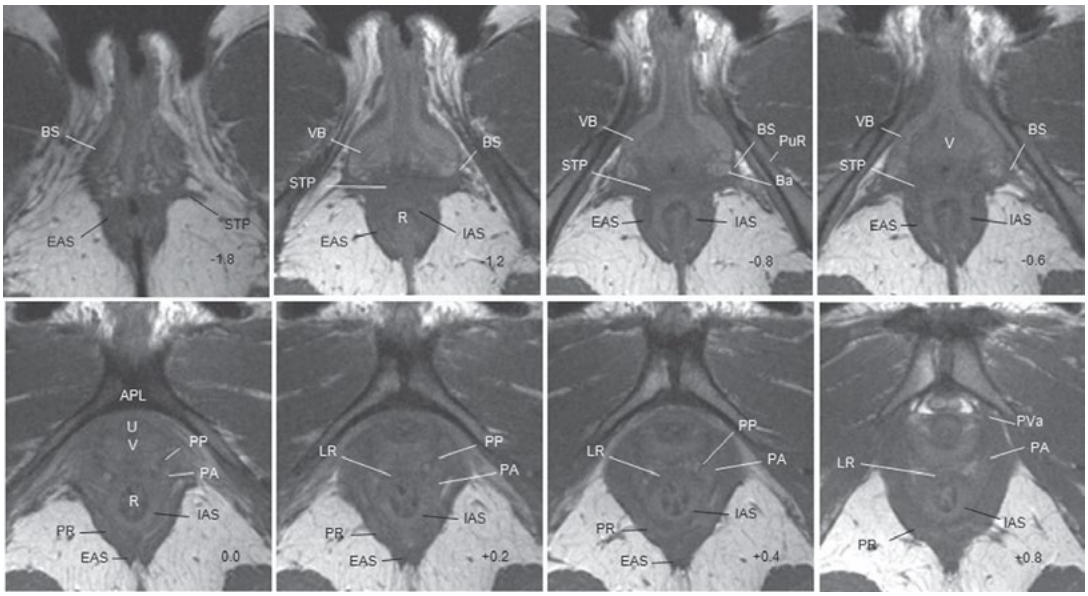


Figure 34: Arcuate pubic ligament (APL) as reference slice. Negative numbers are caudal and positive numbers are cephalad to APL.
B, bladder; Ba, Bartholins; IAS, internal anal sphincter; IC, iliococcygeus; PB, perineal body; PR, puborectalis; PS, pubic symphysis; PuR, pubic rami; R, rectum; U, urethra; V, vagina; VB, vestibular bulb (72).

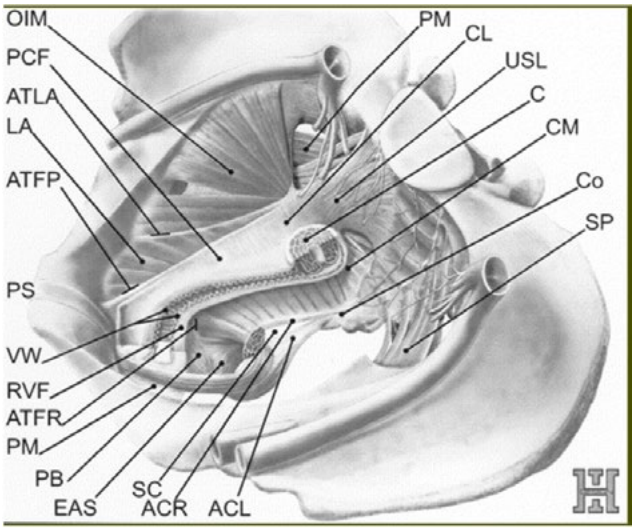


Figure 35: Left lateral view from above the female pelvis. The vagina, endopelvic fascia, and levator ani muscle are cut in the sagittal plane. Urethra, urinary bladder, and rectum have been removed. OIM, obturator internus muscle; PCF, pubocervical fascia; ATLA, arcus tendineus levator ani; LA, levator ani muscle; ATFP, arcus tendineus fasciae pelvis; PS, pubic symphysis; VW, vaginal wall; RVF, rectovaginal fascia; ATFR, arcus tendineus fasciae rectovaginalis; PM, perineal membrane; PB, perineal body; EAS, external anal sphincter; SC, space of Courtney; ACR, anococcygeal raphe; ACL, anococcygeal ligament; PM, piriformis muscle; CL, cardinal ligament; USL, uterosacral ligament; C, cervix of the uterus; CM, coccygeus muscle; Co, coccyx; SP, sacral plexus. Illustration: Ivan Helekal (74).

cle near the perineal body is also seen best in the axial plane. The coronal view is perpendicular to the fiber direction of the puborectal and pubovisceral muscles and shows them as “clusters” of muscle on either side of the vagina. The sagittal plane consistently demonstrates the puborectal muscle passing dorsal to the rectum to form a sling that can be seen as a “bump”. This plane is also parallel to the pubovisceral muscle fiber direction and shows the puboperineal muscle (77)(**Figure 36**).

Betschart et al (78) described a technique to quantify muscle fascicle directions in the levator ani (LA): Among levator subdivisions, significant angle differences were observed between PVM and PRM (60 degrees), and between ICM and PRM (52 degrees). An 84 degrees difference was observed between PVM and EAS. The smallest angle difference was between PVM and ICM (8 degrees). The difference between PRM and EAS was 24 degrees.

Recent studies looked at the levator ani muscle volume in relation to BMI or age. In two studies by Morris and levator ani muscle did not show evidence of significant age- or body-weight related levator ani muscle atrophy (79, 80). Contradictory results and an age-dependent thinning of the levator ani muscle showed a study by Komemushi and colleagues: for patients aged ≤65 years, both men and women significant differences in the median muscle thickness (men: 3.8 mm vs 3.1 mm, P ≤ 0.0001; women: 4.1 mm vs 2.6 mm, P ≤ 0.0001) were shown (81). Swenson and colleagues showed also an increase of the levator bowl volume with aging and a more posterior distension of the muscle, independent of childbirth changes to the genital hiatus (82).

4.4. Pathophysiology of Pelvic Floor Disorders

4.4.1. Levator Ani (LA) Muscle Defects

Lammers et al (83) assessed the inter- and intraobserver reliability of the diagnosis of pubovisceral muscle avulsions and measurements of the levator hiatus on MRI and confirmed that pubovisceral muscle avulsions and levator hiatus measurements can be assessed with good to excellent reliability on MRI.

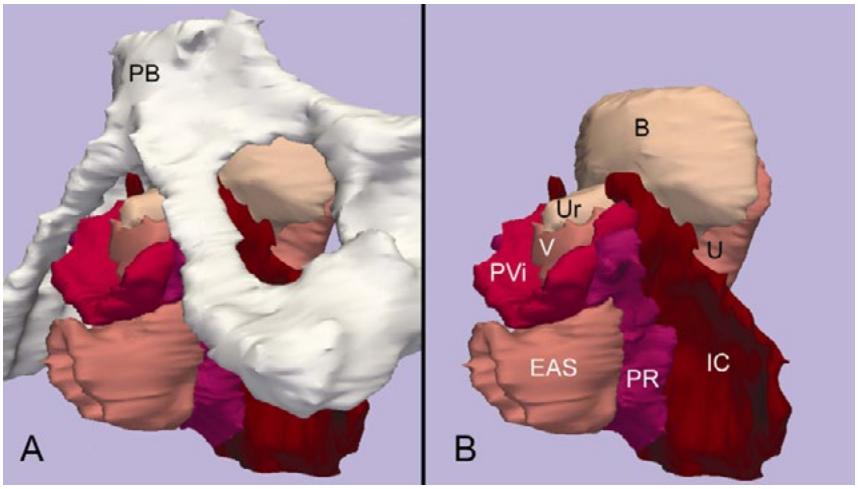


Figure 36: Three-dimensional model of levator ani subdivisions including the pubic bone and pelvic viscera. This model was created by using the magnetic resonance images shown in Figures 2, 3, and 4. The pubovaginal, puboperineal, and puboanal muscles are all combined into a single structure, the pubovisceral muscle. Inferior, left 3-quarter view. B. The same model without the pubic bone. PB, pubic bone; V, vagina; U, uterus; Ur, urethra; B, bladder; IC, iliococcygeus muscle; PR, puborectal muscle; PVi, pubovisceral muscle; EAS, external anal sphincter. © DeLancey 2006. Margulies (77).

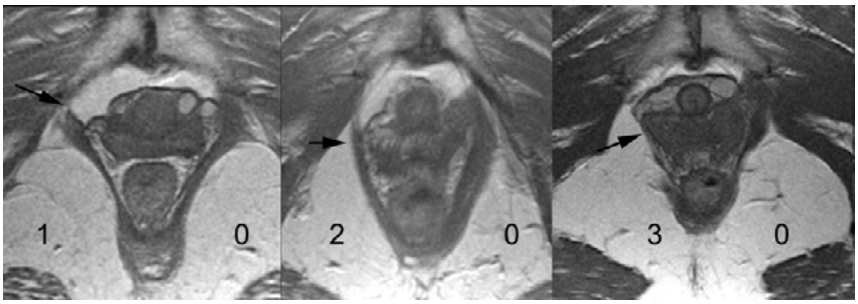


Figure 37: Examples of grades of defects in the pubovisceral portion of the levator ani muscle in axial magnetic resonance images at the level of the mid urethra. These were selected to illustrate degrees of defects in individuals with a normal contralateral pubovisceral muscle. The score for each side is indicated on the figure, and the black arrows indicate the location of the missing muscle. A. A grade 1 defect; B. A grade 2 defect; and C. A grade 3 defect. © DeLancey 2006 (84).

In a case control study with group matching for age, race, and hysterectomy status (84), women with prolapse (cases) were compared to those with normal support (controls). Major defects were those that lost more than 50% of the muscle bulk. Cases were more likely to have major levator ani defects than controls (55% compared with 16%), but equally likely to have minor defects (16% compared with 22%) **(Figures 37 & 38).** Women with defects generated less vaginal closure force during a pelvic muscle contraction than women without defects (2.0 Newtons compared with 3.1 Newtons) and women with prolapse also generated less vaginal closure force during pelvic muscle contraction than controls (2.0 Newtons compared with 3.2 Newtons). This confirmed earlier uncontrolled observations with ultrasound (85).

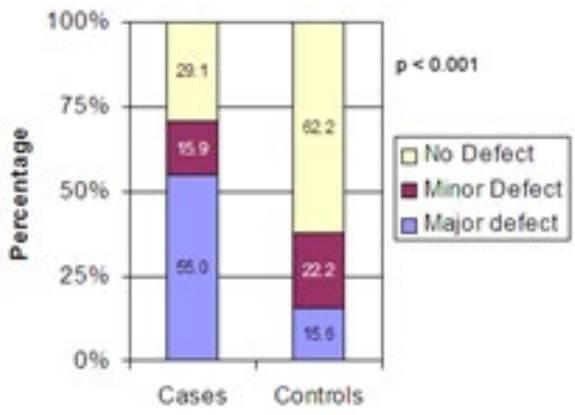


Figure 38: Percentages of cases and controls with no defects, minor defects, and major defects; P_.001. © DeLancey 2006 (84).

It is important to distinguish between muscle thickness and muscle damage. A woman with a normally thin but intact muscle may have less muscle substance than a woman with naturally bulky muscles who has a defect that has involved 25% of her muscle bulk. The issue of muscle damage is relevant to seeing who is injured, while that of muscle bulk, with the capability of the muscle to close the hiatus. Hoyte et al (86) examined 10 women with prolapse, 10 with urodynamic stress incontinence, and 10 asymptomatic volunteers. Mean 3-dimensional parameters in the 3 groups showed levator volumes of 32.2, 23.3, and 18.4 cm^3 (P <0.005); hiatus widths of 25.7, 34.7, and 40.3 mm (P <0.005); left levator sling muscle gaps of 15.6, 20.3, and 23.8 mm (P =0.03), right levator sling muscle gaps of 15.6, 22.5, and 30.8 mm, (P =.003), and levator shape (90%, 40%, and 20% dome shaped; P <0.005). Subsequently, using a novel thickness mapping (87), they found thicker, bulkier anterior portions of the levators in asymptomatic women, compared with women with prolapse or urodynamic stress incontinence while the more posterior portions of the muscle were not affected.

Hsu and colleagues quantified levator ani muscle cross-sectional area as a function of prolapse and muscle defect status (88). Using muscle cross-sections from 3-D reconstructions they found that women with visible levator ani defects on MR have less muscle ventrally compared with women with intact muscles. Women with major levator ani defects had larger cross-sectional areas in the dorsal component than women with minor or no defects indicating a compensatory hypertrophy in this area. Furthermore, after controlling for prolapse, women with levator defects appear to have a more caudal location of their perineal structures and larger hiatuses at rest, maximum contraction, and maximum Valsalva maneuver (89).

Among women with POP, those with major LAD appear less likely to experience stress incontinence when “coughing, laughing, or sneezing” (odds ratio (OR) 0.27) and when “twisting, reaching, lifting, or bending over” (OR 0.26) than women with normal muscles. They are less likely to have obstructive symptoms characterized by assuming an “unusual toileting position” or “changing positions... to start or complete urination” (OR 0.27). Women with minor LAD appear more likely to experience stress incontinence with exercise (OR 3.1) and urge incontinence (OR 4.0) than those with normal muscles. Lower urinary tract symptoms are therefore less common among women with prolapse and major levator ani defects and more common among those with minor defects (90). This may be explained by the fact that the women with major LA defects have larger prolapses than those who do not have major LA defects. It is a clinical observation that prolapse often reduces the occurrence of stress incontinence (urethral kinking?) and this hypothesis is consistent with the observations mentioned above.

Cai et al (91) evaluated levator ani morphology and function in healthy nulliparous women using static and dynamic MRI. They found no morphologic abnormality in healthy nulliparous women. However, in 15% (12/80) of women, pelvic organ descent below the pubococcygeal line was observed. In these women, the width of the pubic portion of the levator ani was significantly reduced during straining, whereas the levator plate angle, the levator hiatus area, and the H and M line lengths were enlarged. These changes were associated with weakened levator ani function and pelvic floor laxity.

Longitudinal studies on the changes of the pelvic floor before, during and after pregnancy are scarce. In one study, 19 subjects seeking assisted reproductive medicine underwent a pre-pregnancy pelvic MRI and 10 of the women underwent a post-pregnancy pelvic MRI 6 months after delivery. Pregnancy and delivery resulted in increased pelvic mobility in both vaginal delivery and elective cesarean delivery patients and in 20% of the women a levator injury was described (92).

Not only birth-related injuries have been addressed by MRI, also pregnancy-related USL and LA changes were subject of imaging research. In a sequential MRI exam three time points during pregnancy and two times postpartum (at 6 weeks and 12 months), the levator ani muscle and the uterosacral ligament after a c-section were still longer postpartum at 12 weeks than at week 16 of gestational age (93).

4.4.2. Identifying the Injury Zone within the Levator Ani

Muscle most often involved by Injury

MRI based 3D models show that in women with bilateral puborectal muscle avulsion after vaginal delivery, the damage affects the pubic origin of the muscle. This structural change alters the support to the whole endopelvic fascia and destabilizes both the anterior and the posterior vaginal walls (94). In women with significant muscle on one side and damaged muscle in the same individual (95) the injury involves the muscle's origin from the posterior pubic bone **(Figure 39).** Distortion of the surrounding connective tissue with lateral spilling of the vagina towards the obturator internus muscle is observed in 50% of women. The defect is right sided in 71% of patients. The average difference of the amount of muscle lost in these types of injury between the normal side and the defective side is up to 81% at locations nearest the pubic origin (96). Almost all of the volume difference (13.7%, P=0.0004) is attributable to a reduction in the pubic portion (24.6%), not the iliococcygeal portion of the muscle.

An estimate of levator ani muscle stretch during delivery was published using MRI of a live childbirth. Three-dimensional magnetic resonance image sequences were obtained from coronal and axial planes before the expulsion phase without pushing and during the expulsion phase, occurring over 2 contractions. A maximum circumferential stretch of 248% on the posterior-medial portion of the levator ani muscle was shown (97).

4.4.3. Changes in the Hiatus Size and Levator Plate Angle with Prolapse

The levator ani muscle's constant activity closes the genital hiatus. In addition to evaluating defect status and muscle bulk, MRI has revealed changes to the levator hiatus and angle of the levator plate (that midline portion of the muscle between the anus and the coccyx) which is presumed to be influenced by muscle action. Hsu and colleagues (98) studied 68 women with pelvic organ prolapse and 74 normal controls. During Valsalva, controls had a mean levator plate angle of 44.3 degrees. Cases had 9.1 degrees (21%) more caudally directed levator plate angle compared to controls (53.4 degrees vs. 44.3 degrees), 15% larger levator hiatus length (7.8 cm vs 6.8 cm), and 24% more caudal perineal body location (6.8 cm vs 5.5 cm). Increases in levator plate angle were correlated with increased levator hiatus length (r = 0.42) and perineal body location (r =.51). The bladder neck descent at straining is also correlated with the levator plate angle at rest, hiatus length at rest and at straining (99). Uterine cervix descent at straining is correlated with increased hiatus length and width at straining, and greater levator plate angle (p=0.007) at straining. Paradoxically anterior rectal

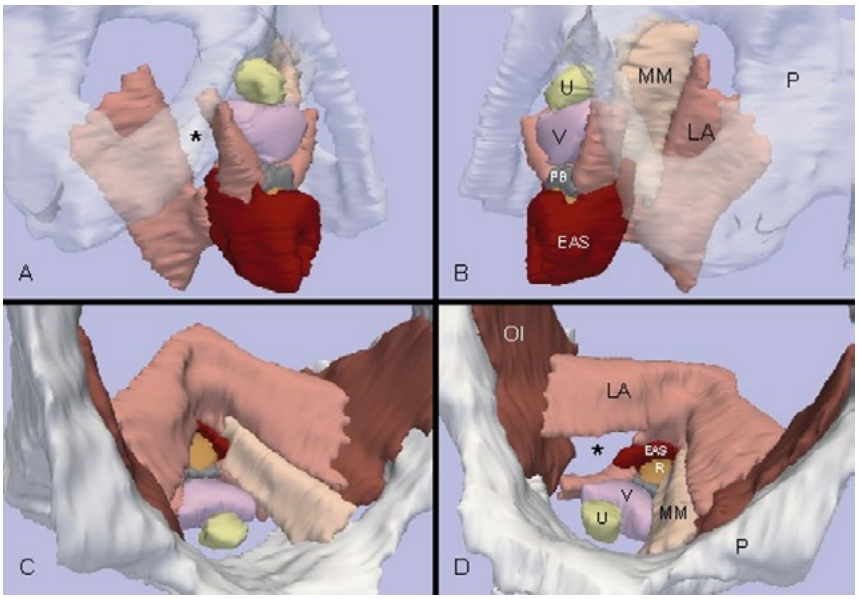


Figure 39: Three-dimensional model generated from the axial MR scans shown in Figure 1. A, and B, Oblique right and left inferolateral views, similar to the dorsal lithotomy position, are shown. In these panels the pubic bone is semitransparent and the obturator internus muscle is not shown. C, and D, Oblique right and left views peering over the pubic bone and down to the pelvic floor are shown. The urethra, vagina, and rectum have been truncated so as not to obscure the views of the levator muscles. EAS, external anal sphincter; LA, levator ani; MM, mirror image of the missing muscle; P, pubis; PB, perineal body; U, urethra; V, vagina. The missing muscle in A and D is denoted (asterisk). © DeLancey 2006 (95) .

bulging at straining is inversely correlated with the hiatus width at rest (p = 0.04).

Perineal descent and localized outward bulging of the levator ani during Valsalva was evaluated by Gearhart and colleagues (100). In this study, dynamic MRI of symptomatic patients with pelvic floor prolapse demonstrated unsuspected levator ani hernia. Patients with POP, fecal and/or urinary incontinence, or chronic constipation were evaluated. Fifteen percent of patients (12/80) had unilateral (n = 8) or bilateral (n = 4) levator ani hernias on MRI. Perineal descent on physical examination was associated with a levator ani hernia in nine patients.

4.4.4. MRI and the Bony Pelvis

Studies of the bony pelvis dimensions and their associations with POP, levator ani defects and stress incontinence have recently been undertaken. Stein et al showed that bony pelvis dimensions are similar at the level of the muscular pelvic floor in white women with and without POP (101). Further evaluation of the bony pelvis using MRI scans has also improved our understanding of the natural history of stress urinary incontinence as well as the associations of the bony pelvis dimensions with the prevalence of levator defects (102). Other studies investigating the role that different pelvis shapes play for specific diseases will be described in subsequent sections of this review.

Pipitone and colleagues analyzed musculoskeletal findings in 18 women with postpartum pelvic pain. They found a high number of musculoskeletal abnormalities 4.5 months after vaginal deliveries. In 94.4% lesions were found with MRI and they correlated highly with the symptoms. Most prevalent chronic injuries were bone oedema, pelvic bone fractures and levator ani injuries (103).

4.4.5. MRI of Pelvic Floor After Vaginal Delivery

There are changes observed in the levator ani and pelvic floor musculature immediately after delivery, which change over time. Boreham (104) evaluated the normal visibility of the levator in post term nulliparas using 3-dimensional (3-D) MRI. LA insertion into the symphysis was visible in 93%, and the iliococcygeus muscle assumed a convex shape (arch) in 92% of 84 nulliparas. Mean LA volume was 13.5 (3.7) cm^3. Interestingly there was a positive association between LA volume and higher fetal station with increasing BMI. The muscle signal intensity appears increased at 1 day postpartum on T2 weighted images, but normal by 6 months. The urogenital and levator hiatus decreases significantly by 2 weeks postpartum (105). Lienemann (106) found thinning of the puborectal muscle in primiparous women after vaginal delivery (0.6 cm vs. 0.8 cm) and increased descent of the bladder, vaginal fornix, and anorectal junction during straining compared to healthy asymptomatic nulliparous volunteers.

The descent of the bladder and cervix on straining appears greater in women who delivered vaginally compared to those who had cesarean delivery and to nulliparous women. There is a positive correlation between the duration of labor and the area of the levator sling and also between birthweight and the descent of the cervix on straining (107).

The role of levator ani muscle damage and stress soon after birth has also been studied. An investigation of 80 nulliparous asymptomatic women and 160 vaginally primiparous women half of whom had new stress incontinence after their first birth was conducted 9 months after delivery. A visible defect in the levator ani muscle was identified in 32 primiparous. Twenty-nine of these 32 defects were in the pubovisceral portion of the levator and three were in the iliococcygeal portion. None of the nulliparous women showed these abnormalities (108). In a further study of this cohort (109) evaluation of obstetric factors associated with levator ani injury after first vaginal birth showed increased odds ratios for levator defect: forceps use 14.7, anal sphincter rupture 8.1 and episiotomy 3.1 but not vacuum delivery (0.9) epidural use (0.9) or oxytocin use (0.8). Women with levator injury were 3.5 years older and had a 78-minute longer second stage of labor. Differences in gestational age, birth weight, and head circumference were not statistically significant.

Dannecker (110) compared women after spontaneous vaginal delivery to those delivered by vacuum extraction and a control group of healthy nulliparous volunteers. Significant differences for individual POPQ component measurements were noted for points Aa and Ba, TVL, and GH (spontaneous delivery versus control) and in addition for Ap, Bp, and D (vacuum extraction versus control). Significant differences were observed for the position of bladder base, bladder neck, posterior vaginal fornix, anorectal junction, hiatus perimeter and depth of rectocele. Looking into comparisons with the spontaneous vaginal delivery group, on clinical examination, there was more evidence of anterior vaginal wall descent after vaginal delivery, and TVL and GH. Differences between the groups with regard to points Ap and Bp reached only marginal significance. With MRI measurements primiparous women who underwent spontaneous vaginal delivery as compared to nulliparous women showed considerable and statistically significant descent of almost all assessed structures at rest and on straining. Bladder base, bladder neck and the anorectal junction descended even below the respective reference lines. The bladder neck showed considerably increased mobility, and the genital hiatus showed an increased change on straining. The depth of rectocele increased more than three times. One of 26 women (4%) had a rectocele >3 cm. POPQ measurements that differed significantly between primiparous women after vacuum extraction and nulliparous women of the control group indicated more evidence of anterior and posterior vaginal wall descent after vacuum extraction. In addition TVL and GH was increased and PB was decreased after vacuum extraction. MRI measurements after vacuum extraction, showed considerably increased descent and mobility of the bladder base and bladder neck on straining, and descent of the anorectal junction was prominent. The mean depth of rectocele was four times bigger than in the nulliparous group. Four of 49 women (9%) had a rectocele >3 cm.

Branham and colleagues (111) evaluated postpartum changes in the levator ani muscle in relation to obstetric events. In those subjects recovering to normal MR by 6 months an average of nearly 60% increase in right puborectalis muscle thickness compared with that seen at 6 weeks indicated the extent of the injury. Younger white primiparous women had a better recovery at 6 months than older white women. Subjects experiencing more global injury, in particular to the iliococcygeous, tended not to recover muscle bulk.

Heilbrun and colleagues investigated the correlation between the presence of major LAM injuries on MRI with fecal incontinence (FI), POP, and urinary incontinence (UI) in primiparous women 6-12 months postpartum using a scoring system to characterize LAM injuries on MRI. Major LAM injuries were observed in 19.1% women who delivered vaginally with external anal sphincter (EAS) injuries, 3.5% who delivered vaginally without EAS injury, and 0% who delivered by cesarean section before labor (P=.0005). Among women with EAS injuries, those with major LAM injuries trended toward more FI, 35.3% vs. 16.7% (P=.10) and POP, 35.3% vs 15.5% (P=.09), but not UI (P=1.0). These data confirm that both EAS and LAM are important for fecal continence and that multiple injuries contribute to pelvic floor dysfunction (112) .

Handa and colleagues used MRI to measure bony and soft tissue pelvic dimensions in 246 primiparas, 6-12-months postpartum. A deeper sacral hollow was significantly associated with fecal incontinence (P = 0.005). Urinary incontinence was marginally associated with a wider intertuberous diameter (P = 0.017) and pelvic arch (P = 0.017). There were no significant differences in pelvimetry measures between women with and without prolapse in this study (113).

In another prospective study, 51 primiparous women (vaginal delivery group: 30 women; elective caesarean delivery group: 21 women) underwent static and dynamic MRI at 1 week, 6 weeks, 3 months, and 6 months postpartum to measure pelvic floor MRI values. Pelvic floor recovery primarily occurred during the early phase after delivery in both groups. Elective caesarean delivery had a non-significant protective effect on postpartum pelvic floor structure and function compared to vaginal delivery (114).

4.4.6. MRI and Biomechanical Investigation of the Pelvic Floor

MRI has allowed anatomically based biomechanical models to be constructed. Simulations have demonstrated important interactions between muscle and connective tissue in providing anterior vaginal wall support (115). MRI has enabled construction of finite element analysis (116, 117). It has also allowed for capture of 3D shape variation of the levator ani during straining where complete volumetric imaging is prohibited by the inherent temporal resolution of the scanning technique (118).

Chen developed and validated recently a 3D finite element computer model of the anterior vaginal wall and its supports based on spatial data from MR scans of normal women. They determined the combinations of muscle and connective tissue impairments that result in cystocele formation, as observed on dynamic MRI geometry from a healthy nulliparous woman. It included simplified representations of the anterior vaginal wall, levator muscle, cardinal and uterosacral ligaments, arcus tendineus fascia pelvis and levator ani, paravaginal attachments, and the posterior compartment. The authors found that development of a cystocele requires a levator muscle impairment, an increase in abdominal pressure, and weakening of apical and paravaginal support (119). These simulations provide a way to see what specific changes in structural components do to pelvic organ support in ways that would be impossible to study in living women.

Peng et al (120) assessed urethral support by developing a pelvic model from an asymptomatic female patient's MR images using the finite element method. Weakening the vaginal walls, puborectalis muscle, and pubococcygeus muscle generated the top three largest urethral excursion angles. Weakening all three levator ani components together caused a larger weakening effect than the sum of each individually weakened component, indicating a nonlinearly additive pattern. The authors concluded that the vaginal walls, puborectalis, and pubococcygeus are the most important individual structures in providing urethral support. The levator ani muscle group therefore provides urethral support in a well-coordinated way with a nonlinearly additive pattern according to the authors of this study.

A recent study by Sheng et al on urethral closure pressure 8 months after a vaginal delivery with risk factors for a levator avulsion revealed that the presence of a pubovisceral muscle tear did not influence resting urethral closure. However, women with a pubovisceral muscle tear achieved a 25% lower urethral closure pressure during an attempted pelvic muscle contraction than those without a pubovisceral muscle tear (121). Levator ani muscle integrity and pelvic floor function are interrelated in this pressure analysis.

4.4.7. Racial Differences in Pelvic Dimensions

There are differences that exist in the occurrence of women from different racial backgrounds. Several groups have evaluated racial differences in the bony pelvis and the levator ani muscles (122-124). In a study by Handa et al (122), a wider transverse diameter (odds ratio 3.4) and a shorter obstetrical conjugate (odds ratio 0.2) were associated with pelvic floor dysfunction after controlling for age, race, and parity. Hoyte and colleagues found that levator ani volume was significantly greater in African-American (AA) asymptomatic nulliparous women without pelvic floor dysfunction compared to white American (WA) ones (mean = 26.8 vs. 19.8 cm3, P = .002). The levator-symphysis gap was smaller in the AA (left-18.2, right-18.8 mm) versus the WA group (22.4, 22.6 mm, P = .003, .048) on the left and right. Significant differences were also seen in bladder neck position, urethral angle, and the pubic arch angle (123). In another study with 3D MRI levator thickness was significantly greater bilaterally in black nulliparas compared to white ones, yet obturator internus muscle thicknesses were similar (124).

Handa found that the pelvic inlet was wider among white women than African-American women (10.7+/-0.7 cm compared with 10.0.+0.7 cm, P<.001). The outlet was also wider (mean intertuberous diameter 12.3+/-1.0 cm compared with 11.8+/-0.9 cm, P<.001). There were no significant differences between racial groups in interspinous diameter, angle of the subpubic arch, anteroposterior conjugate, levator thickness, or levator hiatus (125).

A broader group of races was studied by Rizk et al with MR in asymptomatic multiethnic nulliparous young volunteers from 5 ethnic groups (Emirati, other Arab, Filipino, Indian/Pakistani, and European/white volunteers), with the white volunteers as the reference group (126). The white volunteers were taller (P <.0001) than the other women. Their levator hiatus was longer than the Emirati women (P=.03) and wider than the Filipino women (P=.04). The bladder neck descent on straining was also greater than the other groups (P <.00001). The white women also had the longest transverse diameter of the pelvic inlet (P=.002). Their sagittal outlet diameter was longer than the Emirati and Arab women (P=.02), and their interspinous diameter was longer than the Arab women (P=.002).

4.5. Pelvic Organ Prolapse

MRI has proven to be a key assessment for understanding pelvic organ prolapse; a problem that arises from damage to connective tissue, muscles, and nerves that are invisible on standard radiography. With the advent of 3D ultrasound and MRI, the actual structures involved in the cause of prolapse can be seen and examined. This is possible not only in static scans that reveal morphological details of the pelvic structure, but also in dynamic scans where the movements of the various organs can be studied.

Evaluation of the degree of anterior compartment (bladder) and apical compartment (cervix) prolapse at maximal Valsalva using dynamic MRI showed a strong correlation between how far the bladder base and uterine cervix were below normal with $r^2 = 0.53$ indicating that slightly over half of the observed variation in anterior compartment support may be explained by apical support (127). Further analysis in the same patients showed that vaginal length was the strongest secondary factor determining 30% of the variation after apical descent was taken into account. This finding that a longer vaginal wall was associated with increasing cystocele size was unexpected, but seems consistent with clinical observations (128).

Hsu et al found that vaginal thickness is similar in women with and those without pelvic organ prolapse. However, in prolapse patients the vaginal perimeter and cross-sectional areas are 11% and 20% larger respectively (129).

Broekhuis et al studied the relationship between patient symptoms using questionnaires' domain scores and the perineal position on dynamic MR imaging of 69 women. They found that POP symptoms were associated with the degree of descent of the perineum but perineal descent was not related to anorectal and/or urinary incontinence symptoms (130).

In another study examining correlations of patients' symptoms with findings on clinical examination and dynamic MR imaging of the pelvic floor, only the domain score genital prolapse was significantly correlated in the positive direction with the degree of POP as assessed by POP-Q and dynamic MR imaging (r(s) = 0.64 and 0.27, respectively), whereas the domain score urinary incontinence was inversely correlated (r(s) = -0.32 and -0.35, respectively). The sensation or visualization of a bulge in the vagina was the only symptom which correlated positively with the degree of POP, with clinical examination and dynamic MR imaging showing similar correlation in this respect (131).

Broekhuis et al concluded that correlations for the POP staging with the use of POP-Q, dynamic MR imaging, and perineal ultrasonography are only observed in the anterior compartment (132).

4.6. MRI for Clinical Evaluation of Prolapse

4.6.1. Enterocele

In the past, enteroceles were usually only appreciated on radiographic examination after repeated straining after evacuation and usually required opacification of the vagina in order to demonstrate the insinuation of small bowel loops between the rectum and vagina (133). MRI has proven to be a much simpler and less invasive technique for the evaluation of enteroceles. In comparisons between physical examination, intraoperative findings and MR images in women with and without prolapse. MRI was significantly superior in detecting enterocele when compared to physical examinations with a sensitivity of 87%, specificity of 80%, and positive predictive value of 91% (17)(**Figure 40**). Similarly, MRI had a much higher sensitivity for detection of enteroceles when compared to physical exam and dynamic cystoproctography (134). Whether or not this technique alters clinical outcome remains to be seen.

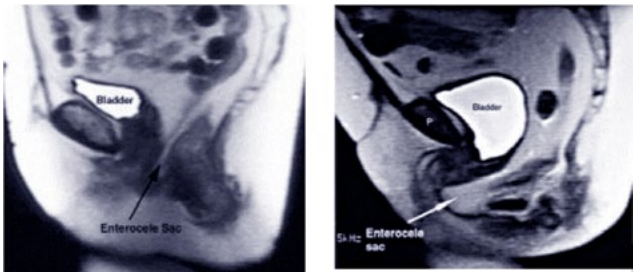


Figure 40: Pelvic floor MRI: Enterocele at rest a) and during Valsalva b).

4.6.2. Cystocele

MRI has a sensitivity of 100%, specificity of 83%, and positive predictive value of 97% when evaluating for cystocele compared to intraoperative findings. In addition, urethral hypermobility and postvoid urine residual can be documented, as well as evaluation of ureteral obstruction, hydroureteronephrosis and other pelvic abnormalities **(Figures 41 a, b).**

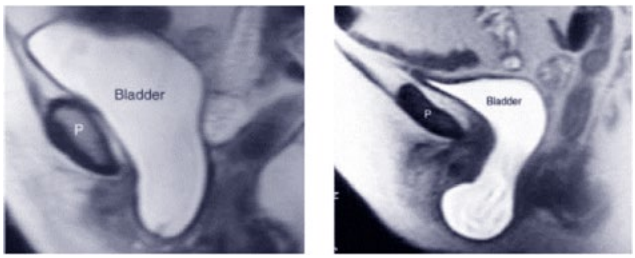


Figure 41: Pelvic floor MRI: grade 2 (a) and grade 3 (b) cystocele.

MRI can also be helpful in documenting the status of pelvic organ support as part of a program to assess operative efficacy (135, 136) and differentiating such problems as Müllerian remnant cysts from cystocele (137).

Larson et al showed that in women with anterior wall prolapse, Valsalva causes downward translation of the vagina along its length. A transition point separates a proximal region supported by levator muscles and a distal, unsupported region no longer in contact with the perineal body. In this latter region, sagittal and frontal plane

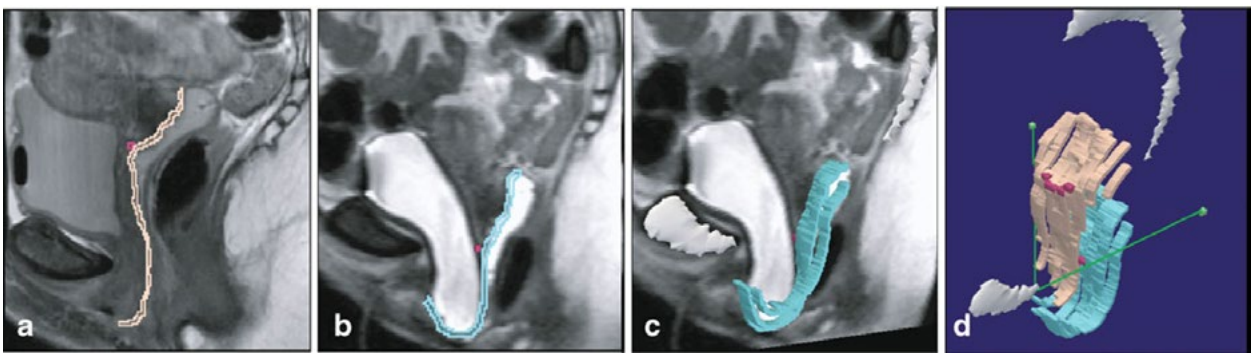


Figure 42: Anterior vaginal wall models at rest and with Valsalva. A Midsagittal MR slice with subsequent outline of vaginal wall at rest (180) and with Valsalva (turquoise, panel b). Uterovaginal junction shown with dark pink square. c Addition of midsagittal pelvic bones (white) and anterior vaginal wall model. d Powerpoint image of both resting and straining anterior vaginal wall models and their relationship to the normalized ATFP, shown here as green line extending from the pubic symphysis to the ischial spines (green square), or the P-IS line. © DeLancey 2009 (138).

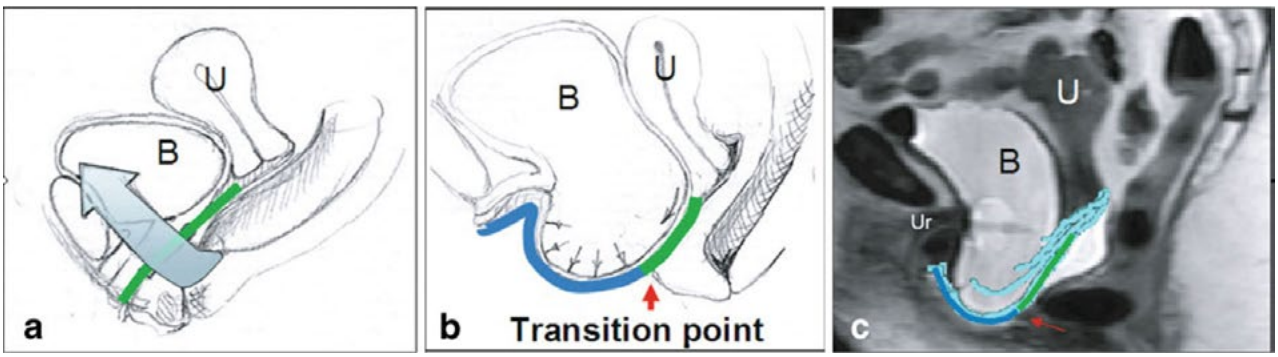


Figure 43: Midsagittal view of pelvis with normal support (a) and with prolapse (b). Green represents area where levators (blue arrow) provide cranial reaction forces to counteract the action of intraabdominal pressure and caudal movement of the anterior wall. The red arrow delineates the transition to unsupported region lacking this opposing set of reaction forces (blue line), thereby creating a pressure differential acting caudally on that region. c Red arrow illustrates this point on midsagittal MRI with modeled anterior vaginal wall. U uterus, B bladder, Ur urethra. © DeLancey 2009 (138).

"cupping" occurs. The distal vagina rotates inferiorly along an arc centered on the inferior pubis. Downward translation, cupping, and distal rotation are therefore novel characteristics of cystocele demonstrated by 3-D MR imaging (138)(**Figures 42 & 43).**

In cystoceles, the distal anterior vaginal wall (AVW) may no longer be in contact with the posterior vaginal wall or perineal body as it bulges through the introitus. The exposed vaginal wall length has been quantified using dynamic MR imaging. The authors found a bilinear relationship between exposed vaginal wall length and most dependent bladder location as well as apical location. It is when the bladder descent is beyond the inflection point that exposed vaginal wall length increases significantly (139).

4.6.3. Rectocele

The reported sensitivity of pelvic examination for diagnosis of rectocele ranges from 31% to 80% (4, 5, 7, 140, 141). This is usually secondary to organ competition for space in the vagina with other significant prolapse (8). In addition, it is often difficult to reliably distinguish an enterocele from a high rectocele. **Figure 44** shows a rectocele diagnosed by dynamic MRI. A rectocele is easily seen when filled with gas, fluid, or gel. Although highly specific, when no rectal or vaginal opacification is used, MRI can miss up to 24% or rectoceles (17). When rectal opacification is used, a correct diagnosis of rectocele can be made in 100% of patients studied when compared to intraoperative findings (21). Rectal opacification by introducing sonographic transmission gel or gadolinium into the rectum is therefore necessary to increase MRI's ability to diagnose rectocele.. In complex situations such as rectal intussusception (142) MR can provide important information by distinguishing mucosal from full-thickness descent. MR defecography also shows movements of the whole pelvic floor. In this study, 30% of the patients studied were found to have associated abnormal anterior and/or middle pelvic organ descent that would not necessarily be seen in traditional evacuation proctography (unless opacification of vaginal, bladder and intestine are carried out).

Quite important and not replaceable by any other imaging is the diagnosis of intussuception in MR defecography (143). Intussuception has therapeutic consequences as the symptoms and intestinal problem would not be resolved by colpoperineoplasty.

At maximal Valsalva on MRI, structures are more caudal and the hiatus longer in women with posterior prolapse. The posterior vaginal wall is longer; this length and point Bp strongly correlate with MRI prolapse size (r=0.5; P=.002; r=0.7; P<.001, respectively) (144).

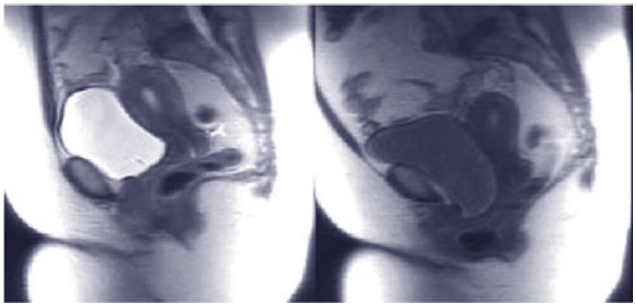


Figure 44: Resting (a) and straining (b) midline sagittal section showing a rectocele that traps intestinal contents.

What remains unclear is the relationship between anatomical findings and functional problems. The diagnosis of an anatomical abnormality does not mandate surgery. Simply identifying a rectocele on an imaging study based on the location of the intestinal lumen to a reference line does not mean that correction of the rectocele will cure defecation problems. Rectocele surgery is not without complications and the risk of dyspareunia after posterior colporrhaphy is real. Attention should be paid to make sure that symptoms are truly depending on stool trapping and the condition must be shown on imaging.

4.6.4. Uterine Prolapse

Although uterine prolapse is easily diagnosed on physical examination MRI is an excellent modality to record the structural relationships with the bladder and rectum in patients with uterine prolapse **(Figure 45).** In addition to depicting the position of the uterus and adjacent organs, it has the ancillary benefits of evaluating uterine size, position, orientation (retroversion) and pathology (fibroids, tumors, Nabothian cysts. etc.), but also ovarian pathology (cyst or mass) which may sometimes prove useful if these problems have not been picked up on physical examination. This is helpful information in determining the route of hysterectomy. Furthermore, MR imaging provides information on the presence or absence of cystocele, rectocele, urethral hypermobility and urethral diverticula, and evaluates for ureteral obstruction (11, 12, 15-17, 145). Gousse et al. report a sensitivity of 83%, a specificity of 100% and a positive predictive value of 100% when comparing dynamic MR imaging to

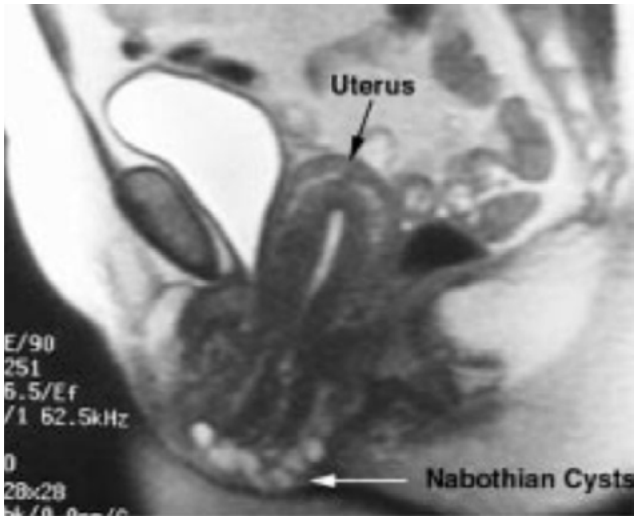


Figure 45: Pelvic Floor MRI: Uterine Prolapse.

intraoperative findings. These numbers were similar when compared to physical examination alone (17). More importantly, MRI was able to clearly define the other compartments of the pelvic floor and diagnose uterine and/or ovarian disorders in 30 of 100 patients evaluated (17).

4.7. Assessing Treatment Outcome

4.7.1. Pelvic Organ Prolapse Operations

Several studies have evaluated the anatomic changes seen after surgical procedures using MRI to better understand how surgical therapies affect pelvic support and structures. Lienemann et al. (146) evaluated women after abdominal sacrocolpopexy and found that functional MRI identified the exact sacral fixation points after the procedure and easily identified the axis of the vagina and the exact position of the synthetic material used for the repairs. Shatkin-Margolis et al. reported a significant improvement of the length of the M- and H-line, the anorectal angle, cystocele and vaginal prolapse after native-tissue fixation of the vaginal apex to the uterosacral ligaments, bilaterally and concurrent anterior and posterior colporrhaphies along with a perineorrhaphy (147). Sze (148) used MRI to study vaginal configuration on MR after abdominal sacrocolpopexy and sacrospinous ligament suspension. This study demonstrated the differences in the geometry of these two operations and should prove helpful in establishing outcome variables for different surgical procedures. Similarly Rane (149) used MRI to compare the vaginal configuration following transvaginal sacrospinous fixation, posterior intravaginal slingplasty (PIVS) (infracoccygeal sacropexy) and sacrocolpopexy (SCP) and demonstrated improvements in the restoration of vaginal configuration and differences between the procedures in final anatomy. Boukerrou (150) compared outcomes of 1) abdominal sacral cervicopexy, 2) vaginal hysterectomy with paravaginal repair, sacrospinous suspension and posterior colporrhaphy and 3) sacrospinous suspension and posterior repair without paravaginal suspension with MRI. The correction provided by vaginal route was found to result in a return of the bladder and the vaginal apex to their normal positions. In addition, vaginal shortening and postoperative change in vaginal orientation were not present postoperatively.

Nicolau-Toulouse et al (151) evaluated the anatomic outcomes of bilateral sacrospinous vault fixation (BSSVF) with synthetic, polypropylene mesh arms using MRI in a small case series of women with symptomatic pelvic organ prolapse (POP) with and without uterus. They confirmed that BSSVF with synthetic mesh restores the anatomy between the vagina and the ischial spines.

Relationships between assessment of surgical correction studied with MR imaging and symptoms have been studied. Gufler (152) compared preoperative evaluations with those two to four months after surgery. Of the seven patients who had symptoms postoperatively, only two had abnormal findings on physical examination but MRI showed pathologic findings in five of the seven patients. Huebner et al assessed symptomatic changes after anterior levatorplasty with morphologic changes visualized by MR defecography (153). Anterior levatorplasty improved quality of life in patients with symptomatic rectocele and correction of rectocele is accurately documented by MR defecography, however only moderate correlation between morphologic and clinical improvements was observed.

MRI has also been used for the evaluation of the effectiveness of POP surgical mesh procedures.

Dynamic MRI may evaluate the support of anterior and posterior pelvic floor structures by anterior and posterior polypropylene implant respectively. But dynamic MRI evaluations in a small series by Siegmann and colleagues suggest that if one compartment of the pelvic floor is repaired another compartment frequently (73.3%) develops dysfunction. These results did not correspond to clinical symptoms on short-term follow-up (3 months) indicating the need for long-term follow-up studies to prove if dynamic MRI can reliably identify significant POP after surgery and before the onset of symptoms (154). In another small series of ten women by Kasturi et al (155) undergoing intervention for POP with Prolift, postoperative MRIs supported the inert nature of polypropylene mesh.

Larson et al examined structural relationships between anterior mesh kit suspension points and the upper vagina in women with normal support. Using MRI generated 3D models, they found that the anterior vagina extended above superior attachment points in 100% of women at rest and in 73% during Valsalva. It extended posterior to them in 82% and 100% (rest and Valsalva, respectively). The mean percentage of anterior vaginal length above superior anchoring sites was 40 +/- 14% at rest and 29 +/- 12% during Valsalva. The upper vagina was therefore found to lie above and posterior to superior suspension points in the majority of women with normal support (156).

In an observational study, the 1-year outcomes after mesh repair in patients with POP were evaluated using clinical examination (CE), dynamic magnetic resonance imaging (dMRI), and the prolapse quality-of-life (P-QOL) questionnaire. Sixty-nine women were treated with Seratom(R) or Perigee mesh implants. Advanced cystoceles and enteroceles were underestimated by CE using the POP-Q system compared to dMRI ($P = 0.003$ and $P < 0.001$), vice versa dMRI overestimated POP compared to CE (157).

4.7.2. Visualisation of Implants

In case of mesh and sling complications, MRI might be a useful tool to localize the mesh material in T2-weighted sequences. The polypropylene material will be visualized as a hypointense structure (158). A study by Brocker et al. demonstrated that vaginally inserted Fe3O4- polypropylene implants were shrinking for at least 40% in length (159). The location and dimension of the implanted mesh could be well visualized. Mesh placement variations might be important in the diagnosis and illustration of postoperative complications (159). Another study with a MR-visible polyvinylidene fluoride mesh containing paramagnetic Fe3O4 microparticles did not show

a significant deformation of the mesh material at two time points (6 weeks and 8 months) after insertion (160).

4.7.3. Pelvic Muscle Exercises

Studies on the effects of pelvic muscle training on the pelvic floor (161) demonstrate reduced levator ani surface area and volume encircled by the levator ani muscle during contraction. When elite athletes are compared to normal women significant differences appear in the cross-sectional area and width of the pelvic floor muscles, (162). These types of studies are being facilitated by improved techniques of aligning contracted and non-contracted muscle (163).

The effect of pelvic muscle training with or without instrumentation was assessed by a study of Dierick and colleagues. The impact of a 3-week period of intensive pelvic floor muscles training (PFMT) on the puborectalis (PR) and iliococcygeus (IL) muscles showed on static MRI a decrease in muscle volumes on both sides of the iliococcygeus muscle ($p = 0.040$, $p = 0.045$) as well as a decrease in signal intensities of right and left puborectalis muscle ($p = 0.040$, $p = 0.021$). These morphological changes after PFMT suggest a decrease in adipose content of PR (164).

Whether pelvic floor morphometry predicts the success of pelvic floor muscle training or not was the aim of a study by Dumoulin et al (165). In the MRI morphometry a urethrovesical junction height at rest of 11.4mm appeared to be predictive for a response to PFMT (165).

4.7.4. Comparison of MRI with other examinations and assessment of reliability

Dynamic contrast roentography and multiphasic fluoroscopic cystocolpoproctography (CCP) have previously been considered the best radiological studies for detecting POP. These studies rely on the opacification with contrast material of the bladder, vagina, small bowel, and rectum with all organs opacified together or in phases with each organ opacified individually prior to each straining phase (5, 149) (153, 161). These studies fail to detect up to 20 percent of all enteroceles (145, 166-168). Therefore, MRI has proven to be a much simpler and less invasive technique for the evaluation of enteroceles. In addition, MRI is able to differentiate the enteroceles according to their contents (small bowel, large bowel, rectosigmoidocele or mesenteric fat). MRI is also an excellent study to differentiate high rectoceles from enteroceles, thus allowing adequate surgical planning and safer planes of dissection (16, 17, 21, 134). Although multiphasic MRI with opacification of organs and multiphasic fluoroscopic cystocolpoproctography have similar detection rates for enterocele (166), excellent images can be obtained from dynamic MRI without contrast for opacification of the small bowel or rectal contrast. Thus the minimal added information obtained by contrast administration does not seem to warrant the invasiveness of organ opacification at this time (17, 133, 167). However, MRI without rectal contrast shows statistically fewer pelvic floor abnormalities than CCP. Except for enteroceles, MRI with rectal contrast shows statistically similar frequency of POP as CCP (169).

Evacuation proctography has been used to diagnose enterocele, rectoceles, perineal descent and rectal intussusception. Dynamic contrast roentography or fluoroscopic cystocolpoproctography have also been used (5, 140, 141, 166, 170) to diagnose rectoceles. The disadvantages of these techniques are the inability to visualize the soft tissue planes comprising the pelvic floor, their invasiveness, and their use of significant levels of ionizing radiation. Without the use of rectal opacification, MRI appears to be a poor choice for the evaluation of rectoceles missing up to 25% of such defects. With rectal opacification a correct diagnosis of rectocele can be made in 100% of patients in comparison to intraoperative findings (21). Triphasic dynamic MRI and triphasic fluoroscopic cystocolpoproctography have similar detection rates for rectocele (166). Upright dynamic MR defecating proctography has been reported (171). Although these studies might prove to be more sensitive in detecting anorectal anomalies, their utility seems to be more pronounced in patients with disorders of defecation include anismus, intussusception, and others, and may be too invasive to justify their routine use in the evaluation of rectocele.

Kaufman (172) evaluated dynamic pelvic MRI and dynamic cystocolpoproctography in the surgical management of females with complex pelvic floor disorders. Physical examination, dynamic MRI, and dynamic cystocolpoproctography were concordant for rectocele, enterocele, cystocele, and perineal descent in only 41% of patients. Dynamic imaging lead to changes in the initial operative plan for 41% of patients. Dynamic MR was the only modality that identified levator ani hernias. Dynamic cystocolpoproctography identified sigmoidoceles and internal rectal prolapse more often than physical examination or dynamic MR. Whether this type of imaging creates measurably better outcomes remains to be seen. Singh et al (49) showed a reasonably good correlation between clinical staging and MRI staging (Kappa = 0.61) with the mid pubic line being used as a surrogate for the hymenal ring. In addition, specific features such as the levator-vaginal angle the area of the genital hiatus could be assessed quantitatively on MRI.

Torricelli (51) studied ten healthy volunteers and 30 patients with suspected pelvic floor deficiency with and without POP. They found good concordance between physical examination and MRI with four cases of uterine prolapse and three cases of enterocele seen on MRI that had not been suspected on pelvic examination. Whether these would have been detected at the time of surgery was not discussed. Deval (52) compared intraoperative findings as a gold standard for MRI based diagnosis. The sensitivity, specificity, and positive predictive value of MRI were 70%, 100%, 100% for cystoceles; 42%, 81%, 60% for vaginal vault or uterine prolapse; 100%, 83%, 75% for enteroceles; 87%, 72%, 66% for rectocele. Although all of these measurements are somewhat subjective, these figures show that it is possible to quantify the individual elements of pelvic floor dysfunction in reasonable parameters.

In a recent study, the value of dynamic pelvic floor MRI was assessed in comparison to standard clinical examination in treatment decisions made by an interdisciplinary team of specialists including a urologist, gynecologist, a proctological, and colorectal surgeon. The authors concluded that MRI has the advantage of allowing diagnosis of clinically occult enteroceles. In addition, in nearly half of cases, MRI changed management or the surgical approach relative to the clinical evaluation (173).

Different studies undertook comparisons or combinations of MRI and tomographic ultrasound imaging in the detection of pelvic floor muscle lesions (1, 174-177). Ultrasound and MRI depict puborectalis and pubovisceral avulsion both well and with a good consistency, however, iliococcygeus muscle avulsion as a sign of major levator trauma is diagnosed more accurately in MRI (174).

Whether a preoperative MRI results in a better surgical outcome was topic in a cost-effectiveness study by Wyman and colleagues. A preoperative MRI resulted in a 17% increased chance of successful initial surgery and a decreased risk of repeat surgery with an ICER of $2298 per avoided cost of surgical failure (178) and the authors concluded that MRI as an accurate preoperative diagnostic will reduce costs for repeat surgeries.

4.8. Conclusions

Proof that MR imaging has value will eventually need to come from increased operative success rates. Better documentation of preoperative and postoperative anatomy could allow us to seek reasons of operative failure. Because MR provides a detailed picture of a woman's pre-operative anatomy, once operative failures are discovered, it would be possible to look back at images from women with successful and unsuccessful operations to seek anatomical explanations for failure.

Advancements in MRI technology with the addition of 3D imaging as well as studies correlating imaging findings with clinical examination and symptom scores may establish further the clinical applications of these modalities.

III. IMAGING IN ANAL INCONTINENCE

1. BACKGROUND

Anal incontinence may result from anatomical and/or neurological disruption of the anal sphincter complex. Prior to the development of anorectal imagining techniques, anal sphincter disruption was detected by digital palpation supported by EMG needle mapping and ano-rectal manometry. Use of endoanal ultrasonograpghy (EAUS) for anal sphincter imaging was first described by Wild in 1956 (1), but remained neglected for many decades because of the limitation of technology then available (2). In 1989 Law and Bartum defined the technique of EAUS and endosonographic anatomy of the anal sphincter complex (3). Since then, EAUS has become the gold standard of imaging the anal sphincter complex.

Development of 3-D rendering technique over the last decade has enabled a better quality imaging of the anal sphincter complex using the EAUS. Recently other imaging modalities such as Transvaginal, transperineal and translabial ultrasonography, MRI, Defecaography and Sonoelastography have been described to assess the anal sphincter complex in patients with anal incontinence.

2. INDICATIONS

Anal sphincter imaging has become an integral part of the assessment of anal incontinence. Following detailed history and examination, the patient should be offered anal sphincter imaging (either 2D or 3D EAUS) depending on the availability of imaging modalities and the expertise. Even though ano-rectal physiological studies indicate dysfunction of the anal sphincter complex, they do not identify the anatomical site and the degree of anal sphincter disruption. EAUS has been the gold standard of detecting anal sphincter disruption or atrophy. EAUS is also used in the follow up of women after obstetric anal sphincter injuries to assess the success of the primary repair and to advice on subsequent delivery (4). EAUS has been used intra-operatively to identify the damaged EAS prior to secondary repair and also to identify the IAS defects prior to injecting bulking agents.

3. IMAGING MODALITIES

3.1. Ultrasonography

3.1.1. Endoanal Ultrasound (EAUS)

EAUS is performed using a 360^0 rotating rectal probe with a 7 - 10 MHz transducer (focal range 2-4.5cm) with minimum beam width of 1.1mm. Several systems are currently available, and recently integrated 3D systems are also available (B&K Medical, Sandoften 9, 2820 Gentofte, Denmark). Women should be examined prone with an endoanal system to minimise anatomical distortion. Figure 46 shows a schematic diagram of the anal sphincter complex in relation to the endoanal probe (4).

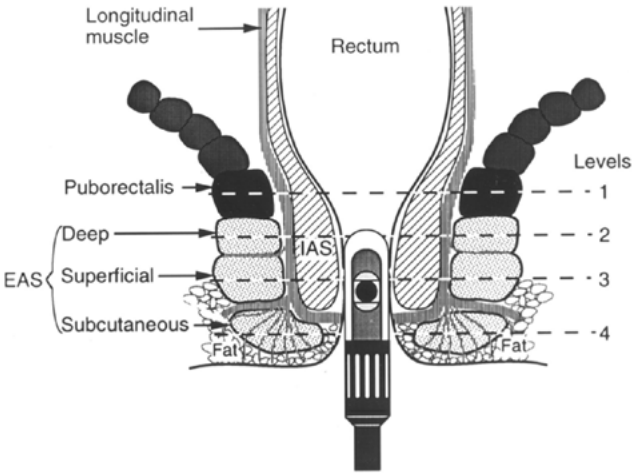


Figure 46: A schematic diagram of the anal sphincter complex in relation to endoanal probe.

The standard EAUS image of the anal canal is of 4 layers (Figure 47):

1. The subepithelial layer is moderately reflective.
2. The internal sphincter is the most obvious landmark and is a well-defined low reflective ring. The internal sphincter varies in thickness with age, being <1mm in neonate, 1-2mm in young adults, 2-3 in middle age and >3mm in the elderly.
3. The longitudinal layer is a complex structure with a large fibroelastic and muscle component, the latter formed from the puboanalis as well as the longitudinal muscle of the rectum (Figure 47).
4. The external sphincter is better defined in men than women, where it tends to be less hypoechoic. It is distinguished mainly by interface reflections between muscle/fat planes either side (Figure 47). In women the external sphincter is shorter anteriorly than posteriorly, which must not be misinterpreted as a tear. The transverse perineii muscles fuse anterior with the sphincter, whereas in men they remain separate.

With experience the examination can be performed in about 5 minutes and provides an ideal method for a rapid assessment of sphincter integrity and thickness.

A recent observational study showed a statistically significant correlation between decreased maximal resting pressure and decreased internal anal sphincter (IAS) thickness or an IAS defect. The correlation between Maximum Squeeze Pressure and external sphincter pathology was significantly less consistent (5).

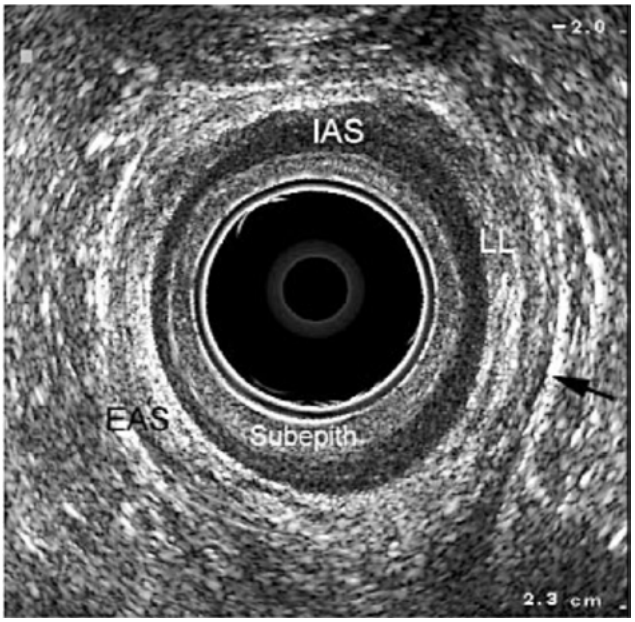


Figure 47 : Axial endosonography in the mid canal in a normal 38-year-old female. Subepith: subepithial layer; IAS: internal anal sphincter; LL: longitudinal layer; EAS: external anal sphincter. The outer border of the external sphincter is defined by an inter- face reflection at the fat/muscle boundary (arrow).

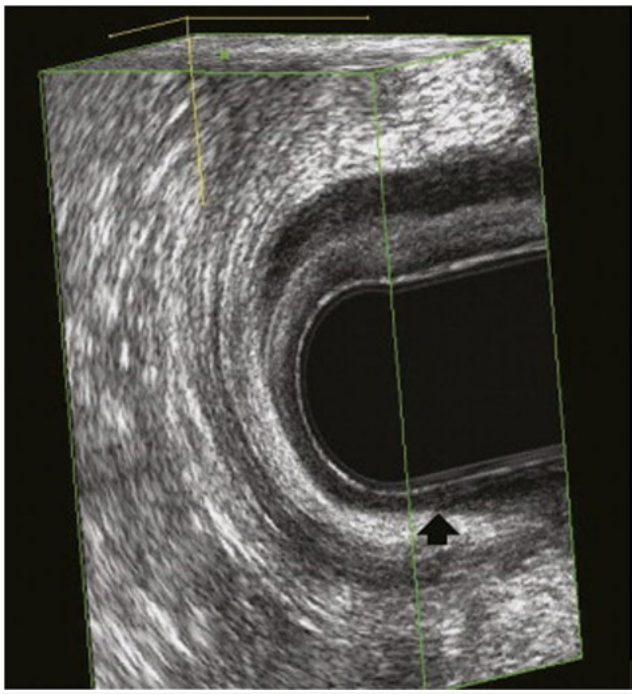


Figure 49: Complete defect of the internal anal sphincter (7).

3.1.2. Dimensional Endoanal Ultrasonography (3-D EAUS)

With 3D-EAUS, the anal canal is scanned in a conventional manner, and dedicated software provides a final 3D appearance (3D rendering). The data obtained from a series of closely spaced EUS images (0.25 mm) are combined to create a 3D volume displayed as a cube. The image can then be freely rotated and it is possible to visualize defects at different angles and to get the most information out of the data (6). The advent of 3D ultrasonographic multiplanar reconstruction of the anal canal has further improved the detection of anal sphincter injuries with nearly 95-100% sensitivity and specificity (7). With 3D-EAUS, the aspect, localization (circumference involved, height), size (in degrees or percentage of circumference) and number of sphincter defects can be described in detail, together with a calculation of the volume of such defects (8). Defects of the puborectalis fibers of the levator ani are less common and these can be seen as heterogeneous remodelling or shortening of the two bands is visible after episiotomy or pelvic floor injury during vaginal delivery. Its role in the development of AI is probably underestimated and characterization, particularly in terms of volume, would be of interest to assess the functional impact (7). Two scoring systems has been introduced to objectively evaluate the anal sphincter defects detected in 3D EAUS (9, 10), and both these scoring system have shown acceptable intra observer and inter observer agreement (10).

Although EAUS has been accepted as the gold standard of imaging anal sphincter complex, the equipment and the expertise may not be readily available in some centres. Some patients may find EAUS technique embarrassing and unacceptable. Hard endoanal cone of EAUS may cause the disruption of normal anal canal anatomy. Because of these drawbacks, other imaging modalities such as endovaginal, transperineal and translabial ultrasonography have been evaluated to assess the anal sphincter complex.

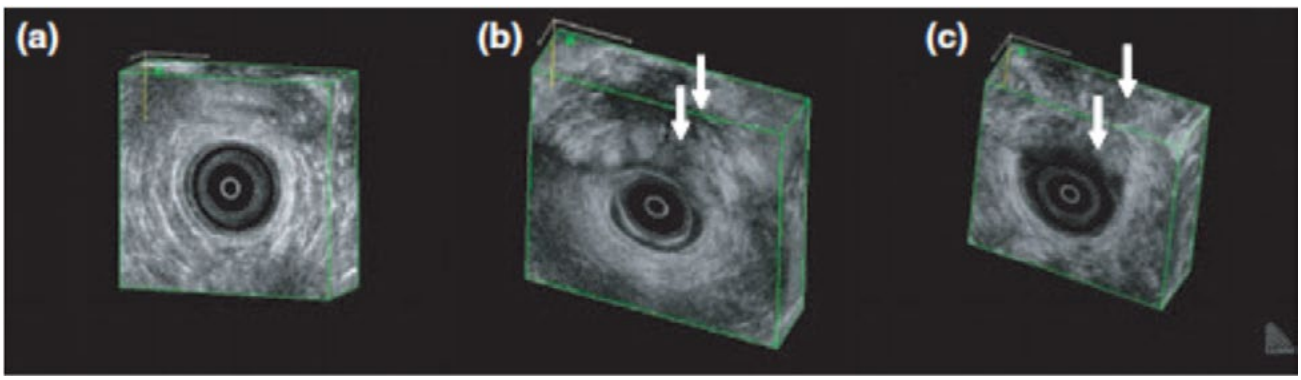


Figure 48: Three-dimensional endoanal ultrasound showing no (a), partial (b) or complete EAS defect (c). Arrows indicate an EAS defect in the sagittal view (11).

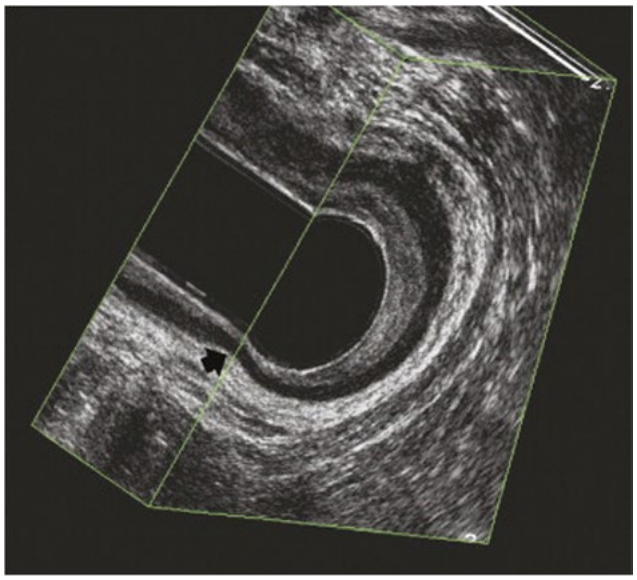


Figure 50: Partial defect of the internal anal sphincter (7).

3.1.3. Transvaginal Ultrasonography

Sultan et all first described the vaginal use of 360^0 rotating probe used for the EAUS and obtained clear images of anal sphincter complex (12). Since then different types of probes including side-fire transrectal probe, a standard transvaginal probe and modified vaginal probe has been used to evaluate the anal sphincter complex with variable sensitivity and specificity for detecting anal sphincter injury (13).

3.1.4. Transperineal ultrasonography

Transperineal ultrasonography (TPU) to image the anal sphincter complex was first described by Peschers et al (14) and found to have a good inter observer reliability in detecting IAS and EAS defects compared with EAUS (15). A recent study by Roos et al (13) comparing the endovaginal and transperineal ultrasonography to detect obstetric anal sphincter have concluded that both these modalities are not sensitive enough to detect anal sphincter defects.

3.1.5. Translabial ultrasonography

Translabial ultrasound (TLU) offers an alternative imaging modality of the anal sphincter complex and has proven to be well-tolerated by patients. It has been used to describe anal sphincter complex integrity (14, 16). Hall et all evaluated 60 women with TLU and reported that mean sphincter measurements are given for symptomatic and asymptomatic intact women and are comparable to previously reported endoanal MRI and endoanal ultrasound measurements (17). The advantages of TLU are that the equipment needed is readily available to all gynecology and radiology imaging laboratories.

3.1.6. Integrated Multicompartmental Pelvic Floor Ultrasonography

Pelvic organ dysfunction includes multiple conditions such as pelvic organ prolapse, urinary incontinence, anal incontinence, defecatory disorders and sexual dysfunction. Based on this concept, integrated multicompartmental Pelvic Floor imaging including two-dimensional (2D), three-dimensional (3D) and 4D pelvic floor ultrasonography as well as transvaginal, endoanal and transperineal techniques, has been described from a global and multicompartmental perspective (18). Value of this approach in routine assessment of pelvic floor dysfunction is yet to be evaluated.

3.1.7. Dynamic Anorectal Endosonography (DAE).

DAE uses a rigid biplane transrectal probe with a frequency of 7 MHz with the tip of the probe covered with a water-filled balloon to maintain the acoustic window for the ultrasound waves. By slowly and manually rotating the linear probe through 360°, various layers constituting the anal wall (mucosa, internal anal sphincter, and external anal sphincter), the layer forming the rectal wall, and the perirectal tissues (puborectalis muscle, bladder, and vagina, or prostate) has been demonstrated. After the initial examination, the patient makes a defecation effort with the probe left in the same position (19). Study 56 women using DAE and Dynamic MRI Defecography showed that a significantly more internal anal sphincter defects were found with DAE than with dynamic MRI defecography, but there was no significant difference for the diagnosis of external anal sphincter defects (19).

3.1.8. Sonoelastography

Sonoelastography is a new imaging technique based on differences in radiofrequency signals following endogenous/exogenous compression due to different elastic properties of the targeted tissues or organs (20). This technique has been evaluated in pathological conditions of breast, thyroid, pancreas and prostate. The elastographic pictures registered simultaneously with conventional gray-scale B-mode images during sonography or endosonography are assumed to distinguish malignant from inflamed areas and thus facilitate the diagnostic work-up. Based on this concept it is assumed that Sonoelastograhy is able to diagnose different condition causing anal incontinence. However there is only one published study comparing the conventional endoanal ultrasonography and elastography (21). This prospective study included 50 patients with fecal incontinence following ano-rectal surgery and Crohn's disease. Elastogram color distribution within the sphincter representing elastic properties was quantified using a visual analogue scale and an off-line computerized area calculation program. The IAS, a smooth muscle, and the EAS, a striated muscle, have different elastogram color distributions, probably reflecting their different elastic properties. The absence of significant correlations with the major clinical and functional parameters suggests that in routine clinical practice ultrasound real-time elastography may not yield additional information in patients with fecal incontinence except in patients who had radiation.

3.2. MRI

Anatomy of the anal sphincter complex has been redefined over the past 20 years by the use of body coil, endoanal coil and phased-array coil magnetic resonance imaging (MRI). However these different MRI techniques have led to conflicting anatomical descriptions of the anal sphincter complex (22). Endoanal coil MRI studies by Rociu et al (23, 24) have suggested that the levator ani muscle has only a transverse portion and that the EAS muscle is composed of only a subcutaneous and a superficial portion describing five image layers (Figure 51).

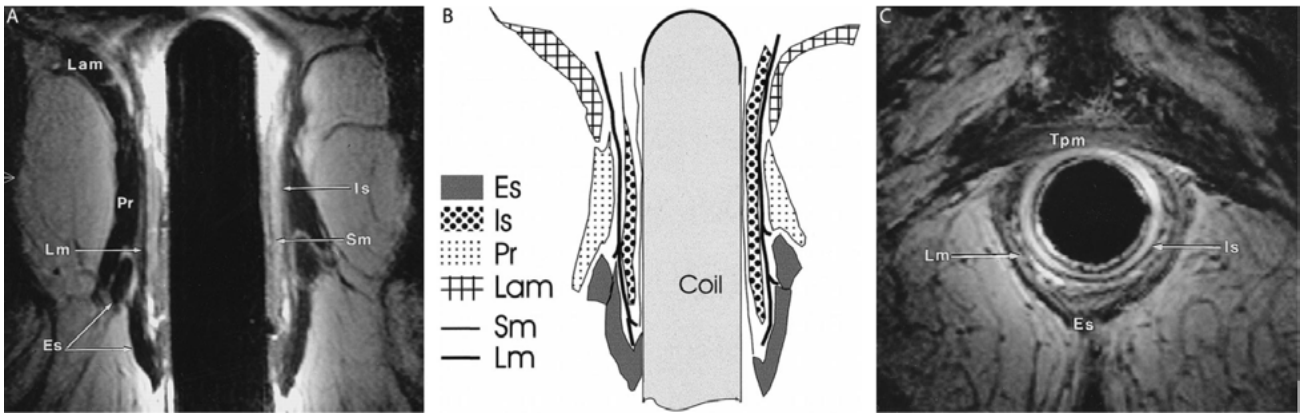


Figure 51: T2-weighted turbo spin-echo endoanal coil MRI studies by Rociu et al (23, 24).

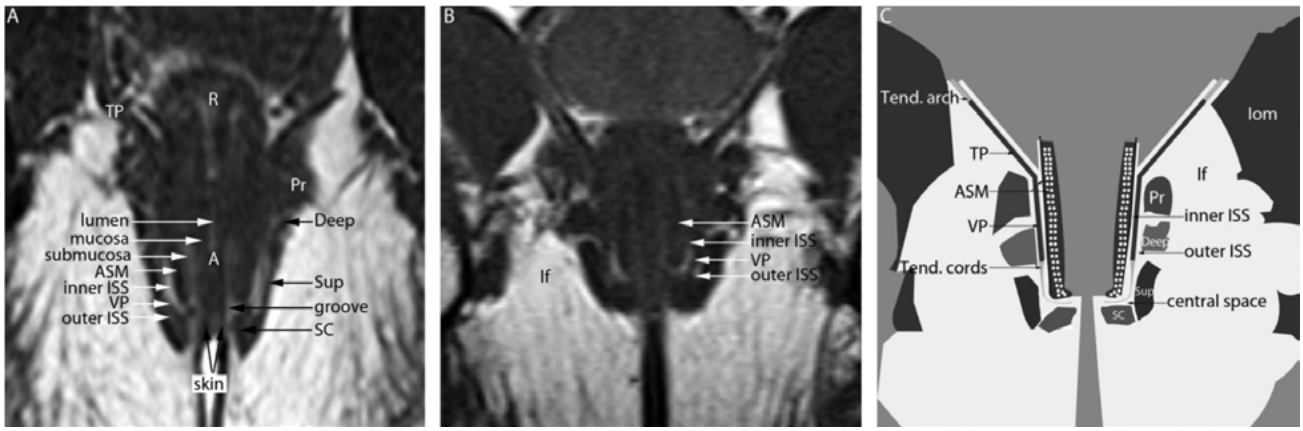


Figure 52: Midcoronal T1-weighted turbo spin-echo body coil MRI images (27).

However, body coil MRI studies by Guo and Li (25) suggested that the levator ani muscle also has a vertical portion (vertical levator), and separate body coil MRI studies by Hsu et al (26) suggested that the EAS muscle has 3 separate components which has been identified in EAUS as well.

A more recent study by Guo et al (27) using multiplanar body-coil MRI studies demonstrated that the anal region actually has 7 image layers: the mucosa, submucosa, anal smooth muscle, inner space, vertical levator, outer space, and the EAS muscle (Figure 52). The authors reported that endoanal MRI does not reliably outline the superficial layers of the anal region because a blind zone is created in the anal canal near the coil. This blind zone lead investigators to effectively ignore the mucosa, submucosa, anal smooth muscle, intersphincteric groove, and subcutaneous sphincter and thus accounts for the early endoanal MRI description of the anal region as comprising only 5 image layers.

Images of the anal sphincter complex obtained using endoanal MRI are thought to be superior to MRI performed with a body coil because of increased signal to noise ratio resulting in high spatial resolution images. Although the endoanal MRI allows the comprehensive assessment of atrophy and focal defects of the external canal, the internal sphincter is less well defined (28). A meta-analysis of nine studies, comparing endoanal MRI with endoanal ultrasound or surgical diagnosis in 157 patients by Tan et al (29) has shown that Endoanal MRI was sensitive and specific for the detection of external sphincter injury and especially sphincter atrophy. It may be useful as an alternative to endoanal ultrasound in patients presenting with fecal incontinence. However, the limited availability of dedicated endoanal coils outside specialist units has resulted in less widespread familiarity with this technique and further clinical studies are needed to identify its best application in clinical practice.

In addition to the damage to the anal sphincter complex, levator ani muscle (LAM) injury has also been postulated as a cause for anal incontinence especially after childbirth. A recent MRI study by Heilbrun et al (30) reported major LAM injuries in 19% of women who delivered vaginally with external anal sphincter (EAS) injuries compared to 3% delivered vaginally without EAS injury, and 0% delivered by caesarean section before labour. Among women with EAS injuries, those with major LAM injuries tend to have more anal incontinence symptoms than those who did not have LAM injury. These data suggests that both EAS and LAM are important to maintain faecal continence.

3.3. Evacuation Defecography (Proctography)

Evacuation defecography is indicated in patients with constipation, and in patients with obstructive defection associated with anal incontinence caused by overflow incontinence or post defecation leakage. In these patients, defecography is useful to visualise an outlet obstruction due to an anatomical (e.g. enterocele, rectocele, intussusception) or a functional (e.g. anismus) cause. Evacuation defecography is also useful to demonstrate bladder and uterovaginal prolapse as well as pelvic floor descent (Figure 53 a-b) but gives limited information as to rectal function. Evacuation defecography

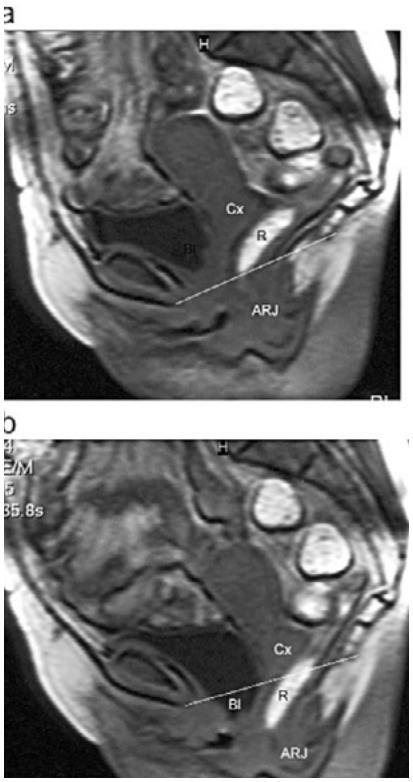


Figure 53: Sagittal views from a dynamic MRI examination. The dotted line indicates the position of the pubococcygeal line. At rest (a) there is some descent as the anorectal junction (ARJ) is more than 1 cm below this. During pelvic stress (b) there is marked pelvic floor descent, with descent of the cervix (Cx) and bladder base (Bl).

has shown a good reproducibility of diagnosing enterocele, anterior rectocele and their grading in patients with faecal incontinence (31).

The rectum is opacified with 120ml of a barium paste and the small bowel with a dilute barium suspension given orally about 30mins before. The patient is seated sideways within the fluoroscopic unit on a radiolucent commode. Evacuation of the barium paste is recorded either on video or on cut film at 1 frame/sec using a low

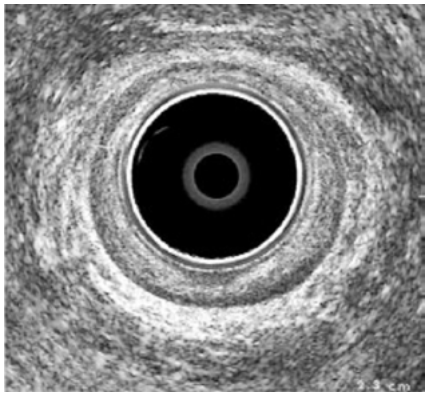


Figure 55: Endosonography with an axial image in the mid canal of an elderly patient, aged 73 years with passive faecal incontinence. The internal sphincter measures only 1.1mm (markers) indicative of internal sphincter degeneration.

dose protocol. At rest the anorectal junction is at the level of the ischial tuberosities and the anal canal closed. Evacuation is rapid (<30sec) and the rectum below the main fold should be emptied completely. During evacuation the anorectal angle widens as the anorectal junction descends and the anal canal opens. At the end of evacuation pelvic floor tone returns and the puborectalis pulls the anorectal junction upwards and forwards back to the resting position. Intra-anal intussusception creates a thick double fold of rectum, which impacts into the anal canal on straining at the end of rectal evacuation. Rectal prolapse represents an extension of this process, with passage of the intussusception through the anal canal and inversion of the rectum (Figure 54 a-c).

Compared to conventional evacuation defecography, Dynamic MR defecography at a vertical open magnet unit has become popular recently as it produces multiplanar images with increased soft tissue contrast and avoids radiation exposure. However, the comparative results between conventional defecography and dynamic MR defecography in patients with prolapse and anal incontinence are variable (32, 33). Some of these variations have been attributed to the difference in technique. The main drawback of MR defecography is the supine position required which causes sub optimal assessment of prolapse and evacation (32). Since vertical open-magnet MR imaging units are not widely available, the role of MR defecography in the diagnostic work-up of faecal incontinence is still limited.

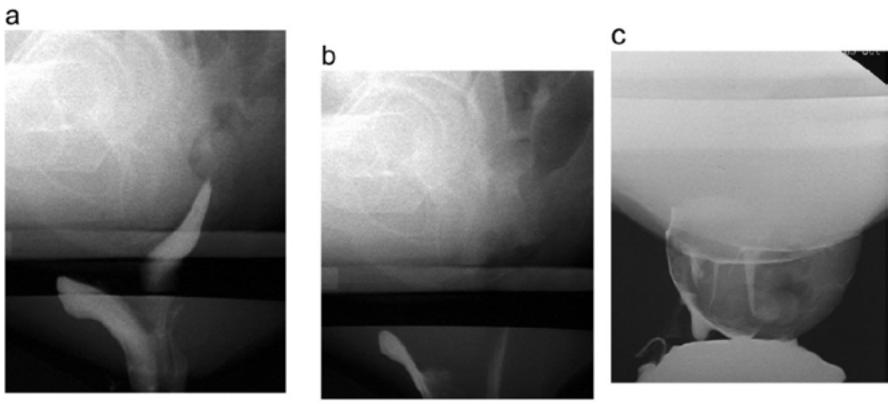


Figure 54: Evacuation proctogram showing the development of rectal prolapse. Intussusception starts at the end of rectal emptying (a) and rapidly passes through the anal canal (b) to form the external prolapse(c).

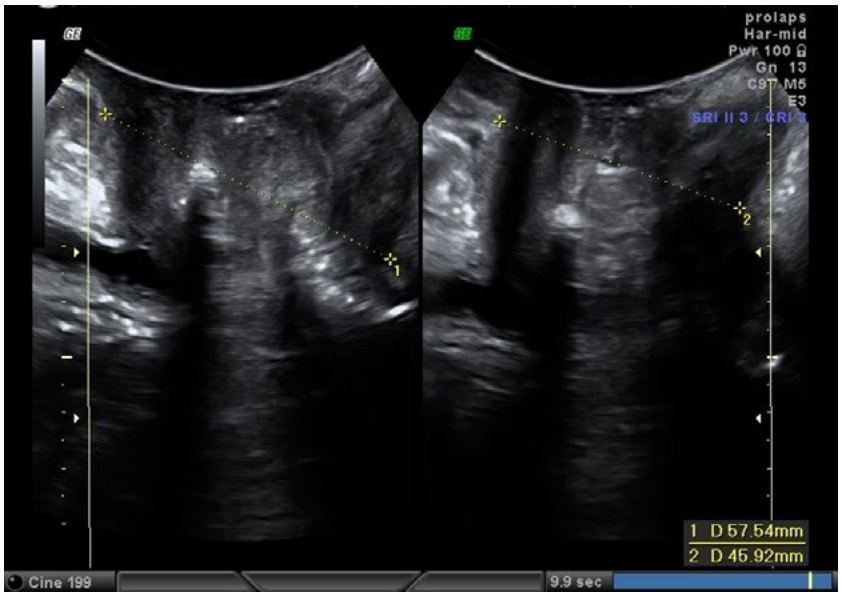


Figure 56 Perineal midsagittal two-dimensional view at rest and on contraction. Levator contraction with ventro-cranial displacement of the urethra.Measurement of minimal dimension of genital hiatus (from symphysis pubis to levator ani muscle)

4. SPHINCTERIC DISORDERS

4.1. The Internal Anal Sphincter (IAS)

IAS is responsible for the maintenance of resting anal pressure and plays a vital role in maintaining anal continence. Isolated IAS defects are associated with surgery for ano-rectal malignancies, anal fissure and undetected obstetric anal sphincter injuries. These patients may present with passive faecal soiling and seepage rather than frank faecal incontinence.

Abnormalities of thickness are usually related to the patient's age. A sphincter less than 2mm thick in a patient more than 50 years of age is indicative of internal sphincter degeneration (Figure 55) and is associated with passive faecal incontinence.

Obstetric trauma to the internal sphincter parallels that of the external sphincter in extent, but should always be in the anterior half, so that any defect between 3 and 9 is due to some other cause.

Sphincterotomy may be more extensive than was planned, particularly in women, and 3D studies are especially helpful to assess the longitudinal extent of the defect. The length of the sphincter divided relates directly to the risk of incontinence (34). Dilatation procedures are hazardous and may completely fragment (Figure 56) the internal sphincter.

4.2. The External Anal Sphincter

When striated muscle is stretched beyond the limits of its elasticity fibres rupture and heal with granulation tissue and eventually fibrosis. Most chronic tears are seen with scar formation, and present as a uniform area of low reflectivity distorting and obliterating normal anatomical planes (Figure 54). A key to the diagnosis is lack of symmetry with the anterior part of the external sphincter not fusing at 12 o'clock as the probe is moved slowly down the canal. This may also be seen on 3D studies in the coronal plane (Figure 57). Other perineal structures, such as the puboanalis and transverse perineii are frequently torn and distinguishing these tears from external sphincter trauma requires experience, and again may be helped by 3D multiplanar imaging. The distinction is important as tears of the puboanalis or transverse perineii are not associated with a significant fall in squeeze pressure (35), and it is only damage to the external sphincter that results in a significant change. Childbirth damage to the puborectalis part of the levator ani muscle with intact EAS and IAS has been reported as a distinct cause for anal incontinence. 3-D EAUS is reported to be superior in detecting this type of injury (36).

In healthy young adults a good correlation has been found between measurements of layers thicknesses on endosonography and endocoil MRI, with an Ri of 0.96 for the external sphincter (37). The outer border of the external sphincter is easier to see on MRI, but fibrosis is not so markedly different in signal from normal muscle, so that the conspicuity of tears may not be as obvious as with endosonography.

Atrophy of EAS is a more difficult problem. Determining the thickness of the external sphincter on EAUS depends on visualising its borders from interface reflections between the longitudinal layer on the inside and subadventitial fat on the outer border. As atrophy involves a reduction of muscle fibres and an increase in fat, the outer interface reflection is lost and the thickness of the external sphincter cannot be measured. Such loss of definition of the outer border of the external sphincter on endosonography has a positive predictive value of 71% for atrophy (38). Using 3D EAUS and a grading system based on definition (Figure 56) and echogenicity of the external sphincter showed a comparable accuracy to endocoil MRI in detecting atrophy (39).

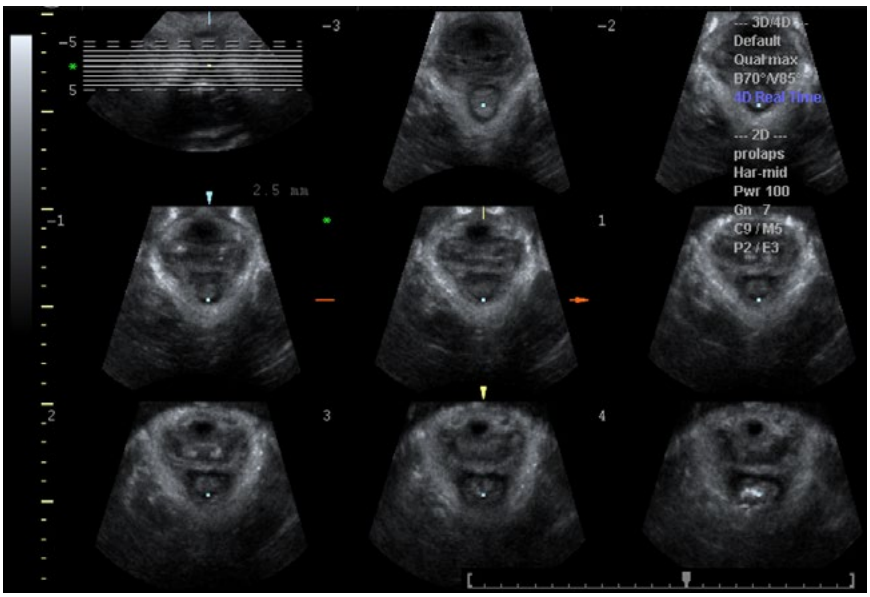


Figure 57a Tomographic ultrasound imaging in oblique axial plane. Normal attachment of the levator ani muscle.

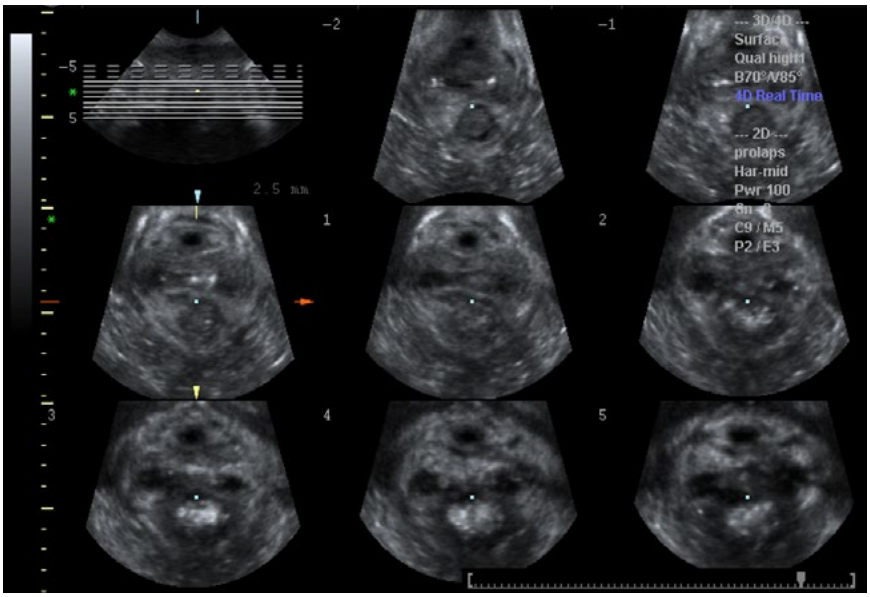


Figure 57b Tomographic ultrasound imaging in oblique axial plane. Bilateral avulsion of the levator ani muscle from the symphysis pubis.

5. CONCLUSIONS

Claims for superiority of one or other modality for the detection of sphincter tears probably depend largely on individual experience, but the relative low cost and speed of EAUS makes this an ideal screening procedure to assess sphincter integrity. A leading issue is the significance of occult sphincter tears (diagnosed on endosonography but not apparent clinically) following vaginal delivery. Although these may be detected by careful examination immediately post-partum (40), retrospective detection will still require EAUS. A meta-analysis of 717 vaginal deliveries revealed a 26.9% incidence of anal sphincter tears in primiparous, with 8.5% new tears in multiparous women. Overall, 29.7% of women with tears were symptomatic, compared to only 3.4% without tears. The probability of faecal incontinence being due to a sphincter tear was 76.8-82.8% (41). Recent studies confirm the strong relationship between obstetric sphincter damage and faecal incontinence (42), and its late onset (43, 44). Subsequent deliveries increase the risk of incontinence particularly if there has been a tear at the first delivery (45). Tears that involve the internal sphincter increase the severity of incontinence (46). A sphincter tear at EAUS is therefore an important finding, but how this is used to decide management a little

more controversial. Secondary anal sphincter repair has fallen out of fashion a little following the finding that results deteriorate over a few years (47), although a more recent study (48) suggests a better response.

Fluoroscopic studies have little role in faecal incontinence, unless there is an underlying rectal abnormality such as obstructive defactory symptoms and prolapse. Dynamic MRI studies have the added value of demonstrating prolapse in the rest of the pelvis, but apart from the lack of ionising radiation, has no real advantage for studying rectal function.

EAUS therefore remains the first line imaging investigation for anal incontinence, giving accurate information as to external and/or internal sphincter tears and the likelihood of atrophy. Dynamic studies of rectal evacuation are required only if there is some other problem suspected, such as prolapse. The advantages of using MRI are the lack of ionising radiation and a global view of the pelvic floor. Although imaging gives hard evidence of sphincter damage, this is really only part of a much more complex functional problem, and colorectal abnormalities may be just as important (49) with tears accounting for perhaps only 45% of incontinence (50).

6. RECOMMENDATIONS

- EAUS is the first line imaging investigation for faecal incontinence providing accurate information as to external and/or internal sphincter tears and the likelihood of atrophy. [Level of Evidence 3, Grade of Recommendation C].
- 3-D EAUS offer better quality images and diagnosis of the depth of anal sphincter injury. However routine use is not recommended because of the cost. [Level of Evidence 3, Grade of Recommendation C].
- Routine use of transperineal, transvaginal and translabial ultrasonography to image the anal sphincter complex are not recommended. [Level of Evidence 3, Grade of Recommendation C].
- Dynamic imaging of rectal function is required when rectal abnormalities such as prolapse are suspected [Level of Evidence 3, Grade of Recommendation C].
- MRI offers no advantage over other imaging modalities except for the lack of ionising radiation and global view of the pelvis [Level of Evidence 3, Grade of Recommendation C]

7. SUGGESTED RESEARCH AREAS

Better image quality with 3D EAUS and MRI have improved the understanding of pelvic floor anatomy, and this in turn has enabled the sonographic anatomy to be re-evaluated. However, conflicting views of anal sphincter anatomy remain with different MRI modalities as well as when comparison of sonographic abnormalities with ano-rectal function.

- Are clinical symptoms related to the size and the site of anal sphincter defect (51) or not (52)?
- Significance of the imaging in detecting anal sphincter injury especially immediately after childbirth in preventing future anal incontinence (40, 53).
- The value of ano-rectal physiological studies combined with imaging in assessing the success of surgical repair of anal sphincter complex (54).
- Identify (and modify) the risk factors leading to anal sphincter injury especially during childbirth and develop preventive strategies (55).

The most valuable aspect of 3-D ultrasonography and MRI imaging is that they give a global view of the pelvis, capable of investigating urological, gynaecological and coloproctological problems at the same time (18). Many patients do not have faecal incontinence as an isolated symptom, but also have urinary, prolapse or defecatory problems. The overview provided by imaging sets the way for a combined approach to the pelvic floor and should be the prime area future investigation (18).

IV. PAD TESTING

The use of a perineal electronic nappy using electrical conductivity to estimate the amount of urine leakage was first proposed by James et al.(1, 2). Accuracy of this technique was, however, questioned by others and the technique was improved (3-8). Walsh & Mills and Sutherst et al. introduced a more simple approach by estimating leakage by perineal pad weight gain (9, 10). These tests were not standardised until Bates et al. described a “structured” one hour pad test which was endorsed by the International Continence Society in 1988 (11). This test, however, was shown to have poor interdepartmental correlation and to be highly dependent on bladder volume (12, 13). In an attempt to make pad tests more reliable 24 hour and 48 hour pad tests were developed. A more precise estimation of urine loss was shown, but they were more cumbersome. The Pyridium pad test was also proposed for diagnosing urinary incontinence (14).

1. DEFINITION

The pad test is a diagnostic method to detect and quantify urine loss based on weight gain of absorbent pads during a test period under standardised conditions.

2. INDICATION AND METHODOLOGY

A pad test allows the detection and quantification of urine loss, but it is not diagnostic of the cause of the incontinence. Several different standards have been developed. Tests can be divided into four groups according to the length of the test: <1h, 1h, 24h and 48 h. (Table 4).

Although pad testing has been proposed mainly for research purposes it may also have a role in our clinical practice.

Quantification of urinary incontinence can be of importance in our daily practice. A large cohort study to evaluate the appropriateness of continence product prescription showed a poor correaltion between patient pad count and 48 hour pad testing (R^2 0.12, 0.19 for men and 0.11 for women) suggesting that pad testing is a more accurate measure of UI severity (15). In large cohort of women undergoing surgery for correction of vesico-vaginal fistula in Africa, a negative 1-hour pad test performed at the time oh hospital discharge had a highly negative predictive value for continue continence at follow-up (16). In women undergoing surgery for pelvic organ prolapse, 1-hour pad test with prolapse reduction with pessary can be used to diagnose occult stress urinary incontinence. A positive test before prolapse surgery was associated with and increased risk of mid-urethral sling postoperatively (17).

Table 4: types of pad test

Author	Time	Bladder load	Exercise
Hahn & Fall (18)	20 min	50% of MCC*	stair climbing, 100 steps, coughing (10x), running (1 min), wash hands (1 min) jumping(1 min)
ICS (11)	1h	Drink 500 ml (15 min) before test	walking & stair climbing (30 min), standing up 10x, coughing (10x), running (1 min), bending (5x), wash hands (1 min)
Jorgensen et al. (19)	24h		Everyday activities
Jakobseny et al. (20)	48h		Everyday activities

Maximum Cystometric Capacity

3. OFFICE-BASED PAD TESTING

Pad tests up to 2 hours were developed to be performed in outpatient clinics or hospital wards under supervised conditions. Bladder volume is predefined to reduce variability and a structured set of exercises is usually implemented to elicit the occurrence of urine loss.

3.1. Short Pad Test

Quantification:
These tests are based on a fixed bladder volume and a standard set of activities to facilitate the occurrence of urine loss, if any, over a short period of time. Jakobseny et al. found that the 40 minute test with a bladder volume of 75% maximum cystometric capacity and similar activities as a 1-hour ward test produced consistently larger amounts of urine loss than a standard 1-hour ward test (20). The difference was attributed to significantly larger bladder volumes during performance of physical activity in a 40 minute pad test.

Kinn & Larsson reported no correlation between a short 10 minute test with fixed bladder volume and the degree of incontinence as judged from the symptoms (21).

Hahn & Fall in a 20 minute test with half cystometric capacity showed no false negative results in 50 women with stress urinary incontinence although there was a discrepancy in 12% of patients between the perception of incontinence severity and pad test results (18).

These data suggest that short pad tests are more provocative than activities of daily living.

Acceptance: a randomized cross-over study suggests that 16% of patients undergoing a 20 minutes pad test were very statisfied with it and 84% were satisfied. A good level of agreement between the two etst was measured (kappa R = 0.84)(22).

Reproducibility:
The correlation factor (Pitman's nonparametric permutation test) between two separate 20 minute tests was 0.94 ($p<0.001$) (18). Kinn and Kinn & Larsson showed that the 10 minute test with a fixed pre-test bladder volume of 75% of maximal capacity was moderatey reproducible (r=0.74) (21).

A 20 minute pad test with an infused volume equal to the volume that elicited a strong desire to void during cystometry was proposed to tailor bladder filling the capacity of the individual patient. A good correlation was found in a test-retest study with a Spearman's rho of 0.788 ($p < 0.0001$) and an intraclass correlation coefcient was 0.793 (95% confdence interval, 0.704–0.882; $p < 0.0001$)(23).

Using a 1 hour pad test, a standardised bladder volume of 300ml and standardised physical activity mean differences of leakage was 8.5 ml and coefficient of repeatability was 33.6 ml (24).

3.2. One-Hour Pad Test

The use of a one-hour pad test has been investigated thoroughly for validity, reproducibility and sensitivity to change.

Quantification
Jakobseny et al. reported that a one hour test detected less leakage at 3 g compared to a 40 minute (7 g) and a 48 hour pad test (37 g) (20). In the elderly, a one-hour ward test did not demonstrate incontinence in 66% of those complaining of incontinence compared to 90% with a 24 in-patient monitoring of urine leakage (25). A one hour pad test was found to reflect everyday incontinence in only 48% of patients in comparison to 81% with a 48 hour test and 77% with a 40 minute test. Jorgensen et al. noted that 90% completed the test and 69% had test results which correlated with daily leakage (19). Lose et al. found a poor to moderate correlation of the modified one-hour test (200-300 ml in the bladder) with a history of stress urinary incontinence (n=31) (26). Mouritsen et al. showed that a 1-hour ward pad test did not detect grade I stress incontinence in 46%, grade II in 27% and grade III in 66% (27). Thind & Gerstenberg compared a 1-hour ward pad test to a 24-hour home pad test and found that a 1-hour pad test had a 36% false-negative rate as compared to a 24-hour home pad test (28).

Comparison of 24 hour and 7 days pad test in men with psotradical prostatectomy urinary incontinence suggests a good level of agreement using the Bland -Alman Plot with no bias found in the linear regression model ($r=0.19$ $p=0.24$) but the 7 days pad test is more apt to capture maximum urine leakage compared to the short test (29).

Reproducibility
Klarskov & Hald demonstrated in 3 consecutive 1-hour pad tests, a correlation coefficient of 0.75 and 0.97 depending on the activity regimen (30). The test, however, was quite demanding and a lot of patients did not complete the full testing. Christensen et al. compared a one-hour pad test in two different urological and one obstetrics & gynaecological departments (20 women) (13). The test results in two urological departments did not differ with an average pad gain of 24g and 21 g ($p>0.1$). However, pad test results between the departments of urology and gynaecology differed significantly, with average pad weight gain 9 g and 24 g respectively ($p<0.05$).

Lose and co-workers showed a significant variation between 1-hour ward test and retest in 18 patients (correlation coefficient 0.68) (12). In 50% of patients the leakage volume was variable due to differing bladder volume. When the results of the 1-hour pad test were cor-

rected for urine volume, the correlation coefficient value increased to 0.96. Simons et al found the reproducibility of the standard 1 hour pad test to be poor (31).

Validity
Walsh & Mills in the elderly and Holm-Bentzen et al. in patients with an AMS artificial sphincter showed that the one hour pad test did not correlate with subjective patient satisfaction but this may due to other lower urinary tract symptoms (9, 32).

Bladder **volume**
Jorgensen et al showed test-retest correlation was improved when the bladder volume was taken into account and the correlation value (r) raised from 0.68 to 0.93 (19). Fantl et al used a one hour test with the bladder filled to capacity and had a test-retest correlation of 0.97 which was improved if the fluid loss was expressed as a percentage of bladder volume (33). Lose et al. using a 1-hour pad test with standardised bladder volume of 50% of maximal cystometric capacity (MCC) showed in 25 women a test retest correlation of 0.97 but the intertest variation was up to 24g (34). Jakobsen et al. compared a 1-hour pad test with a bladder filled to 50% and 75% of maximal cystometric capacity and found that the final bladder volume was equal in both groups showing the importance of diuresis even with equal starting bladder capacities (35). The amount of leakage in both groups was the same. Simons et al. found the volume in the bladder after a standard 1 hour pad test varies by –44 to +66g in a test-retest situation (31). The fluid volume in the bladder appears to be critical in making the pad test reproducible and increasing the sensitivity of the test for detecting leakage.

Aslan et al compared a 1 hour pad test loss with the symptom impact index (SII) and the symptom severity index (SSI) (36). Only the SSI showed a relationship between the severity of the score and the pad test loss. The 1 hour pad test has also been used in assessing the validity of the Incontinence Impact Questionnaire and the Urogenital Distress Inventory unfortunately both had poor correlations with the pad test (37). This is to be expected as the questionnaires assess other urinary symptoms rather than just leakage.

Diagnosis
Fluid loss was significantly greater in patients with detrusor overactivity in comparison to urodynamic stress incontinence (33, 38). The reverse finding was reported by Matharu and co-workers (39). There is high variability in patients with detrusor overactivity making the test impractical as a diagnostic tool.

Sensitivity to change
The 1 hour pad test has been shown to be useful in detecting significant improvements after pelvic floor exercises for men suffering urinary incontinence after radical prostatectomy (40). Ward et al. found the standard 1 hour pad test to show significant reductions in loss after tension free vaginal tape procedures from 18g (IQR 6-37) and Burch colposuspension from 16g (IQR 6-38) both decreasing to 0g (IQR 0) (41). The 1 hour pad test has also been tested for the reduction in loss after conservative and surgical therapy (42). The changes were significant but there was moderate correlation (r = 0.53) with the changes in the St. George Urinary Incontinence Score.

3.3. Two-Hour Pad Test

A test period of 60-120 minutes after a 1 litre fluid load was proposed as the optimal duration for the pad test because of a consistently high bladder volume (43). Han et al showed, however, that a 1-hour pad test is more practical (44). In children a 2-hour ward pad test yielded 70% positive results for incontinence (45). Richmond et al. compared two exercise regimens with a 2-hour pad test and showed no significant differences regarding which order the exercises were performed (46). Walters et al. performed a 2-hour pad test with standard exercise in 40 women with SUI showing 78% positive tests (>1g pad gain) after 1 hour and 98% after the second hour (47). Overall, the two-hour pad test was found to be superior to the one-hour one. There was no correlation between pad test results and the severity of a symptoms score.

4. HOME BASED PAD TESTING

These tests were developed to diagnose and measure urine loss in a situation as close as possible to standard daily life of the patient. The longer observation period usually requires a less structured procedure.

4.1. 12-Hour Pad Test

Quantification:
Hellstrom et al. demonstrated in 30 children with incontinence a positive 12-hour home pad test in 68%. When a standard fluid load (13 ml/kg) was instituted in 20 children, the frequency of the positive test increased to 80% (45).

4.2. 24-Hour Pad Test

Quantification:
Lose et al. found a 90% correlation of a 24-hour pad test with a history of stress incontinence in 31 women (26). This was better than the results of a 1-hour test. Thirteen of 31 patients were found to be continent after a 1-hour ward test in comparison to only 3 with a 24-hour home pad test. Mouritsen et al. showed that the 24-h home test was well tolerated and as good at detecting incontinence as a 48-h test (27). Griffiths et al. found only a 10% false negative rate of a 24-hour pad test in an elderly population (25). Using non-parametric coefficient of correlation, they found a significant difference between the 1-hour test and the 24 hour test. Lose et al. found that a 24h home test performed during daily activities was more sensitive that a 1-hour ward test with standardised bladder volume of 200-300 ml (26). High fluid intake did not change the results of a 24-h home test, but a low fluid intake reduced a positive test by 56% (48). Ryhammer et al. showed that 24-h test is superior to subjective self-reported assessment of urinary incontinence (49).

Reproducibility
Lose et al showed poor correlation in a test-retest study with a variation of more than 100% (26) although Groutz et al. using Lin's concordance correlation coefficient (CCC), found the 24-h test to be very reliable instrument (50). Increasing test duration to 48 and 72 hours slightly improved reliability but decreased patient compliance.

The values for the pad test increase in asymptomatic men and women were reported by Karantanis et al with the median value 0.3g (IQR 0.2 – 0.6; 95th centile 1.3g). It is surprising that the loss is so low and the same for men and women (51).

Diagnosis
Matharu et al found women with urodynamic stress incontinence leaked more than women with detrusor overactivity but the amounts were not diagnostic for the individual abnormalities (39). Pad test loss is unaffected by the degree of hypermobility however there is increased loss associated with urethral sphincter incompetence diagnosed by a vesical leak point pressure less than 60 cmH_2O (52).

Validity
Karantanis et al found the 24-hour pad test was poorly correlated in women with urodynamic stress incontinence with incontinence episodes on a 3 day urinary diary (Kendall's corr coeff b = 0.4) and the ICIQ-SF (r = 0.4) (53). Singh et al. reported that fewer (52%) women after surgery were willing to complete a 24 hour pad test at follow up (54).

4.3. 48-Hour Pad Test

Quantification:
Jakobseny et al. showed that 48-hour pad test reflects everyday incontinence in 81% of patients (20). No statistical analysis data were given. Ekelund et al., found patients own weighing correlate well to control weighing at the clinic in 48-h pad test (r=0.99) (55).

Nygaard and Zmolek in 14 continent women showed a mean pad weight, attributed to sweat for all exercise sessions of 3.19 $\pm$ 3.16 g (the Kendall coefficient of concordance of the test-retest reliability was 0.96) but there was a lot of variation between patients (59). Pyridium staining was not helpful in increasing specificity. Similar results with Pyridium were reported by Wall et al. in a 1-hour ward test (14). In his study (n=18) the Pyridium test was 100% positive in patients with SUI but had false positive results in normal women (52%).

Mean pad weight loss due to evaporation or leakage (was calculated to be 1.003 g, and ranged from -6.5 to +3.85 g (SD 1.85 g) (9). Lose et al. showed no evidence of evaporation over 7 days if the pad was stored in a plastic bag (26). Versi et al. showed pads wetted with saline showed no difference in weight after 1 week and less than 10% weight loss after 8 weeks (57). Twelve pads were weighed by the patient and a healthcare worker with a coefficient of variance =1.55% with a mean deviation of 49%.

Comments
Pad tests can either be used as a qualitative diagnostic tool to diagnose urinary incontinence and as a quantitative test to grade its severity. Pad test is unable to distinguish among different types of incontinence such as stress, urgency or mixed urinary incontinence. The ICS definition of urinary incontinence (the complaint of any involuntary leakage of urine) does not describe how the diag-

Table 5: test-retest correlation

Author	Test	Correlation coefficient	Symptoms
Klarskov &Hald 1984 (30)	1-h	0.96	SUI&UUI
Lose et al 1986 (12)	1-h	0.68	SUI & MIX
Fantl et al. 1987 (33)	1-h (vol)	0.97	SUI
Fantl et al. 1987 (33)	1-h (vol)	0.84	SUI & UUI
Lose et al. 1988 (34)	45-m (vol)	0.97	SUI & MIX
Victor et al. 1987 (56)	24-h	0.66	SUI
Lose et al. 1989 (26)	24-h	0.82	LUTS
Mouritsen et al. 1989 (27)	24-h	0.87	MIX
Versi et al. (1996) (57)	24-h	0.9	LUTS
Groutz et al. (2000) (50)	24-h	0.89	LUTS
Victor et al. 1987 (56)	48-h	0.9	SUI
Versi et al. (1996) (57)	48-h	0.94	LUTS
Groutz et al. (2000) (50)	48-h	0.95	LUTS

Table 6. Pad-weight gain (g) in normal women

Author	Time	No	Mean (g)	Range (g)	SD	SEM	Note
Hahn &Fall 1991 (58)	20 min	10	0				
Nygaard & Zmolek, 1995 (59)	39.5 min	14	3.19	0.1-12.4	3.16		Exercise
Versi & Cardozo 1986 (60)	1h	90	0.39	0-1.15		0.04	
Sutherst et al. 1981 (61)	1h	50	0.26	0-2.1	0.36		
Walsh & Mills, 1981 (9)	2h	6	1.2	0.1-4.0	1.35		Daily activity
Lose et al. 1989 (26)	24h	46	4	0-10			
Jorgensen et al. 1987 (19)	24h	23	4	0-10			
Mouritsen et al. 1989 (27)	24h	25	2.6	0-7			
Karantanis et al. 2003 (51)	24h	120	0.3	0-1.3			
Versi et al. 1996 (57)	48h	15	7.13		4.32		

nosis is made but clearly refers to a patient's complaint that excludes urodynamics and rather points at the patient perception of the condition. Following this line of thought, research in this area has moved away from the evaluation of diagnostic accuracy of pad test versus a urodynamic diagnosis of UI and entered the more interesting field of the relationship between the patient perception of UI and pad test. Franco and co-workers in London, UK tested the correlation between different questionnaires for UI and 1-hour pad test showing that only the ICIQ-SF reached statistical significance with a Kendall's τb of 0.177 and a P value of 0.037 while no significant correlation was found for a 0 to 10 Vas score, a patient-based 3-point symptom severity scale, Stamey grade, Urogenital Distress Inventory and the Incontinence Impact Questionnaire (IIQ-7) (62). In another study from Wijma and co-workers, the diagnostic accuracy of pad test for self-reported symptoms of UI was evaluated during pregnancy and after childbirth and the authors conclude that the diagnostic value of pad testing has no clinical relevance in this setting (63). A similar analysis, performed in a male population undergoing sling surgery for post-radical prostatectomy incontinence suggested a good correlation between ICIQ-SF and the Patient Global Perception of Improvement (PGPI) with a 24-hour pad test (64).

Studies from the Urinary Incontinence Treatment Network in US investigated the relation between different measures of incontinence severity and showed how pad weight from a 24-hour test had a good correlation with the incontinence episode frequency derived from a 3-day bladder diary (Spearman correlation coefficient 0.61 but a much lower degree of correlation was found with questionnaires such as the Medical, Epidemiological, and Social Aspect of Aging (r=0.33), the Urogenital Distress Inventory (r=0.17) and the Incontinence Impact Questionnaire (r=0.34) (65). In the same study, the use of pad testing as a prognostic parameter for treatment outcome was investigated but 24-hour pad testing showed no prognostic value for treatment failure in a study of Burch colposuspension versus autologous rectus fascia sling (66). An interesting result was obtained in a predominantely female population of patients receiving neuromodulation for refractory urgency incontinence in which a 24-hour pad test performed after the initial test stimulation was able to predict long term satisfaction in this difficult patient population (67). In this, as in other studies, the number of pads used per day proved to be an unreliable measure of urinary incontinence (68).

A couple of important methodological issues have been raised concerning the use of pad testing. Khan & Chien eloquently pointed out that test-retest comparison should include methods of blinding and use of an appropriate index of degree of agreement which is the intra-class correlation coefficient. In most of the literature this was not implemented (69). Kromann-Andersen et al. argued that with considerable inter- and intra-individual variation of urine loss, the correlation of test/retest results may be overestimated and suggested different trials for small, modest and large leakage in large numbers of patients (70). This trial has not been carried out.

A recent Health Technology Assessment of pad testing concluded that although high sensitivity and specificity for the diagnosis of UI was reported in some studies, it was difficult to draw any conclusions about the diagnostic accuracy for SUI because of the differences existing in pad test methodology. The number of studies comparing the same pad tests with adequate reporting is insufficient and no formal pooling of published data could be performed (71).

Role of the investigation

The test has been standardised by ICS in 1988 for quantification of urine loss and suggested uses for assessment and comparison of treatment results for different types of urinary incontinence in different centres. Also, the AUA report on Surgical Management of Female Stress Urinary Incontinence includes a pad test (pretreatment evaluation) as a standard of efficiency for clinical trials (72). The Urodynamic Society included a pad test in a Standards of Efficacy for Evaluation of Treatment Outcomes in Urinary Incontinence (73). No suggestion was made in the last two reports of which test to use.

5. CONCLUSIONS

- The 1-hour pad test is not very accurate unless a fixed bladder volume is applied
- Set exercises during the test improve test-retest reliability
- The sequence of exercises has little effect on test results
- A pad weight gain ≥1 g suggests a positive 1h test
- A 24 hour test correlates well with symptoms of incontinence
- A 24-hour test has good reproducibility but poorer compliance
- A pad weight gain ≥1.3g = positive 24 h test
- A test lasting longer than 24 h has little advantage
- A pad test cannot distinguish between USI and DO

6. CONSENSUS STATEMENTS

- The pad test is an optional investigative tool in the routine evaluation of UI**(Level of Evidence 3, Grade of Recommendation C)**
- Pad test is a useful outcome measure in clinical trials and research studies. **(Level of Evidence 3, Grade of Recommendation C)**

The following standards are suggested:

- 20 min-1 h ward/office test with fixed bladder volume (pad weight gain ≥ 1g = positive test) **(Level of Evidence 3, Grade of Recommendation C)**
- 24 h home pad test during daily activity (pad weight gain ≥ 1.3g/24h = positive test) **(Level of Evidence 3, Grade of Recommendation C)**

7. FUTURE RESEARCH AREAS

Proper validation analysis using the coefficient of variability

Evaluation of the ability to detect all the spectrum of urinary incontinence (from mild to severe)

Sensitivity to change in time of incontinence status for 24 hour pad tests

Validity of pad tests with other measures of incontinence such as urinary diaries and symptom questionnaires.

V. NEUROPHYSIOLOGY

1. INTRODUCTION

Neurophysiological investigations of muscles and nerves in the perineum and pelvis originated in the 1930-ties and have evolved with the developments in general clinical neurophysiology. The data from these investigations can assist clinicians in diagnosing neurological disease or injury; the tests can be used intraoperatively for identification of nerves and muscles.

This text details the investigations, their applications and limitations, enabling investigators and clinicians to make a well-informed decision about using these tests.

The present text is based on the previous chapter on clinical neurophysiology prepared for the International Consultations on Incontinence (1), which has been updated by a literature search in Medline using key words incontinence, clinical neurophysiology, electromyography, reflex, evoked potentials, autonomic nervous system tests.

1.1. Classification Of Clinical Neurophysiological Tests

Although different types of tests may be included under the term "neurophysiological", it is particularly the electrophysiological tests that shall be discussed in the present text.

Electrophysiological tests are an extension of the clinical examination, and a functional anatomic approach to classification makes most sense. For the purpose of this categorisation, the nervous system is divided into the somatic and the autonomic nervous systems. The somatic nervous system provides motor innervation to the skeletal muscles and joints, and sensory innervation from skin and muscle spindles. The autonomic nervous system provides motor innervation to the viscera and other end-organs not under voluntary control (e.g., sweat glands). Its sensory fibres are referred to as visceral afferents. Both systems have central pathways (neurons participating in spinal cord and supraspinal control) and peripheral nerves (those going to and from end-organs).

Thus, electrophysiological tests can be divided into: a) somatic motor system tests (EMG, terminal motor latency measurements/ motor nerve conduction studies, and motor evoked potentials (MEP)); b) somatosensory system tests (sensory neurography, somatosensory evoked potentials (SEP)); c) reflexes; and d) the autonomic nervous system tests (for sympathetic or parasympathetic fibres).

Electrophysiological tests may also be categorized "technically" into those limited to simple recording some bioelectrical activity (for instance: electromyography), and those which record particular biological responses to anatomically localized stimulation (these may be subsumed under the term "conduction tests").

1.2. Biological Correlates Of Electrophysiological Tests

It is always difficult to have a perfect correlation between electrophysiological test results and clinical and pathological conditions.

Some abnormalities are sub-clinical. Electrophysiological tests are more relevant and accurate in cases of lower motor neuron lesions. They are less effective in the case of upper motor neuron lesions or in the case of autonomic nervous system dysfunction.

But usually, electrophysiological tests allow the etiological and topographical diagnosis of perineal disorders to be made more precise. A neurological cause and the level of lesion can thus be determined in the case of a urinary, anorectal or genital-sexual disorder.

The prognosis of urinary or anorectal dysfunction during neurological lesions can also be determined by electrophysiological tests.

1.2.1. Conduction Tests: Nerve Conduction, Evoked Potential and Reflex Studies

The electrophysiological responses obtained on stimulation are compound action potentials and relate to populations of biological units (neurons, axons, motor units, muscle fibres, etc.). Latency and amplitude are commonly measured parameters of responses during neurophysiological testing. If the onset of the potential is measured, the latency of a compound potential represents the fastest conduction through a particular neural channel. As a general rule, latency measurements are not markedly affected by technical factors, but provide little information about the loss of biological units (e.g., motor neurons or axons). The amplitude of the compound potential correlates with the number of activated biological units. In theory, the amplitudes are the more relevant physiological parameter, as they reflect the functional or structural loss of biological units. Unfortunately, amplitudes are also strongly influenced by many poorly controllable technical factors. Measurements of latencies and amplitudes of evoked potentials and reflex responses, including sympathetic skin responses, relate not only to conduction in peripheral and central neural pathways, but also to trans-synaptic transmission.

1.2.2. Electromyography (EMG)

Knowledge of the structure and function of the motor unit (Figure 58) is fundamental to understanding the application of EMG. Motor neurons, which innervate striated muscle, lie in the anterior horn of the spinal cord and are called "lower motor neurons". (Neurons that innervate the sphincters lie in Onuf's nucleus in the sacral spinal cord; they are somewhat smaller than those innervating skeletal limb and trunk muscles). Within the muscle, the motor axon branches to innervate a certain number of muscle fibres, which are scattered throughout the muscle. All muscle fibres innervated by one lower motor neuron are activated simultaneously; all these constituents together are called "motor unit". The innervation of muscle fibres is such that it is unlikely that muscle fibres that are part of the same motor unit will be adjacent to one another.

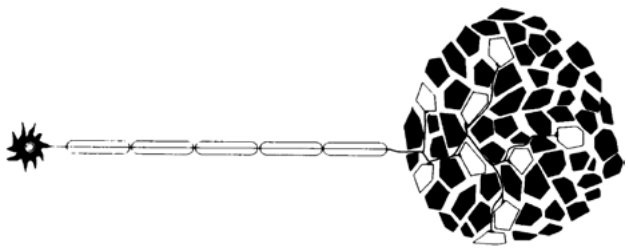


Figure 58: Schematic representation of a motor unit. The alpha motor neuron with its cell body, its myelinated axon and the peripheral nerve endings is shown. The muscle fibres innervated by this alpha motor neuron are shown in white. (Note that the muscle fibres from one motor unit are intermingled with motor fibres from other motor units).

It is difficult to estimate the number of muscle fibres innervated by a single axon (i.e., the "innervation ratio") or the number of motor units supplying a muscle, by clinically available neurophysiological techniques.

1.3. General Methodological Considerations

To date, there are no universally accepted standards for conducting individual uro-genital-anal neurophysiological tests, but the variations of testing in different laboratories are minor.

There are technical standards on equipment safety.

1.3.1. Equipment

Clinical neurophysiological tests are conducted with complex electronic instruments and various devices that come into contact with the patient. Though this equipment is mostly standard, some specially constructed electrodes or stimulating devices have been devised to conform to uro-genito-anal anatomy. As long as the standards of electrical safety are adhered to, the risk to patients is negligible.

Surface electrodes, which are applied to skin or mucosal surfaces, or needle electrodes are used for electrical stimulation and to record bioelectrical activity. The important neurophysiological difference between surface and needle electrodes is their selectivity, and the practical difference is their invasiveness. The choice and application of electrodes is guided by the need for selective recording or stimulation. Less commonly, special devices are used for magnetic and mechanical stimulation.

The electrical stimulation should be specified and characterised both in technical (e.g., rectangular electrical pulse, 0.2 ms, 15 mA) and physiological terms (e.g., 3-times sensory threshold). A stimulus with defined technical parameters may have variable biological effects because of the variable influences of electrode condition, contact, tissue conductivity etc. Supramaximal stimulation is preferred to elicit a compound muscle action potential (CMAP) or sensory nerve action potential. Supramaximal stimuli yield responses with the largest amplitude and shortest latency and are the least variable and most reproducible. The sites at which stimulation electrodes are applied should be described using anatomical terms.

1.3.2. Recording

1.3.2.1. Apparatus settings

For recording, the apparatus settings (gain, sweep speed) have to be adapted to the known range of amplitudes, latencies, and duration of the response and it has to be appropriately displayed for analysis. Particularly important is the frequency setting of filters: for surface electrode recordings it is typically 2 Hz – 1 kHz; for concentric needle EMG recordings, it is 5 Hz – 10 kHz.

Placement of electrodes on the scalp for evoked potential recordings is defined according to the 10-20 International EEG System.

1.3.2.2. Reproducibility and Reliability

Any potential recorded should be reproducible; therefore, as a rule, at least two to three consecutive recording procedures need to be performed. To improve the signal-to-noise ratio some small amplitude responses need to be averaged. Therefore, many repetitions of stimulation/recording need to be done (typically 100-200). Even such an averaged recording needs to be repeated at least twice. Responses whose nervous pathways include synapses may show marked fatiguability with stimulus repetition (e.g., SSR), others are facilitated (the bulbocavernosus reflex).

1.3.2.3. Waveform Analysis

For a particular recorded potential, its shape, latency, and amplitude are analysed. Morphologically, a particular response (or part of it) needs to be recognised as present or absent. The shape of potentials is important to accurately determine the latency and duration (if applicable) and amplitude of the response. The onset of the response obtained on stimulation (for M-waves, MEP and sacral reflex testing) or the individual peaks of the potentials (for SEP) are used to determine the latency. The amplitudes are analysed relative to the baseline or "peak to peak".

2. CLINICAL NEUROPHYSIOLOGICAL TESTS

2.1. Somatic Motor System Tests

2.1.1. Electromyography (EMG)

The term "EMG" is used for several different procedures, the common denominator of which is the recording of bioelectrical activity from muscle. In practice, EMG is used a) to record the activity of a particular striated muscle as a functional unit (as for instance in combined urethral sphincter EMG and a pressure-flow study - see kinesiological EMG); b) to indicate that a particular muscle has been activated, either by stimulation applied to its motor innervation (M-wave, MEP) or to sensory pathways (reflex response); c) to differentiate between normal, denervated, reinnervated, and myopathic striated muscle; and d) to measure neuromuscular transmission (the latter is not relevant for clinical diagnostics in pelvic floor muscles).

EMG recordings from smooth muscles are as yet only experimental.

2.1.1.1. General Technique for Needle EMG in Pelvic Floor Striated Muscles

All tests requiring needle electrodes are invasive and some pain is inevitable, even with use of local anaesthetics. Local anaesthesia is infrequently used for needle EMG examination. Intramuscular electrodes need to be appropriately placed in the target muscle.

The pelvic floor and perineal muscles can be examined, including the levator ani, the bulbocavernosus muscle and the striated anal and urethral sphincter muscle. Facility with needle examination requires some practice. As a rule, several sites from one or more skin penetrations are sampled, which is difficult in small muscles.

The audio output from the loudspeaker of the EMG apparatus helps in assessment of the quality of recording as well as in recognition of the electrophysiologic phenomena.

2.1.1.2. Concentric needle EMG (CNEMG)

The examination is conducted with a single use, disposable electrode, and all different "types of EMG" mentioned above can be performed with this electrode. It consists of a central insulated platinum wire inserted through a steel cannula and the tip ground to give an elliptical area which can record spike or near activity from about 20 muscle fibres (2). The number of motor units recorded therefore depends both upon the local arrangement of motor units within the muscle fascicle and the level of contraction of the muscle.

In principle, CNEMG can provide information on a) muscle insertion activity, b) abnormal spontaneous activity within the muscle (Figure 59), c) MUPs, d) interference pattern (IP), neuromuscular jitter.

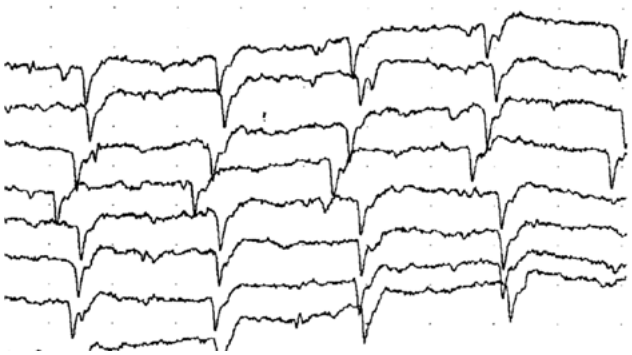


Figure 59: Concentric needle EMG recording from right bulbocavernosus muscle of a 49-years old male with urinary incontinence diagnosed as possible Multiple system atrophy. Pathological spontaneous activity (a burst of positive sharp waves) is shown.

In normal striated muscle, needle movement elicits a short burst of "insertion activity," which is due to mechanical stimulation of excitable muscle cell membranes. This is recorded at a gain setting of 50 µV per division (sweep speed 5 – 10 ms/division), which is also used to record spontaneous activity. Absence of insertion activity with appropriately placed needle electrode usually means a complete denervation atrophy of the examined muscle.

The amount of recruitable motor units during voluntary and reflex activation can also be estimated. Normally, MUPs should intermingle to produce an "interference" pattern on the oscilloscope during muscle contraction, and during a strong cough. In addition, the number of continuously active MUPs during relaxation (3), MUP variability (neuromuscular jitter) as well as MUP recruitment on reflex and voluntary activation (kinesiological parameters) can be observed (4).

MUPs (and occasionally encountered end-plate activity) are recordable in normal resting sphincter muscles in a relaxed subject. This is in contrast to limb muscles where relaxation is associated with "electrical silence" by EMG. In addition to continuously firing motor units, new MUPs are recruited voluntarily and reflexly in the sphincters. It has been shown that the two MUP populations differ in their characteristics: reflexly or voluntarily activated "high-threshold MUPs" being larger than continuously active "low-threshold MUPs". As a consequence, standardised level of activity at which a template based multi-MUP analysis obtains 3-5 MUPs on a single muscle site was suggested (5).

Although EMG abnormalities of striated muscle are detected as a result of a host of different lesions and diseases, there are in principle only two standard manifestations which can occur: a) disease of the muscle fibres themselves ("myogenic" changes), and b) changes in their innervation ("neuropathic" changes). Myogenic changes may result from muscle disease, probably also from direct trauma (e.g., the anal sphincter tear during vaginal delivery). Neurogenic changes may be attributable to injury at any level along the lower motor neuron supplying the particular muscle, extending from the motor neuron body, sacral nerve roots to the small branches within the muscle. (In the pelvic floor muscles, only neurogenic changes are well recognised and routinely evaluated).

In partially denervated sphincter muscle there is – by definition – a loss of motor units (MUs). This can be estimated during relaxation by counting the number of continuously firing low-threshold MUPs. In patients with cauda equina or conus medullaris lesions, fewer MUPs fire continuously during relaxation (6), probably due to partial axonal loss. The main obstacle to qualified assessment of reduced number of activated MUs and activation of MUs at increased firing rates (as occurs in limb muscles) is a lack of concomitant measurement of level of contraction of the examined muscle (this can be readily assessed when studying limb muscles).

There are two approaches to analysing the bioelectrical activity of motor units: either analysis of individual motor unit potentials (MUPs), or analysis of the overall activity of intermingled MUPs. (This is the so called "interference pattern" – IP. Exploring different sites of the activated muscle with a needle electrode provides "samples" of intermingled motor unit potentials (IP epochs), which can be analysed).

Generally, three different techniques of MUP analysis (manual-MUP, single-MUP and multi-MUP) and 1 technique of IP analysis (turn/amplitude – T/A) are available on advanced EMG systems (6).

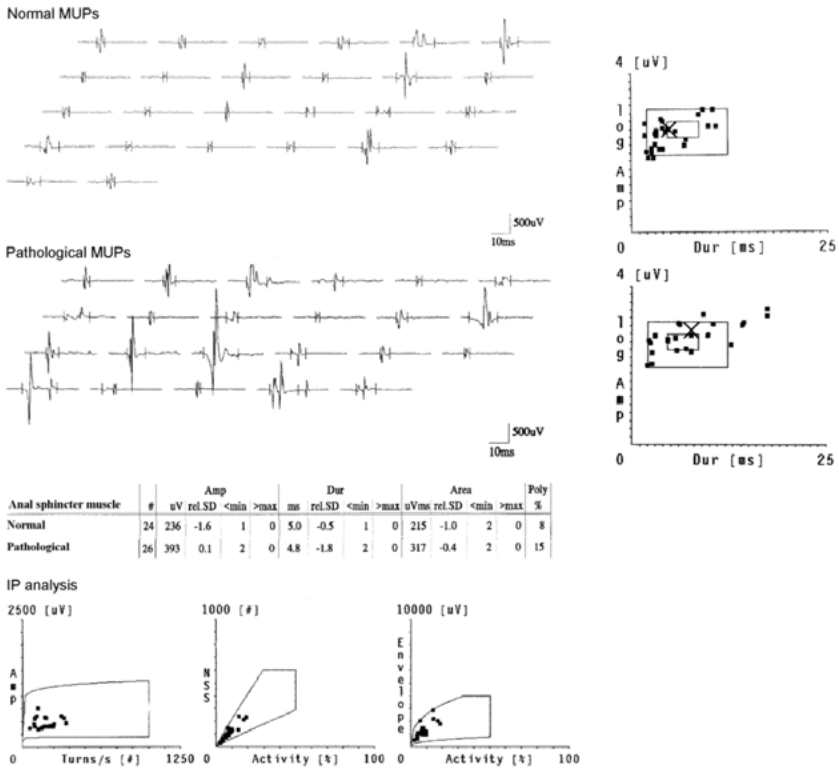
It is easy to grasp the "motor unit potential analysis", as it is simply a measurement (by different methods) of the "parameters" of single individual MUPs (i.e., its amplitude, duration, number of phases…). The changes in MUP parameters furthermore are "direct" results of understandable physiological changes and are thus "meaningful" to the interpreter.

The changes in IP parameters are, however, less readily grasped. These are: numbers of turns per second (any peak or trough of the signal where the activity changes by more than 100 µV); amplitude/turn (change in volts between two turns); number of short segments (parts of signal that has "sharp" activity) percent activity (percent of epoch with sharp activity); envelope (peak to trough amplitude exceeded by 1% of peaks/troughs). These parameters relate both to MUP parameters and to the activation level of the muscle. Recorded data are log transformed and linear regression lines are created. Amplitude/turn, and number of turns/second data from normal subjects can be used to create upper and lower boundaries (95 % confidence intervals) for assembly of future data from individual patients. Individual data create a scatter plot ("cloud") which compares to the normative boundaries. (See Figure 60). It has been asserted that this approach does not require a standardized muscle contraction, but the shape of the "cloud" is dependent on the strength of muscle contraction. Therefore, it has been suggested to standardize the method by measuring pressure exerted by the contracting sphincter (7).

Both the template based multi-MUP analysis of MUP and T/A analysis of IP are fast (5-10 and 2-3 minutes per muscle, respectively), easy to apply, and, technically, represent clinically useful techniques.

2.1.1.2.1. CNEMG Findings Due to Denervation and Reinnervation

After complete denervation, all motor unit activity ceases. In a denervated muscle, complete "electrical silence" is noted in the first days after such an event. The diagnosis of complete denervation is confirmed by the absence of muscle response during electrical stimulation. Because motor axons take days to degenerate after injury, this proof is not available for up to 5-7 days after a denervation injury. However, it is rarely necessary to demonstrate complete denervation in the acute stage because the clinical condition is usually obvious. Denervated muscle fibres become hyperexcitable and start to fire spontaneously giving rise to abnormal spontane-



Anal sphincter muscle	#	Amp uV	Amp rel.SD	Amp <min	Amp >max	Dur ms	Dur rel.SD	Dur <min	Dur >max	Area uVms	Area rel.SD	Area <min	Area >max	Poly %
Normal	24	236	-1.6	1	0	5.0	-0.5	1	0	215	-1.0	2	0	8
Pathological	26	393	0.1	2	0	4.8	-1.8	2	0	317	-0.4	2	0	15

Figure 60: Comparison of normal (above) and pathological (below) motor unit potentials (MUPs) sampled by multi-MUP analysis from the right halves of the subcutaneous parts of the external anal sphincter (EAS) muscles. To the right logarithm (amplitude) vs. duration plots of the MUPs are shown; the inner rectangle presents normative range for mean.

ous activity, but these may take up to three weeks to appear. The "insertion activity" becomes prolonged and short biphasic spikes (fibrillation potentials) and biphasic potentials with prominent positive deflections (positive sharp waves) appear (Figure 59). Thus, concentric needle EMG (CNEMG) correlates of denervation are pathologically prolonged insertion activity and pathological spontaneous activity. Completely denervated muscle may be reinnervated by axonal regrowth from the proximal nerve stump with few muscle fibres constituting "nascent" motor units. These are short, bi- and triphasic, soon becoming polyphasic, serrated and with prolonged duration. In partially denervated muscle, collateral reinnervation takes place. Surviving motor axons will sprout and grow out to reinnervate those muscle fibres that have lost their nerve supply. This results in a change in the arrangement of muscle fibres within the unit. Whereas in healthy muscle, it is unusual for two adjacent muscle fibres to be part of the same motor unit, following reinnervation, several muscle fibres belonging to the same motor unit come to be adjacent to one another. CNEMG correlates are changes in MUPs (duration, amplitude, number of phases, turns, etc). Early in the process of reinnervation, the newly outgrown motor sprouts are thin. Therefore, they conduct slowly such that the time taken for excitatory impulses to spread through the axonal tree is abnormally prolonged. Moreover, the neuromuscular transmission is unstable due to immaturity of the motor endplates. The CNEMG correlate is instability of long-duration complex potentials.

In partially denervated muscle, some MUPs remain and mingle eventually with abnormal spontaneous activity. Changes due to collateral reinnervation are reflected by: prolongation of the wave form of the MUP (Figure 60) which may have small, late components ("satellite potentials"). MUPs show "instability" due to insecure transmission in newly formed axon sprouts and endplates. This "instability of potentials" (meaning both "jitter" and "blocking" of individual components in a complex potential) is not routinely assessed during sphincter EMG (8). In striated muscle, the diameter of reinnervating axonal sprouts and conduction velocity increase with time, thereby improving synchrony of activation in the reinnervated motor unit. Thus, MUP amplitude increases while MUP duration reverts towards normal. However, in degenerative neurological diseases (such as multiple system atrophy), long duration motor units are a prominent feature of anal sphincter reinnervation (9). It is important to note that in patients with more severe neurogenic lesions, reinnervation may be inefficient resulting in MUP with parameters below confidence limits describing size (area, duration) (10).

The changes in MUP parameters (along with changed number of MUPs and changes in activation frequency of MUPs) will be reflected also in IP parameters.

Abnormalities of parameters evaluated by needle EMG are in principle non-specific, i.e., most abnormalities can occur both in neuropathic or myopathic conditions. It is the overall clinical picture that dictates interpretation of results. It has been suggested that the combination of MUP thickness and number of turns might be even more accurate (11) than previously suggested combination of MUP area, duration, and number of turns (12).

2.1.1.2.2. CNEMG of the External Anal Sphincter

The external anal sphincter (EAS) is the most practical indicator muscle for sacral myotomes because it is easy to access, has enough muscle bulk for exact EMG analysis, and its examination is not too uncomfortable.

The needle electrode is inserted into the subcutaneous EAS muscle about 1 cm from the anal orifice to a depth of a 3-6 mm under the non-keratinised epithelium. For the deeper part of the EAS muscle 1-3 cm deep insertions are made at the anal orifice, at an angle of about 30° to the anal canal axis (13). In most patients only examination of the subcutaneous EAS muscle is necessary. Separate examinations of the left and right EAS muscles are recommended. The needle is inserted into the middle of the anterior and posterior halves of each side ("quadrants") of the EAS muscle. After insertion in two positions on each side the electrode is turned backwards and forwards in a systematic manner. At least 4 sites in each of the subcutaneous and/or the deeper EAS muscle are thus analysed (13, 14).

Use of quantitative MUP and IP analyses of the EAS is further facilitated by the availability of normative values (15) that can be introduced into the EMG systems' software. It has been shown that normative data are not significantly affected by age, gender (15), number of uncomplicated vaginal deliveries (16), mild chronic constipation (17), and the part of EAS muscle (i.e. subcutaneous or deeper) examined (16).

Intramuscular electrode insertion into other perineal muscles and pelvic floor muscles is not standardized and is described in textbooks and primary literature.

2.1.1.3. Single fibre EMG (SFEMG)

SFEMG is nowadays used practically only in diagnostics of neuromuscular transmission disorders, and not anymore in the pelvic floor muscles.

The SFEMG electrode has similar external proportions to a concentric needle electrode, but with a smaller recording surface. It will pick up activity from within a hemispherical muscle volume 300 µm in diameter, much smaller than the volume of 2-3 mm diameter from which a concentric needle electrode records (2). Apart from the neuromuscular jitter it can also record data which reflect motor unit morphology (muscle fiber density)(8), but for this purpose it has several disadvantages in comparison to the concentric needle EMG.

2.1.1.4. Kinesiological EMG

Kinesiological EMG is the term for the type of EMG recording aimed only to assess the pattern of an individual muscle's activity/inactivity during defined manoeuvres (Figure 61), typically during urodynamics. Any type of electrode can be used to make kinesiological recordings. The electrical activity of a muscle is described as present or absent (and can also be quantified). Technical issues will be dealt here; the relevance for diagnostics will be discussed in the Chapter on dynamic testing.

Although either standard EMG equipment or EMG facilities contained within urodynamic systems can be used, the better visual and audio control provided by standard EMG equipment facilitate optimal electrode placement and improve recordings (18). When using surface electrodes there are problems related to validity of signal (e.g., artefacts, contamination from other muscles). The quality of the EMG recorded from the external urethral sphincter (EUS) muscle is improved by a catheter-mounted surface electrode device that applies mild suction (19). With intramuscular electrodes, the procedure is more invasive, and there are questions as to whether the whole muscle in large pelvic floor muscles is properly represented by the sampled muscle portions. Intramuscular electrodes should ideally be fine wire electrodes, as they do not dislodge, and no pain is induced with muscle contraction.

The kinesiological sphincter EMG recordings in health show continuous activity of MUPs at rest. It can be recorded in many but not all detection sites of the levator ani muscle. The urethral and anal sphincter as well as the other pelvic floor musculature (e.g. pubococcygei) can be voluntarily activated typically for less than 1 minute (20). Timely activation of the levator ani muscle has been demonstrated to be an important aspect of stable bladder neck support; its activation precedes activity of other muscles in the cough reflex (21). A consistent contraction sequence of the superficial and deep pelvic floor muscles is found in continent but not in incontinent women (22).

Sphincter activity during voiding is characterised by the cessation of all EMG activity prior to detrusor contraction. Needle electrodes are more useful than perineal patch electrodes to demonstrate MU quiescence during voiding (23, 24).

Pathologic incoordination of the detrusor and sphincter is called detrusor sphincter dyssynergia. In selected patients with neurogenic detrusor overactivity, EMG of the EUS muscle can be used to demonstrate the onset of detrusor contractions (20).

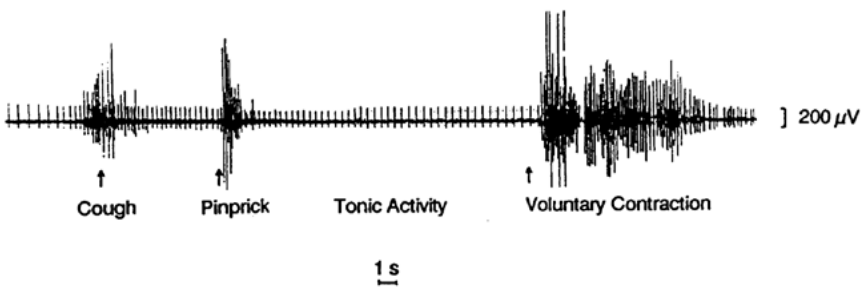


Figure 61: Kinesiological EMG recording from the urethral sphincter muscle of a healthy 53-year-old continent female. Recruitment of motor units on reflex manoeuvres and on a command to contract is shown; regular continuous activity of motor units represents "tonic activity". (Recorded with concentric needle electrode).

Apart from polygraph urodynamic recordings to assess detrusor-sphincter coordination, the diagnostic usefulness of kinesiologic EMG has not been established.

2.1.1.4.1. Surface Electromyography Using Non-invasive Electrode Arrays

Surface EMG recording using non-invasive electrode arrays and multichannel EMG amplifiers can localize muscle innervation zones and asymmetry in muscle innervation (25), and analyze discharge patterns of MUPs, and propagation velocities along the muscle fibers (26). While it is expected that the new sophisticated computer assisted analysis techniques will help diagnosing sphincter function (for instance the "circumferential urinary sphincter surface electromyography")(27) the clinical value of new methods has not yet been widely explored and validated. Surface EMG recording can be also used in order to quantify external anal fatigability which is probably one of the mechanisms of fecal incontinence (28).

2.1.1.5. Clinical application of EMG

There are many clinical applications of electrophysiological testing.

These tests make it possible to detect a neurological lesion in case of a urinary or anorectal disorder, to specify the importance, the lesion level and sometimes the prognosis.

2.1.1.5.1. Neurogenic Conditions

Trauma, surgery (for instance: radical prostatectomy)(29), and neurologic disease have all been implicated in denervation of pelvic floor and perineal muscles and pelvic organs. In a series of 194 consecutive patients referred for electrodiagnostic evaluation, quantitative needle EMG of the EAS muscles supported a diagnosis of a cauda equina or conus medullaris lesion in 36 patients, a lesion of the EAS muscle in 6, a pudendal nerve lesion in 2, and a sacral plexus lesion in 1 patient. Furthermore, neuropathic findings in the EAS were compatible with a diagnosis of multisystem atrophy in 11 and were most probably caused by severe polyneuropathy in 2 patients. In another 11 patients, the etiology of the pathologic findings could not be established at time of electrodiagnostic testing (30).

Lesions of the cauda equina or conus medullaris commonly cause pelvic floor dysfunction. These have mainly been a consequence of neural compression within the spinal canal caused by intervertebral disc herniation, spinal fractures, epidural hematomas, and intraspinal tumors; or a result of spinal surgery, mainly on lumbar discs (31, 32). Electrodiagnostic tests are also useful in the assessment of neurogenic lesions in children with spinal dysraphism (33). After detailed clinical examination of the lumbosacral segments (with particular emphasis on perianal sensation), neurophysiologic testing assesses the severity of the lesion and may clarify the diagnosis. In the authors' series, 10 percent of patients with cauda equina lesions reported normal perianal sensation (34). Electrodiagnostic tests that need to be considered are bilateral needle EMG of the EAS muscle and the bulbocavernosus muscle in subacute situations; and electrophysiologic evaluation of the bulbocavernosus reflex (35, 36). Detection of spontaneous denervation activity by needle EMG (in the bulbocavernosus muscle!) is common from approximately 3 weeks to several months after injury. Later, MUP analysis becomes more important for demonstrating reinnervation. Most of these lesions cause partial denervation; a traumatic lesion to the lumbosacral spine or pelvis is probably the only acquired condition in which complete denervation of the perineal muscles can be observed (6, 10, 37).

Following a cauda equina or a conus medullaris lesion, the MUP of pelvic floor and perineal muscles are prolonged and polyphasic, of increased amplitude, area, number of turns (6). Surgical dissections can also affect the innervation of the sphincter and lead to loss of motor units and reinnervation of those surviving (38). After pelvic trauma, gross changes of denervation and reinnervation may be detected in pelvic floor muscles. Abnormalities in polyneuropathy, as for instance diabetic, are usually minor (39).

Neuropathic changes can be recorded in sphincter muscles of patients with multiple system atrophy (MSA), a progressive neurodegenerative disease, which can be mistaken for Parkinson's disease (PD) (40). Among 30 patients with a pathologic diagnosis of multisystem atrophy, 24 had abnormal, 5 had a borderline, and only 1 had a normal sphincter EMG (41). Sphincter EMG has been proposed to distinguish MSA from Parkinson's disease but is probably not specific in the later stages of parkinsonism and may not be sensitive enough in the early phase of the disease (42-45). Some studies have failed to demonstrate the effectiveness of MUP analysis in sphincter muscles (46, 47), probably because of the exclusion of late components from MUP duration (9). Extensive discussion on the subject can be found elsewhere (48). The changes of chronic reinnervation may also be found in progressive supranuclear palsy (49, 50), and in Machado–Joseph disease (51), in which neuronal loss in Onuf's nucleus has also been demonstrated histologically (52).

In patients with acute idiopathic autonomic neuropathy and lower urinary tract (LUT) dysfunction the EMG of external sphincter muscles was reported as normal (53).

2.1.1.5.2. Changes in Primary Muscle Disease

In skeletal muscle, the "typical" features of a myopathy are small, low amplitude polyphasic units recruited at mild effort. There are few reports of pelvic floor muscle EMG in generalised myopathy. In a nulliparous woman with limb-girdle muscular dystrophy, histology revealed involvement of pelvic floor muscles, but concentric needle EMG of the urethral sphincter was normal (54). Myopathic EMG changes were observed in the puborectalis and the EAS in patients with myotonic dystrophy (55), but not in another group of patients with myopathy (56).

2.1.1.5.3. Stress Incontinence

Pelvic floor muscle denervation has been implicated in the pathophysiology of genuine stress incontinence (GSI) (57). EMG techniques have been used to identify sphincter injury after childbirth and to evaluate women with GSI. Stress incontinence and genitourinary prolapse were associated with partial denervation of the pelvic floor (58). The changes were most marked in women who were incontinent after delivery, who had a prolonged second stage of labour, and had given birth to heavier babies. In a recent study, nearly all EMG parameters showed significant differences between continent and SUI women consistent with better motor unit recruitment in continent women. Continent women had larger-amplitude, longer-duration MUPs with increased turns and better MUP recruitment during bladder filling ($P < 0.05$) (59).

Myogenic histological changes in pelvic floor muscles after vaginal delivery were also reported (60), with some EMG support by another group (61). "Myopathic EMG changes" (i.e. short, small MUPs) may, however, be a consequence of deficient reinnervation (37). There were claims urethral sphincter EMG can assist in selecting the type of surgery for patients with intrinsic sphincter deficiency (60).

Although CNEMG of the urethral sphincter seems the logical choice in patients with urinary incontinence of possibly neurogenic origin, only a small amount of pathological muscle tissue remains in many incontinent parous women, which makes EMG of the muscle impractical (38). CNEMG findings generally will not affect therapeutic considerations (62).

2.1.1.5.4. Idiopathic Faecal Incontinence

"Idiopathic" faecal incontinence refers to patients in whom this symptom is not attributable to an underlying disorder, but it has been often implied that it is a neurogenic condition. Vaginal delivery is proven to cause structural sphincter defects; it may cause outright sphincter denervation in rare cases, but its more widespread implication in causing "idiopathic" incontinence is controversial. CNEMG may be helpful in selected patients with faecal incontinence if a specific neurogenic condition (e.g., trauma or disease affecting the conus, sacral roots, sacral plexus or pudendal nerves) is suspected on clinical grounds. External anal sphincter muscle innervation pattern evaluation by multichannel surface EMG has been claimed to offer information to the obstetrician to prevent damaging epiziotomies (63).

2.1.1.5.5. Idiopathic Urinary Retention in Women

In the external urethral sphincter of young women with urinary retention (or obstructed voiding) complex repetitive discharges (and decelerating bursts) in profuse amounts have been described (64, 65). The abnormality was reported to be a predictor of the long-term success of therapeutic sacral neuromodulation (66). In a group of such women an occult generalized dysautonomia was found (67). It has been known before that repetitive discharges develop in chronically partially denervated sphincters, and that they are present even in a proportion of asymptomatic women. Recently, it has been shown that this activity changes during the menstrual cycle (more commonly found in the luteal phase of the menstrual cycle in asymptomatic women). The importance of this abnormal EMG activity in the aetiology of urinary retention in young women remains uncertain (68). Currently, the diagnosis of Fowler syndrome remains a clinical one, based on a multimodal assessment of the patient.

2.1.1.5.6. EMG in Urodynamic and Functional Anorectal Studies

In health, voiding is characterised by cessation of motor unit firing in the urethral sphincter prior to detrusor contraction, as can be demonstrated by recording of "kinesiological EMG". Bladder-sphincter coordination is impaired with lesions between the lower sacral segments and the upper pons. Consequently, sphincter activity is not inhibited, and often increases before detrusor contraction (i.e., 'detrusor-sphincter dyssynergia'). On the basis of the temporal relationship between urethral sphincter and detrusor contractions, three types of dyssynergia have been described (69).

There are other clinical situations that mimic detrusor sphincter dyssynergia. Sphincter contraction or at least failure of relaxation during involuntary detrusor contractions can be seen in patients with Parkinson's disease. The pelvic floor muscle contractions of the so-called nonneurogenic voiding dyssynergia may be a learned abnormal behaviour (70), and are a feature of dysfunctional voiding (65). There is insufficient data to determine the nature of the non-relaxation of sphincter activity as demonstrated by EMG signals during micturition (often seen in children and females) by EMG as such. The EMG recording has to be interpreted in the light of the overall clinical picture of the examinee.

The pubococcygeus in the healthy female reveals similar activity patterns to the urethral and anal sphincters at most detection sites: continuous activity at rest, often some increase of activity during bladder filling, and reflex increases in activity during any activation manoeuvre performed by the subject such as talking, deep breathing, coughing. The pubococcygeus relaxes during voiding; the muscles on either side act in unison (20). In stress incontinent patients, the patterns of activation and the co-ordination between the two sides can be lost (71). A delay in muscle activation on coughing has also been demonstrated, as compared to continent women (21).

Little is known about the complex activity patterns of different pelvic floor muscles (the urethral sphincter, urethrovaginal sphincter, anal sphincter muscle, different parts of the levator ani) during different manoeuvres. It is generally assumed that they all act in a co-ordinated fashion functionally as one muscle. However there are demonstrable differences between the intra- and peri-urethral sphincter in healthy females (72) and in activation of the levator ani and the urethral sphincter (73). Co-ordinated behaviour is frequently lost in abnormal conditions.

Kinesiological needle EMG analysis of the urethra with the patient at rest and coughing may predict the outcome after certain types of incontinence surgery (74). However, other studies found that preoperative EMG did not predict patients at risk for postoperative voiding dysfunction (24).

Indeed, while kinesiological EMG (particularly when combined with other urodynamic tests) promises theoretically relevant data, technical standards are lacking, and findings have been reported in single center studies. Further basic research is necessary to delineate the correlation of EMG signals and their interpretation in terms of clinical significance (the significance of EMG data for defining overall LUT function) (75).

Current concepts suggest that defecation requires increased rectal pressure co-ordinated with relaxation of the anal sphincters and pelvic floor muscles. Pelvic floor relaxation allows opening of the anorectal angle and perineal descent, facilitating faecal expulsion. During defecation puborectalis activity is as a rule inhibited, but was unchanged in 9 % and increased in 25 % of healthy subjects (76). Thus, while "paradoxical" puborectalis contraction during defecation is used to diagnose pelvic floor dyssynergia in patients with typical symptoms, this finding may be a variation of the normal. Same considerations regarding the lack of controlled studies, technical standards, etc. apply as stated above for kinesiological EMG in studies of LUT function.

2.1.2. Pudendal Nerve Conduction Tests

Measurement of motor conduction velocity is routinely used to evaluate limb nerves, distinguishing between a demyelinating and axonal neuropathy. To make the measurement requires access to the nerve at two well-separated points and measurement of the distance between them, a requirement that cannot be met in the pelvis. Another way to evaluate peripheral motor nerve function is the measurement of the latency of a muscle response, requiring only a single stimulation site. The muscle response is the compound muscle action potential (CMAP) or M-wave. Because in limb nerves the site of stimulation to obtain only the motor latency (without measuring the actual conduction velocity) is as a rule placed distally on the nerve, it is also called the distal (or terminal) latency. For the pudendal nerve the site of stimulation may be more or less "distally", but the term distal or terminal has – in accordance with general clinical neurophysiology – become generally used. Distal motor latency can be measured by recording with a concentric needle electrode from

the bulbocavernosus, the EAS and the EUS muscles in response to bipolar surface stimulation placed in the perianal/perineal region, or with needle electrode stimulation of the pudendal nerve in the perineum. The most widely employed technique to obtain pudendal nerve terminal motor latency (PNTML) relies on stimulation with a special surface electrode assembly fixed on a gloved index finger, known as the St Mark's stimulator (77). It consists of a bipolar stimulating electrode on the tip of the gloved finger with the recording electrode pair placed proximally on the base of the finger. The finger is inserted into the rectum or vagina and stimulation is applied close to the ischial spine. It is assumed that, using this approach, the pudendal nerve is stimulated close to the ischial spine, and that the response recorded is of the EAS muscle. In women, intravaginal stimulation and recording from the bulbocavernosus muscles has also been undertaken, with similar distal latencies (78). However, the latency of such a response is typically only around 2 msec, which seems unusually short compared with the perineal technique and with conduction in the much thicker motor fibers of peripheral nerves in the limbs. It seems unlikely that the PNTML using the St. Mark's electrode really evaluates conduction along the last 8 cm of the pudendal nerve. Stimulation of the terminal pudendal branches or pelvic floor muscles near their motor points seems more likely, and this is supported by the much longer PNTML (3.7 ± 0.9 msec) obtained with a monopolar intrarectal stimulation electrode (79). If a catheter-mounted electrode is used for recording, EMG responses from the striated muscle of the urethral sphincter can be obtained. Experts differ in their estimation of validity of this test. A prospective evaluation of anorectal physiologic tests in 90 patients with faecal incontinence did not find that PNTML results changed treatment decisions (80). Indeed, the American Gastroenterological Association statement indicated that "PNTML cannot be recommended for evaluation of patients with fecal incontinence (81).

2.1.3. Anterior Sacral Root (Cauda Equina) Stimulation

Anterior root stimulation has been used to study conduction of the sacral nerve roots. Electrical stimulation with needle electrodes at vertebral laminae Th12-LI elicits M-waves in the bulbocavernosus and EAS muscle (82). Transcutaneous stimulation of deeply situated nervous tissue became possible with development of special electrical and magnetic stimulators. When applied over the spine, these stimulators activate the roots as they exit the vertebral canal. Needle EMG rather than non-selective surface electrodes should be used to record pelvic floor and particularly sphincter responses to electrical or magnetic stimulation of the cauda equina. These stimuli non-selectively depolarise underlying neural structures, thereby activating several muscles innervated by lumbosacral segments (83). Lumbosacral stimulation often evokes a large stimulus artifact that can be decreased by positioning the ground electrode between the stimulating and recording electrodes (84). Invasive percutaneous stimulation of individual roots in sacral foramina is used to identify patients with lower urinary and anorectal dysfunction who are likely to benefit from long-term stimulation, e.g., with the Interstim (Medtronic, Inc., Minneapolis, USA). Electrical stimulation of nerve roots at the level of the appropriate sacral foramina results in observable muscle contraction in the foot and perineum. These responses can be identified as MEP or reflex responses on the basis of their latency. Selective stimulation of individual sacral roots is possible by appropriate positioning of surface stimulating electrodes (85).

In conclusion, demonstrating the presence of a perineal MEP on stimulation over lumbosacral spine may occasionally be helpful in patients without voluntarily activated muscles. It also identifies the particular nerve root before introducing therapeutic electrical stimulation. However, the clinical value of the test has yet to be established and there are no sensitivity and specificity data on test results in individual patients.

2.1.4. Motor Evoked Potentials

Using magnetic or electric stimulation, it is possible to depolarise the motor cortex and record a response from the pelvic floor. Magnetic cortical stimulation is better tolerated than electrical stimulation, which has been abandoned in awake subjects, but may be useful for intraoperative monitoring.

By performing the stimulation at two different sites (brain and spinal roots), it is possible to record three different conduction times: a total conduction time, a peripheral conduction time, and a central conduction time (Figure 62). The total conduction time corresponds to the transit time from brain to target muscle. The peripheral conduction time is the transit time from sacral roots to the muscle. The central conduction time is obtained by subtracting the peripheral conduction time from the total conduction time. The total conduction time can be measured both at rest and during a facilitation procedure. MEPs from the EAS, the urethral sphincter, the bulbocavernosus muscle, and the levator ani muscle have been reported, but normative values have only been obtained (for transcranial magnetic stimulation) for the urethral sphincter and the puborectalis muscle in adult women (86). A central conduction time of 15 to 16 msec without and 13 to 14 msec with facilitation is obtained for pelvic floor and sphincter muscles (87-89). The necessity to use concentric needle EMG for recording has been reconfirmed (90).

Substantially longer central conduction times have been found in patients with multiple sclerosis and spinal cord lesions as compared to healthy controls (89-91). However, all patients in this study had clinically recognisable cord disease. Nevertheless, MEPs may be useful in patients with unclear localization of spinal lesions (89).

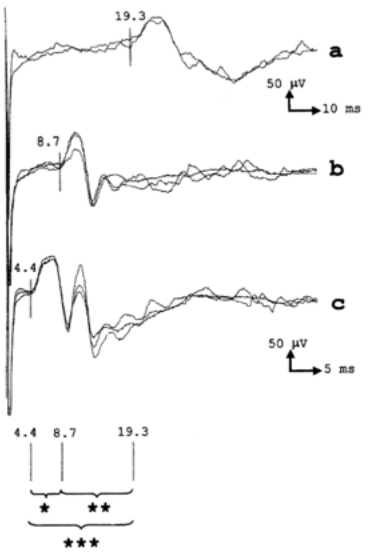


Figure 62: MEPs recorded by concentric needle in the external urethral sphincter of a 51-year-old-woman. Cortical (a), thoracic (b), and sacral (c) stimulation. Central motor conduction time (CMCT) is calculated as cortical - lumbar latency (** = 10.6 ms). Cauda equina motor conduction time is calculated as lumbar - sacral latency (* = 4.3 ms). (From (Brostrom et al., 2003a), with permission).

Conceptually, MEP may help to differentiate between involvement of motor and sensory pathways. However, the clinical utility of these measurements is not established. MEP have opened an avenue of research on excitability of motor cortex. It has been demonstrated that in comparison to the motor area for hand muscles the anal sphincter motor cortex has less intracortical inhibition (92).

2.2. Sensory System Tests

There are several methods of sensory testing for the perineum, the genitourinary and anorectal tract. Clinical testing includes perineal and external genital skin sensation for light touch and pinprick, and sensation of bladder filling during cystometry. Anorectal sensory testing can be clinically assessed through rating of applied stimuli. More objective sensory testing can be performed with quantitative sensory testing (QST), which assesses sensory perception. For evaluation of the integrity of sensory pathways sensory neurography, and somatosensory evoked potentials (SEP) can be used.

2.2.1. Sensory Measurements During Cystometry

During routine cystometry bladder sensation is assessed by recording first sensation of bladder filling, first desire to void and strong desire to void. Although not strictly a neurophysiologic test, measurement of electrical thresholds adds clinically non-obtainable information on sensory function of the lower urinary tract (93). Bladder and urethral sensory thresholds have also been measured using electrical stimulation (93), and mechanical traction on the bladder trigone (93). Electrical currents are applied to the bladder, urethra or genital skin using catheter-mounted or surface electrodes. High-frequency stimulation (> 20 Hz), with a stimulus duration of 0.5 or 1 msec is used because it is more easily perceived in the lower urinary tract. Measurement of sensory thresholds with such stimulation is reproducible, and normative data have been published (93). To date it has been used in only a few conditions (e.g., painful bladder syndrome) (94). There is no established clinical use for any of these tests other than simple reporting of sensation during cystometry.

In addition, palmar SSR and perineal surface EMG recordings can be used for more objectively demonstrating sensations during cystometry. The activity of both appears and increases in parallel with the first sensation of bladder filling, and with the first desire to void, respectively (95). Further studies using these methods are needed to establish their clinical utility.

2.2.2. Assessment of Anorectal Sensation

Rectal sensation is assessed by progressively distending a balloon manually or by a barostat while measuring thresholds for first perception, desire to defecate, and severe discomfort. The intensity of perception during rectal distension can be recorded by a visual analogue scale during phasic distensions of graded intensity (96). The rate and pattern of distension affect rectal perception and internal sphincter relaxation (97).

Anal sensation can be assessed by determining the perception threshold to an electrical stimulus or temperature change in the anal canal. Electrical testing does not activate mucosal receptors. Anal sensitivity to temperature change has been reported reduced in faecal incontinence (98).

2.2.3. Quantitative Sensory Testing

Quantitative sensory testing (QST) of the urogenitoanal system should provide more objective and reproducible data than routine clinical testing. QST sensory modalities applied to the evaluation of urogenital function include vibration (99), temperature (100), and electrical current (101). (See also Sensory Measurements During Cystometry). There is no commonly accepted, detailed, standardised test, and the specificity and sensitivity of the tests are not known. The relationship of cutaneous quantitative sensory tests to bladder and urethral sensation and function is unknown. The physiological, psychophysiological and methodological issues and controversies will not be addressed in this chapter.

2.2.4. Sensory Neurography

Nerve conduction velocities of the dorsal nerve of the penis can be calculated by placing a pair of stimulating electrodes across the glans and a pair of recording electrodes across the base of penis. A nerve action potential can be recorded with an amplitude of about 10 µV. It can also be recorded by stimulating the nerve trans-rectally or transperineally. There is no known association between penile sensory neuropathy and bladder/sphincter dysfunction.

A few studies have recorded activity in sacral roots during electrical stimulation. Intraoperatively, when the sacral roots are exposed, compound sensory action potentials on stimulation of dorsal penile and clitoral nerve may be recorded directly (102). This helps to preserve roots mediating perineal sensation in spastic children undergoing dorsal rhizotomy, and reduce the incidence of postoper-

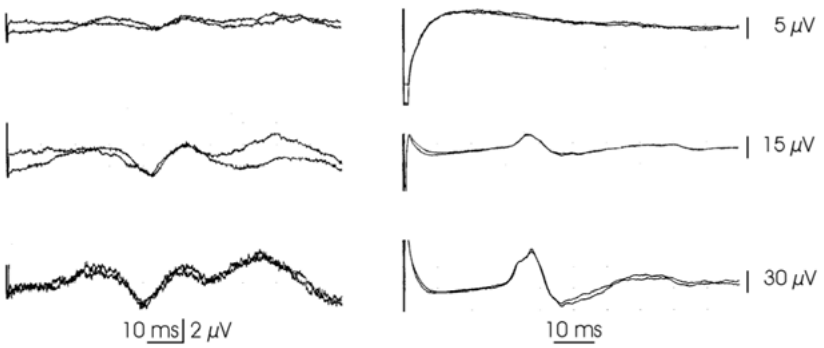


Figure 63: SEPs (traces on the left) and sacral reflexes (traces on the right) in a healthy woman. Cerebral SEPs are recorded from Cz - 2 cm; sacral reflexes from the anal sphincter. The dorsal clitoral nerve is being stimulated with rectangular electrical pulses at 2 Hz. Stimulation and recording are performed with surface electrodes. The cerebral SEP and sacral reflex are recorded simultaneously. In the upper row the stimulation is just above sensory threshold, in the middle row the stimulation is 1.5, and in the lower row at 2-times sensory threshold (pulse duration 0.2 ms; two consecutive averages of 128 responses are superimposed).

ative voiding dysfunction (103). These tests are limited to their very specific intraoperative indications.

2.2.5. Somatosensory Evoked Potentials (SEP)

Somatosensory evoked potentials are electric waveforms of biologic origin elicited by stimulation of a sensory nerve (or a sensory innervated skin area – dermatome). The most commonly performed tests in the urogenitoanal region are pudendal somatosensory evoked potentials (SEP), which assesses conduction in large fibre pathways between the site of nerve stimulation and the parietal sensory cortex. Potentials can also be measured at the spinal level (spinal SEP).

Visceral (thin) fibre pathways are assessed by recording SEPs while stimulating the proximal urethra and bladder, although this is technically not depolarization of nerves, but a mesh of afferents.

2.2.5.1. Pudendal Somatosensory Evoked Potentials

2.2.5.1.1. Cerebral Pudendal SEP

On electrical stimulation of the dorsal penile/clitoral or perineal nerve, a cerebral SEP can be recorded. (Figure 63) This SEP is as a rule of highest amplitude at the central recording site (Cz - 2 cm : Fz of the International 10-20 EEG System) and is highly reproducible. The first positive peak at about 40 ms (called P40) is usually clearly defined in healthy subjects using a stimulus 2-4 times stronger than the sensory threshold (104). The presence and amplitude of subsequent negative and positive waves are quite variable between subjects. Classically described pudendal SEP techniques stimulate both dorsal penile/clitoral nerves, thus reducing the sensitivity of the test. However, techniques of pudendal SEP that isolate each dorsal penile/clitoral nerve may be more sensitive for identifying pathology (105).

Pudendal SEPs have been advocated in patients with neurogenic bladder dysfunction, e.g. in multiple sclerosis (106). However, even in patients with multiple sclerosis and bladder symptoms, the tibial cerebral SEP was more often abnormal than the pudendal SEP. The combination of an abnormal pudendal SEP with a normal tibial SEP suggests isolated conus involvement (107). The pudendal SEP was less useful than neurological examination for identifying neurological disease in patients with uro-genital symptoms (108). Following spinal cord injury, tibial and pudendal SEPs may be of some value for predicting recovery in bladder control (109). Cerebral SEP during penile/clitoral stimulation may be useful for intraoperative monitoring. Pudendal SEP were used to study the mechanism of sacral neuromodulation (110).

2.2.5.1.2. Spinal Pudendal SEP

Stimulating the dorsal penile nerve and recording with surface electrodes at the level of the Th12-L2 vertebrae (and the S1, Th6 or iliac spine as reference) reveals the postsynaptic segmental spinal cord activity (the spinal SEP). Unfortunately, this spinal SEP may be difficult to record even in normal (particularly obese) subjects.

2.2.5.1.3. Nerve conduction velocity of dorsal nerve of penis

The dorsal nerve of the penis is involved in sexual function. The nerve conduction velocity (NCV) of the dorsal nerve of the penis is measured by dividing the distance between the stimulating and the recording electrodes by the latency to the negative peak of the action potential. With the penis stretched with a 1 lb weight, the NCV in normal men is 33 m/sec +/- 3.8 (111-113). Evidence is missing for the interest of this technique in sexual disorders.

2.2.5.1.4. Pudendal nerve terminal sensitive latency

To elicit response endorectal stimulation of the pudendal nerve is delivered just to the left then right of the ischiatic spine using an electrode (114). The sensory potential is recorded in the balanopreputial zone with ring contact electrodes wrapped around the shaft of the penis. From 5 to 40 responses are averaged to obtain the sensory potential. Mean latency value plus or minus standard deviation is 5.35+/-0.97 milliseconds. This method allows comparative study of the right and left terminal sensory branches of the pudendal nerve and may be helpful in the diagnosis of different perineal disorders, such as sexual dysfunction, perineal pain and fecal incontinence, but further experience is necessary.

2.3. Sacral Reflexes

Clinically, two reflexes are commonly elicited in the lower sacral segments: (1) the penilo- or clitoro-cavernosus (i.e. bulbocavernosus) reflex; and (2) the anal reflex (115). To elicit sacral reflexes, electrical (116-123), mechanical (120, 121, 124), or magnetic stimulation (125) can be used. Whereas the latter two modalities have only been applied to the penis (122-124), clitoris, electrical stimuli can be applied to various sites: to the dorsal penile or clitoral nerve; perianally; and, using a catheter-mounted ring electrode, to the bladder neck/proximal urethra (126).

2.3.1. Sacral Reflex on Electrical Stimulation

Electrical stimulation of the dorsal penile or clitoral nerve elicits (somato-somatic) sacral reflexes in perineal muscles with a typical latency approx. 33 ms (29.9 ± 5.7 msec in one study in men (122)), traditionally called the bulbocavernosus reflex (Figure 63). In addition to single-pulse electrical stimulation, two identical electrical pulses separated by a 3-msec interval can be used (i.e., double-pulse electrical stimulation) (122, 123). Double-pulse electrical stimulation is more efficient in eliciting sacral reflexes (122). Stimulation of the perianal skin, bladder neck or proximal urethra elicits sacral reflexes with latencies above 50 ms. This latency is longer compared to responses conveyed by the pudendal nerve, suggesting that the afferent limb for these responses involves visceral afferent fibres accompanying the pelvic nerves, which are thinly myelinated and have a slower conduction velocity than the thicker pudendal afferents. With visceral denervation (e.g., following radical hysterectomy) the viscerosomatic reflexes (from both bladder and urethral stimulation) may be lost while the bulbocavernosus (penilo-/clitoro-cavernosus) reflex is preserved. Loss of bladder-urethral reflex with preservation of bladder-anal reflex has been described with urethral afferent injury after recurrent urethral surgeries (127).

The longer latency anal reflex (the contraction of the EAS on stimulation of the perianal region) is quite variable thus limiting its usefulness as a diagnostic tool.

On perianal stimulation, a short latency response can also be recorded, as a result of depolarisation of motor branches to the EAS, possibly involving antidromic travelling of the depolarisation, with “returning” of the depolarisation orthodromically to the sphincter at a branching point of the motor axon.

EMG recording of the sacral reflex has been shown to be more reliable than the clinically assessed response (e.g. observing and palpating the contraction) in males and particularly in females (128). In men, value of 40, 36 and 36 msec have been suggested as the upper limit of normal for the shortest latency obtained on eliciting a series of reflex responses using single, double and mechanical stimulation, respectively (122). In men with cauda equina lesions penilo-cavernosus reflex could not be elicited in 64%, 47% and 47% of patients on single electrical, double electrical, and me-

chanical stimulation, respectively. Measurement of the reflex latency increased the sensitivity to record abnormalities for 17%, 36%, and 34%, respectively. Furthermore, it has been shown that sacral reflex measurement increase sensitivity of quantitative EMG of the EAS muscles from 73% to 81-83% using the different stimulation techniques mentioned (123).

Sacral reflex testing has been studied extensively and is used in many laboratories in everyday practice to demonstrate objectively the integrity of the S2-S4 reflex arc. The sacral reflex evoked on dorsal penile or clitoral nerve stimulation (the bulbocavernosus or penilo-/clitoro-cavernosus reflex) was shown to be a complex response, often forming two components. The first component with a typical latency of about 33 ms, is the response that has been most often called the bulbocavernosus reflex. It is stable, does not habituate, and has other attributes of an oligosynaptic reflex response (117). The second component has latency similar to the sacral reflexes evoked by stimulation perianally or from the proximal urethra and is not always demonstrable as a discreet response. In those subjects in whom the first reflex component is difficult to elicit, stimulation strength should be increased, but preferably double electrical stimuli should be used. A complete reflex arc lesion should not be inferred by absence of a response if only single pulse is used for stimulation. During voiding sacral reflexes are un-elicitable but in presence of spinal cord lesions such as myelodysplasia this normal suppression is lost.

Sacral reflex responses recorded with needle or wire electrodes can be analysed separately for each side from the EAS or bulbocavernosus muscle. Using unilateral dorsal penile nerve blocks, the existence of two unilateral BCR arcs has been demonstrated. Thus, by detection from the left and right bulbocavernosus (and also the EAS) muscles separate testing of right and left reflex arcs can be performed. Some authors reported that sensitivity of the test can be increased by use of the inter-side latency difference (normative limits: < 3 ms), but finding could not be confirmed by others (normative limits: < 7.2 ms) (122). In cases of unilateral (sacral plexopathy, pudendal neuropathy) or asymmetrical lesions (cauda equina), a healthy reflex arc may obscure a pathological one on clinical elicitation, but not on neurophysiologic measurements of the sacral reflexes.

As described above, penilo-cavernosus reflexes were absent in 47-64%, and delayed in additional 17-19% of patients with conus/cauda lesions. Of these patients 47% were incontinent for urine and 47% for faeces. However, a reflex with a normal latency does not exclude the possibility of an axonal lesion in its reflex arc, as demonstrated by pathologic quantitative EMG of the EAS in 79-86% of patients with conus/cauda lesions (123). Furthermore, much delayed sacral reflex responses are compatible with normal bladder and sexual function as found in patients with hereditary motor and sensory demyelinating neuropathy. In a proportion of women with non-neurogenic sacral dysfunction clitoro-cavernosus reflex latencies were found to be much longer compared to those obtained in women with intact sacral function (129). Sacral reflex recording is suggested as a complementary test to CNEMG examination of pelvic floor muscles in patients with suspected peripheral nervous lesions (4).

In addition to latency, a number of other parameters can also be measured using electrical, but not mechanical stimulation. These are the sensory threshold (i.e., the stimulus strength (mA) at which subjects feels stimulation), and reflex threshold (i.e., the stimulus strength (mA) at which the reproducible penilo/clitoro-cavernosus reflex appears on the screen). They evaluate lower sacral sensory pathways, and excitation level of the sacral reflex pathway, respectively. Although for men normative data for these parameters is available (122), their utility in clinical situation remains unclear. Continuous intraoperative recording of sacral reflex responses on penis/clitoris stimulation is feasible if double pulses or a train of stimuli are used (130).

2.3.2. Sacral Reflex on Mechanical Stimulation

Mechanical stimulation has been used to elicit BCR in both sexes and found to be a robust technique. Either a standard reflex hammer or a customised electromechanical hammer can be used. Using a reflex hammer, the stimulus is applied to a wooden spatula placed on the glans penis or clitoris (122, 123). Such stimulation is painless and can be used in children (124). The latency of the BCR elicited mechanically is comparable to the electrically elicited reflex in the same patients but depends on the electromechanical device used (122, 124).

2.3.3. Sacral Reflex as Assessment of Sacral Spinal Excitability

It is possible to analyze and quantify sacral spinal excitability through bulbocavernosus reflex (BCR) stimulus-response curves (131). Variations in the slope of the stimulus- response curve can be considered as an indicator of the modulation of sacral spinal excitability. This response is amplified during bladder filling as well as in patients with UMN in comparison with a control group. Thus, BCR, through stimulus-response curves, might be an indicator of pelvic-perineal exaggerated reflex response and possibly a tool for evaluating treatment effectiveness.

2.4. Autonomical Function Tests

Most uro-neurophysiological methods discussed so far assess myelinated fibres, but not the autonomic nervous system, especially the parasympathetic component, which is most relevant for pelvic organ functions. Methods for evaluating the autonomic nerves innervating the pelvic viscera are not available. Cystometry indirectly evaluates the parasympathetic innervation to the bladder. However, from a clinical neurophysiological point of view direct electrophysiological testing would be desirable.

2.4.1. Tests in Generalised Autonomic Neuropathy

Cardiovascular autonomic function tests are useful for identifying generalised autonomic dysfunction in patients with bladder or gastrointestinal motility disturbances.

In cases when a general involvement of thin fibres is expected, an indirect way to examine autonomic fibres is to assess thin sensory fibre function. Thin visceral sensory fibres are tested by stimulating the proximal urethra or bladder, and by recording sacral reflex responses or cerebral SEP.

2.4.2. Dartos Reflex

In men, another approach to test lumbosacral sympathetic function is by neurophysiologic measurement of the dartos reflex obtained by electrical cutaneous stimulation of the thigh. The dartos muscle is a sympathetically innervated dermal layer within the scrotum, distinct from the somatically innervated cremasteric muscle. A reliable and reproducible dartos reflex (i.e., scrotal skin contraction) with a latency of about 5 seconds has been demonstrated in healthy men (132).

Technical problems have so far limited smooth muscle electromyography of the detrusor muscle, and of genital smooth muscle. Recently, successful intrinsic (smooth muscle) anal sphincter muscle EMG recordings on electric autonomic nerve stimulations were re-

ported to spare the autonomic nerve supply during surgery in pigs (133).

2.4.3. Sympathetic Skin Response (SSR)

The sympathetic nervous system mediates sweat gland activity in the skin. Changes in sweat gland activity lead to changes in skin resistance. On noxious stimulation (such as a sudden noise, electrical pulse, etc.) a potential shift can be recorded with surface electrodes from the skin of the palms and the soles and has been reported to be a useful parameter in assessment of neuropathy involving non-myelinated nerve fibres. The response, known as the SSR, can also be recorded from perineal skin and the penis. Similarly, the SSR can be recorded from the genital region in women. The SSR is a reflex, which consists of myelinated sensory fibres, a complex central integrative mechanism and a sympathetic efferent limb with postganglionic nonmyelinated C fibres. SSR is the only electrophysiological method directly testing sympathetic fibres; recording from the perineal region assesses sympathetic nerve function of thoracolumbar segments. Limited literature exists regarding the relationship between SSR results and bladder dysfunction. A correlation has been shown between the absence of the SSR response in the foot and bladder neck dyssynergia following spinal cord injury (134). Only complete absence of response can be regarded as abnormal. Its utility in evaluating bladder and urethral dysfunction is not established.

2.4.4. Cremasteric Reflexes

Electromyography of the cremasteric muscle is recorded using disposable needle electrodes (135). Cremasteric muscle reflex is obtained with tactile and/or electrical stimulation of the inner thigh. In theory, sacrolumbar intersegmental reflex circuit and cremasteric muscle activity are useful for evaluating ejaculatory dysfunction but there is a lack of evidence in literature.

3. EVIDENCE BASED USE OF CLINICAL NEUROPHYSIOLOGICAL TESTS

Evidence-based medicine is founded on the assessment of evidence for and against the efficacy of particular types of therapeutic intervention. Clinical neurophysiology testing should thus demonstrate evidence that testing improves outcome (through treatment choice and patient selection). However, testing and therapeutic intervention are different concepts, and neurophysiological testing has another important objective. It is to generate knowledge about the situation to be treated in a given patient, so that the practitioner can formulate rational treatment options based on knowledge rather than do so blindfold; that is, he or she can practice “knowledge-based medicine”.

To judge the importance of this second objective different criteria are needed. Particularly in the referral setting, the physician is confronted with complicated cases in which the underlying pathophysiology is quite uncertain, and what is required is to identify all the factors that may be contributing. Neurophysiology is helpful in assessment of neurogenic dysfunction because it contributes to “knowledge-based medicine”, whether or not there is narrowly defined “evidence” that it improves outcomes.

Of course, it remains true that we should seek evidence of the conventional kind for and against testing. Any test should be subjected to three questions:

1. Does the test have good technical performance?
2. Does the test have good diagnostic performance, ideally against a “gold standard” measure?
3. Does the test have good therapeutic performance, that is, does the use of the test alter clinical management, does the use of the test improve outcome?

Clinical diagnosis requires that measures obtained in individual patients be compared to population norms with the intent of determining whether they are “normal” or “abnormal”. Data can be classified as “abnormal” only with the understanding that they are compared to a sample from the normal population. Predictive statements are made possible by the use of tolerance limits. For most clinical neurophysiological tests, one-tailed tolerance limits are recommended. For any given limit of normality, there is a certain probability of falsely interpreting values (obtaining false-positives or false-negatives). Further confounding these issues is the practice of applying multiple criteria of abnormality. But ultimately, the adequacy of any given normal limit in discriminating between normal and abnormal must be supported by appropriate clinical or clinico-pathological correlations; for uroneurophysiological techniques, such data are scarce.

3.1. Usefulness of Clinical Neurophysiological Tests in Evaluation of Individual Patients

Whenever pathophysiology is uncertain or unpredictable, and especially if irreversible treatment is necessary or contemplated, it seems logical to gather quantitative knowledge of the dysfunction in order to make a rational treatment choice. In most patient groups with neurogenic incontinence, the pathophysiology is unpredictable and comprehensive urodynamic evaluation is essential in order to practice knowledge-based medicine. In selected patients from these groups, clinical neurophysiological testing will clarify issues related to the neural control of lower urinary tract, relevant for understanding pathophysiology (136).

As is generally true for electrophysiological tests, uroneurophysiological examinations are particularly useful for substantiating the clinical diagnosis of a peripheral nerve lesion. The potential usefulness of testing in an individual patient needs to be analysed in the overall clinical setting. The indications for testing are guided primarily by expert opinion, not on definitely established criteria derived from controlled studies.

In the incontinent patient without other signs or symptoms of a neurologic condition, as in most patients with stress/urge, or mixed urinary incontinence electrophysiological testing is as a rule non-contributory (62). Neurophysiological methods may have other uses, as for instance using the EMG signal for correct needle positioning for infiltration of sphincter muscle with botulinum toxin (137), or using tests for intraoperative identification and monitoring of nerves and muscles (132).

3.2. Usefulness of Clinical Neurophysiological Tests in Research

As understanding pathophysiology of neural control of lower urinary tract is essential in the application of more sophisticated therapeutic methods, such as electrical stimulation techniques (138, 139), there is a continuing place for clinical neurophysiology in research on neurogenic urinary and anorectal dysfunction and their therapy. There is ongoing research on already described techniques to validate their usefulness in diagnostics (140), and in intraoperative monitoring (141).

4. CONSENSUS STATEMENT

4.1. Recommendation for Clinical Neurophysiological Testing
The information gained by clinical examination and urodynamic testing may be enhanced by uroneurophysiological tests in selected patient groups with suspected neurogenic urinary incontinence with lesions within the nervous reflex arcs of sacral segments 2 – 5. Concentric needle EMG to diagnose denervation and reinnervation of pelvic floor and perineal muscles, and sacral reflex testing to assess the continuity of the sacral reflex arc, are the recommended tests.

Level of evidence: 2b

Level of recommendation: B

Clinical neurophysiological testing should be performed in accredited laboratories, by trained and certified staff, with formal control of the quality of the results. Ideally, the uroneurophysiologist should be in liaison with general clinical neurophysiologists.

It seems optimal to create interdisciplinary teams between urology, urogynecology, proctology, and neurology departments.

4.2. Recommendation for Technical Standards
Even in the more widely used "general" clinical neurophysiology there is no universal standardisation of tests. This is mainly due to different historical backgrounds of testing developed in different countries. The need to standardise methods is, however, recognised.

Proposals for standardisation for external anal sphincter CNEMG (4) and the bulbocavernosus (penilo/clitoro-cavernosus) reflex (122) have been made, and seem to be widely adopted.

Level of evidence: 2b

Level of recommendation: B

4.3. Future Research Areas
Clinical neurophysiological methods should be further explored and used to better define the neural control in lower urinary tract function, demonstrating both the nervous system's "hardware" (integrity of anatomy) (142) as well as "software" (level of activity, excitation thresholds) for co-ordinated urinary storage and voiding, in physiological and in pathological conditions (143).

There is as yet no standardization of the technical aspects of (kinesiological) EMG within urodynamic (and anorectal) function testing. Furthermore, more research is needed to shed light on the relationship between the EMG signals, pelvic floor muscle function, and overall LUT (anorectal) function (75).

There are also challenges to validate the use of the described techniques for intraoperative identification of structures and monitoring nervous function (144), to define neurophysiological changes induced by therapeutic electrostimulation, and to develop tests to assess directly the sacral parasympathetic system.

VI. OTHER INVESTIGATIONS

1. URINALYSIS

"Urinalysis is a fundamental test that should be performed in all urological patients" (1). In patients with urinary incontinence, urinalysis is not a diagnostic test for the condition, but it is rather used to screen for haematuria, glucosuria, pyuria and bacteriuria and rule out other diagnoses. Even in the absence of controlled studies, there is general expert consensus that the benefits of urinalysis clearly outweigh the costs involved (2). A positive urinalysis will prompt infection treatment and/or the use of additional tests such as endoscopy and urinary tract imaging. In the evaluation of urinary incontinence in the female, urinalysis is recommended since 60% of women develop urgency symptoms at the time of urinary tract infection (UTI). Pyuria was found to be common among incontinent but otherwise asymptomatic, female patients. Pyuria was not necessarily associated with UTI, the significance of sterile pyuria in the elderly population is still unclear (3).

A Norwegian survey of general practitioners' management of female urinary incontinence suggested that urinalysis is the most frequently performed test (73%) and is far more frequent than gynaecological examination (54%) (4). Another survey suggested that urinalysis is one of the three-part assessment of UI together with patient history and physical examination (5).The same apply, according to Stricker, for patient selection for collagen implant (6). A minority of the reviewed papers suggested that urine culture should be carried out together with urinalysis (3, 7). Urinalysis is also considered of importance in the evaluation of nursing home residents who are incontinent (8), in peri- and postmenopausal women (9), in older women reporting urinary incontinence (10). Belmin et al, suggested than significant urine samples can even be obtained from disposable pads in elderly incontinent women (11, 12). It is recommended that geriatric incontinent patients undergo history, physical examination, tests of lower urinary tract function and urinalysis. The latter test is proposed to rule out the presence of UTI (12). The clinical relevance of asymptomatic bacteriuria in the elderly is controversial. Although DuBeau and Resnick suggest the use of urinalysis in the diagnostic algorithm to identify asymptomatic bacteriuria in incontinent residents of nursing homes (13), others consider that the condition does not require any treatment (11). Urinalysis is less sensitive and specific for urinary tract infection in women who have had radiotherapy but the combination of leucocyte esterase and nitrates still has a positive predictive value of 95% (14). Urinalysis in patients with stents and patients on haemodialysis has not been found to be an effective screening test and routine culture is recommended(15, 16).

1.1. Consensus Statement
- It is considered standard practice to perform a urinalysis either by using a dipstick test or examining the spun sediment. (Level of Evidence 3, Grade of Recommendation C)
- If a dipstick test is used, it is recommended chosing of a "multiproperty" strip that includes testing for haematuria, proteinuria, glucose and ketones, leukocytes esterase (indicating the presence of leukocytes in the urine) and nitrite tests (suggesting bacteriuria). (Level of Evidence 3, Grade of Recommendation C)

1.2. Future Research Areas
- Needed to screen analysis of urinalysis in the diagnosis and treatment of UI, MUI and SUI

- Testing bedside point of testing against urinalysis and culture for the diagnosis of urinary tract infection

2. BLOOD TESTS

The prevalence of renal damage or of biochemical abnormalities in the general population of patients with urinary incontinence is very low, but there are subgroups of patients where the prevalence can be higher (e.g., neurogenic incontinence, overflow incontinence). The routine use of a battery of common chemical and/or haematological tests in patients with UI appears to be a prudent rule of good clinical practice in the following situations:

- chronic retention with incontinence
- neurogenic LUT dysfunction
- when surgery is contemplated
- when there is a clinical suspicion
- sodium plasma concentration may be reduced in patients on desmopressin.
- Confirmation of urinary tract infection

Special tests such as measurement of anti-diuretic hormone (ADH) and atrial natriuretic polypeptide have proven useful in research of enuresis in childhood and nocturia in the elderly (17, 18). Changes in the circadian rhythm of these, and probably also other hormones regulating the renal excretion of water, will in the future contribute to a better understanding of pathophysiology. Synthetic ADH analogues have already come into clinical use for the treatment of nocturnal enuresis. However, the clinical value of these specific tests remains to be established.

Serum procalcitonin is a peptide that undergoes proteolysis into calcitonin. It is an acute phase reactant, which rises quickly and reliably in patients with severe bacterial infections. As such, it may serve as a potentially sensitive and specific marker for identification of bacterial illness, particularly in elderly patients (19) and serves in decision support for antibiotic initiation or cessation (20-22).

3. TISSUE ANALYSIS

Pelvic floor-supporting tissues are composed mainly of connective tissue in which fibrous elements such as collagen and elastic fibres and visco-elastic matrix based on proteoglycans are the predominant components of the socalled extracellular matrix. Extracellular matrix is a complex network of numerous macromolecules that fulfill a large number of mechanical, chemical and biological functions (23). While collagens and elastin fibres confer strength and elasticity to tissues, respectively, structural proteoglycans allow tissue cohesiveness. Specifically, collagen is the most prevalent component, with type I fibres usually well organised and associated with ligamentous tissue, while type III collagen is more common in the loose areolar tissue, which makes up the vaginal wall adventitia and surrounds the pelvic organs (24). According to the molecular weight, indeed, proteoglycans are distinguished into large molecules (aggrecan, versican and perlecan) and small molecules, such as decorin, fibromodulin, biglycan, lumican and chondroadherin (25).

The organised structure of the matrix is due to a clear balance between the production of the different constituents and their breakdown. There are many proteolytic enzymes capable of degrading the elements of the extracellular matrix, falling into into three groups: the serine proteases, the cysteine proteases, and matrix metalloproteinases (MMPs) (26).

Several authors evaluated the expression of the different proteins as well as of their precursors and fragments of degradation. With regards to the metabolism of collagen, some studies seem to indicate that women with SUI have a reduced total collagen content in the skin and urogenital tissue (27-29), while other studies reported higher total collagen concentration and higher levels of mRNAs for type I and type III collagen in paraurethral connective tissue (30). Chen et al., evaluating cultures of fibroblasts taken from endopelvic fascia and skin biopsies in 14 patients with stress urinary incontinence and 12 controls, showed that the overall collagen synthesis and the ratio of type III and type I fibres were not significantly different between fibroblasts obtained from women with or without SUI (31) indicating that alteration in the collagen synthesis might not be involved in SUI.

On the other hand, a few studies reported change in the relative percentages of the different fibres, with a decrease in type I and increase in type III ones (32, 33). In women with SUI, Skorupski et al. evaluated the transcription factor Sp1-binding site in the gene encoding a-1 chain of type I collagen, andsuggested that the observed G-T polymorphism is a risk factor for incontinence (34). Again, at the molecular level, some studies evaluated the cycle regulatory proteins in patients with pelvic organ prolapse, showing controversial results. Some papers reported reduced expression of proteins such as p53 and p21 which normally cause cycle G1 arrest suggesting an increase in proliferation capacities for fibroblasts derived from human cardinal ligaments of patients with prolapse (24).

Other authors evaluated markers of collagen degradation. Specifically, Edwall et al. evaluated markers of collagen synthesis and breakdown such as the carboxy-terminal propeptide of type I procollagen (PICP), the carboxy-terminal telopeptide of type I collagen (ICTP), and the amino-terminal propeptide of procollagen III (PIIINP) in urogenital tissue homogenates and peripheral serum from 71 patients with SUI and 31 healthy control women (35). After adjusting for age, BMI, parity, and hormonal status, the patients with SUI had significantly lower serum concentrations of PICP and significantly lower tissue concentrations of PIIINP and ICTP than the controls, suggesting reducing breakdown in the presence of unchanged synthesis of type I collagen and, regarding type III collagen, a potential reduction in either synthesis or breakdown, the second being considered more probable (35). These data may lead to the hypothesis that SUI might be associated with impaired degradation of collagen, leading to reduced turnover and accumulation of aging collagen, negatively affecting the strength and elasticity of urogenital tissue. Further studies on transforming growth factor-β (TGF-β) identified the molecular basis of such mechanism, suggesting that overexpression of TGF-β might trigger the accumulation of aging collagen, inhibiting the expression of collagenases and increasing the production of the tissue inhibitor metalloproteinase (36-38). Moreover, some genes, such as those of the Homebox A (HOXA) family, encoding transcription factors that regulate mammalian embryonic growth and development of the urogenital tract, have been shown to be underexpressed in patients with pelvic organ prolapse, suggesting a further molecular basis for the alterations in collagens (39).

Some other studies investigated the role of proteinases that may degrade elements of the extracellular matrix. Chen et al., evaluating full-thickness peri-urethral vaginal wall tissues from patients with SUI or prolapsed and matched control women, found significant decrease in mRNA and protein expressions of alpha-1 antit-

rypsin (ATT), a neutrophil elastase inhibitor in tissues from affected women, while no difference was found in neutrophil elastase and cathepsin K expressions (40). Similarly, Gabriel et al. studied the expression of different MMPs in 17 women with prolapse and 18 control, identifying higher expression of MMP2 in patients with prolapse (41). These studies allowed to hypothesize that altered catabolism of some components of the extracellular matrix might contribute to the connective tissue alterations observed in pelvic floor dysfunction.

Other studies were focused on the expression of small proteoglycans. Wen et al. studied mRNA and protein levels of biglycan, decorin, and fibromodulin in vaginal wall tissue from women with SUI and menstrual-cycle matched continent women (23). Specifically, the authors demonstrated that the mRNA expression of fibromodulin was significantly lower in patients in the proliferative phase compared to controls, while decorin mRNA expression was higher both in the proliferative and secretory phases in the patients with SUI, supporting the hypothesis that the expression of such small proteoglycans was hormonally modulated and may contribute to the altered pelvic floor connective tissues of women with SUI (23).

Oestrogens interact with specific receptors which, when activated by the ligand, have conformational change, dimerisation and recruitment of co-factors, once translocated into the nucleus, these promote the expression of region of oestrogen-responsive genes, called the oestrogen response elements, leading to the synthesis of proteins (42). Selective modulators of oestrogen receptors modulate the activity of the receptors, working as agonists, partial agonists, or antagonists in a tissue-dependent manner (43). Studies on these molecules supported a new role of oestrogens in SUI and pelvic organ prolapse. Specifically, in a randomised controlled trial testing one of these molecules (levormeloxifene) as osteoporosis treatment, a 3.4-fold increase in the reporting of POP and an almost 5-fold increase in the reporting of UI have been observed (44). To explain such effect, the expression of more than 500 proteins have been studied in the rat model, showing that oestradiol induced the expression of metalloproteinase 7 and 14, reduced the expression of their inhibitors such as TIMP-3, while selective modulators of oestrogens receptors such as raloxifene had minimal effects on metalloproteinase 7, and maintained or restored expression of the mRNA for tissue inhibitor of metalloproteinases-3 (TIMP-3) and other components of the extracellular matrix, such as glypican, and biglycan (42). Although the role of selective oestrogen-receptor modulators (SERMs) in the expression of the component of extracellular matrix has to be further clarified, these findings support the hypothesis that the increased occurrence of urinary incontinence and pelvic organ prolapse observed with oestrogen therapy and SERMs such as levormeloxifene may be related to changes in expression of genes regulating collagen turnover that ultimately weaken the normal structural integrity and support for the genitourinary system (42).

Recent research has focused on the role of urinary biomarkers and the microbiome in the investigation and treatment of urinary incontinence. The idea behind this is that the identification of specific biomarkers may be useful to phenotype patients and select more effective target therapies (45). Urinary nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and adenosine triphosphate (ATP) are increased in many overactive bladder (OAB) patients (45). Urinary NGF has also been suggested as a surrogate marker of detrusor detrusor overactivity (DO) (46). There are numerous genes that are associated with urinary incontinence and pelvic organ prolapse (47). These genes are involved in collagen metabolism, protein–lipid complex remodeling, and extracellular matrix organization. A recent review of the literature (48) highlighted the following: 4 genes were found to be associated with overactive bladder and urge urinary incontinence: adrenergic receptor β3, Rho guanine nucleotide exchange factor 10, Rho-associated coiled-coil containing protein kinase 2, and potassium two pore domain channel subfamily K member-1. Genetic variations in the human β3-adrenoceptor (*β3-AR*) gene may be associated with impaired detrusor relaxation, leading to OAB/DO (20). 13 genes were found to be associated with stress Urinary incontinence (SUI): skin-derived antileukoproteinase, collagen type XVII alpha 1 chain, plakophilin 1, keratin 16, decorin, biglycan, protein bicaudal D homolog 2, growth factor receptor-bound protein 2, signal transducer and activator of transcription 3, apolipoprotein E, Golgi SNAP receptor complex member 1, fibromodulin, and glucocerebrosidase. Seven genes were identified in association with pelvic organ prolapse: homeobox A13, matrix metallopeptidase 9, estrogen receptor 2, collagen type XIV alpha 1 chain, collagen type V alpha 1 chain, collagen type IV alpha 2 chain, and catenin beta 1. Whole genome studies are needed in order to elucidate this further.

Contrary to previous belief, the urinary tract is not sterile. An imbalance in the urinary microbiome may contribute to the development of urinary tract symptoms (48). Growing knowledge and insight into the urinary microbiome may provide understanding of different conditions and optimize their management. Urinary microbiota seems to be related to OAB symptoms, in particular urgency urinary incontinence (45). In women with urge urinary incontinence the microbiome was composed of increased Gardnerella and decreased Lactobacillus, which may have implications for prevention measures (49). This is a growing research area.

3.1. Consensus Statement

To date, tissue analyses are not part of the everyday clinical practice.

3.2. Future Research Areas

- The relationship between tissue composition, genetic composition, the urinary microbiome and risk of UI and POP.
- The relationship between tissue composition, genetic composition, the urinary microbiome and treatment outcome in patients with UI and POP.

VII. CONCLUSIONS

Clinical research involving diagnostic accuracy and clinical benefit of imaging studies and other diagnostic tests is particularly difficult. Recommendation of a diagnostic test is based upon the evidence that the outcome of it provides valuable information for patient management and this often involves evaluating the outcome of surgery. Implementation of good clinical research in this area remains difficult and sometimes lacks adequate founding. We acknowledge that only a few of the imaging techniques and other investigations we reviewed in the current chapter have been properly evaluated with respect to reproducibility, specificity, sensitivity and predictive value in connection with the diagnosis and management of urinary incontinence. Nevertheless, we acknowledge the great amount of work performed in the last four years and the continuous advancement in this field. The use of imaging and other investigations, described in this chapter, remains mostly based on expert opinion, common sense, availability and local expertise, rather than on evidence based clinical research. The diagnostic tests we considered can be subdivided into safety tests, tests with specific and selected indications, investigational tests.

Safety tests - Intended to protect patients' health, they are indicated in all patients complaining of urinary incontinence. They include urinalysis and measurement of post-void residual urine. While a consensus is easily achieved for urinalysis, the clinical benefit and cost-effectiveness of PVR measurement in the primary evaluation of urinary incontinence needs to be confirmed in prospective studies.

Tests with specific and selected indications. Upper urinary tract imaging (as well as renal function assessment) may be indicated in cases of neurogenic urinary incontinence with risk of renal damage, chronic retention with incontinence, incontinence associated with severe genitourinary prolapse and suspicion of extraurethral incontinence. No other imaging technique is recommended in the primary evaluation of uncomplicated urinary incontinence and/or pelvic organ prolapse. Cystourethrography remains a reasonable option only in the preoperative evaluation of complicated and/or recurrent cases. Video urodynamics, is the gold standard in the evaluation of neurogenic incontinence, particularly in the paediatric population, although the clinical benefit of it remains unclear. In female urinary incontinence videourodynamics is not recommended except under specific complex circumstances. MRI remains the gold standard for the diagnosis of urethral diverticula although ultrasonography is a good alternative option. Lumbosacral spine X-rays have specific indications in children with suspect neurogenic incontinence without gluteo-sacral stigmata. Imaging of the CNS should be considered when a neurological disorder is suspected on the basis of clinical, imaging and neurophysiological findings. Urethrocystoscopy is indicated in cases of incontinence with microscopic haematuria, in the evaluation of recurrent or iatrogenic cases, in the evaluation of vesico-vaginal fistula and extra-urethral urinary incontinence.

Endoanal ultrasound and endocoil MRI are the gold standard for the evaluation of anal sphincter disorders, dynamic X-ray imaging remains the standard for evaluating rectal prolapse.

Investigational tests Pelvic floor ultrasound is widely used as an adjunct to physical examination in patients with urinary incontinence and/or pelvic organ prolapse. Although the technique is rapidly evolving and much progress has been made in clinical research in this field, ultrasonography remains optional as evidence of its clinical benefit is not there yet.

MRI of the pelvic floor is rapidly gaining popularity in the evaluation of enteroceles and in the morphological analysis of pelvic floor muscles although evidence of its clinical benefit is still lacking. Both ultrasonography and MRI are the most rapidly evolving techniques and hold promises for potential future clinical applications.

Research in this area is also performed to improve our understanding of the pathophysiology of continence disorders and POP. Functional neuroimaging continues to provide new insight regarding functional anatomy of CNS related to vesicourethral function and dysfunction. The content of the draft reflects the composition of the Committee is made up of clinicians with a particular interest in a specific area of imaging and neurophysiology. The chapter certainly reveals the enthusiasm the authors poured in clinical research into this area, but we believe that the methodology implemented by the Consultation is the best guarantee of a balanced opinion and evidence-based recommendations. We hope that this chapter will stimulate clinical research in this field and will inspire those involved in the management of continence disorders and POP.

Neurophysiological testing should be part of the armamentarium available in the management of neurogenic incontinence and the establishment of good collaboration with neurophysiologists is recommended.

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II. IMAGING IN URINARY INCONTINENCE AND PELVIC FLOOR DYSFUNCTION

1. IMAGING OF THE UPPER URINARY TRACT

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III. IMAGING IN ANAL INCONTINENCE

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COMMITTEE 7

DIAGNOSIS AND MANAGEMENT OF URINARY INCONTINENCE IN CHILDREN

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Co-Chair
Nijman, Rien (Netherlands)

Members
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Tekgul, Serdar (Turkey)
van der Walle, Johan (Belgium)
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Wood, Daniel (United States)
Yang, Stephen Shei-Dei (Taiwan)
Zderic, Stephen (United States)

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I. INTRODUCTION

In this chapter the diagnostic and treatment modalities of urinary incontinence in childhood will be discussed. The whole range of urinary incontinence will be covered, from non-neurogenic to neurogenic and from the normal developed child to those children with special needs. In order to understand the pathophysiology of the most frequently encountered problems in children, we shall also consider the normal development of bladder and sphincter.

Underlying pathophysiology will be outlined and the specific investigations for children will be covered but for general information on epidemiology and urodynamic investigations their respective chapters should be consulted.

1. NORMAL DEVELOPMENT OF BLADDER AND SPHINCTER CONTROL

Normal bladder storage and voiding involve low-pressure and adequate bladder volume filling followed by a continuous detrusor contraction that results in bladder emptying, associated with adequate relaxation of the sphincter complex. This process requires normal sensation and normal bladder outlet resistance. The neurophysiological mechanisms involved in normal bladder storage and evacuation include a complex integration of sympathetic, parasympathetic and somatic innervation which is ultimately controlled by a complex interaction between spinal cord, brain stem, midbrain and higher cortical structures

In newborns, the bladder has been traditionally described as “uninhibited”, and it has been assumed that micturition occurs automatically by a simple spinal cord reflex, with little or no mediation by the higher neural centres. However, studies have indicated that even in full-term fetuses and newborns, micturition is modulated by higher centres and the previous notion that voiding is spontaneous and mediated by a simple spinal reflex is an oversimplification (1). Fetal micturition seems to be a behavioural state-dependent event: intra-uterine micturition is not randomly distributed between sleep and arousal, but occurs almost exclusively while the fetus is awake (1).

During the last trimester the intra-uterine urine production is much higher than in the postnatal period (30ml/hr) and the voiding frequency is approximately 30 times every 24 hours (2). In preterm infants diuresis is higher than in term born children. (3)

Immediately after birth voiding is very infrequent during the first few days of life. The first void may only take place after 12 to 24 hours. In preterm infants the voiding frequency is higher and the voided volume smaller than in term infants. After the first week following birth, frequency increases rapidly and peaks at the age of 2 to 4 weeks to an average of once per hour. It then decreases and remains stable after 6 months to about 10 to 15 times per day. After the first year it decreases to 8 to 10 times per day, while voided volumes increase by three-to-fourfold. (4)

During the postnatal period, micturition control mechanisms undergo further changes and extensive modulation. Using ambulatory bladder monitoring techniques in conjunction with polysomnographic recordings it has been shown that even in newborns the bladder is normally quiescent during sleep and micturition does not occur during these periods (5).

This inhibition (or lack of facilitation) of detrusor contractions during sleep is also observed in infants with neurogenic bladder dysfunction who have marked detrusor overactivity while they are awake. In response to bladder distension during sleep, an infant nearly always exhibits clear electro-encephalographic evidence of cortical arousal, facial grimaces or limb movements, or actual awakening. A significant change in sleep pattern, with a shift from quiet sleep to REM or indeterminate sleep, occurs. Sixty percent of term infants are seen to wake up before the bladder contracts after which voiding occurs (3). This arousal period may be transient and the infant may cry and move for a brief period before micturition and then shortly afterward go back to sleep. Because this wakening response is already well established in newborns, it follows that the control of micturition probably involves more complicated neural pathways and higher centres than has been appreciated. It suggests a close relationship between the locus coeruleus and the control center (the pons and the dorsal tegmentum) of micturition. There is also strong evidence that a pronounced reorganisation of pre-existing synaptic connections and neural pathways involved in bladder control occurs during the early postnatal period.

In newborns micturition occurs at frequent intervals and may have an intermittent pattern although bladder emptying efficiency is usually satisfactory. In over 80 percent of voids the bladder empties completely, but infants do not empty their bladder at every void. Post void residual subsides with age (3).

During infancy voiding pressures are much higher than in adults. It has also been noted that these pressures are higher in boys than in girls (mean pdet max of 118 vs. 75 cm H2O, respectively) (6,7).

These higher detrusor pressures decrease progressively with increasing age. In up to 70 percent of infants (up to the age of 3 years) with normal lower urinary tracts, intermittent patterns of voiding were observed. They tend to disappear with increasing age, and are thought to represent variations between individual infants in the maturation of detrusor and sphincteric coordination during the first 1 to 2 years of life. Videourodynamic studies have confirmed these findings (3,6-9).

Between the age of 1 and 2, conscious sensation of bladder filling develops. The ability to void or inhibit voiding voluntarily at any degree of bladder filling commonly develops in the second and third years of life. Central inhibition is crucial to obtain continence.

During the second and third year of life, there is progressive development towards a socially conscious continence and a more voluntary type of micturition control develops. The child becomes more aware of the sensation of bladder distension and the need to urinate, as well as social norms and embarrassment associated with urinary incontinence. Through an active learning process, the child acquires the ability to voluntarily inhibit and delay voiding until a socially convenient time, then actively initiate urination even when the bladder is not completely full, and and then subsequently allowing urination to proceed to completion. During the first years of life, gradual development to an adult type of voluntary micturition control that conforms to the social norms depends on an intact nervous system, in addition to at least three other events occurring concomitantly:

a) a progressive increase in functional storage capacity,

b) maturation of function and control over the external urinary sphincter,

c) and most importantly, achievement of volitional control over the bladder-sphincteric unit so that the child can voluntarily initiate or inhibit the micturition reflex (10).

The final steps are usually achieved at the age of 3 to 4 years when most children have developed the adult pattern of urinary control and are dry both day and night. The child has learned to inhibit a micturition reflex and postpone voiding and voluntarily initiate micturition at socially acceptable and convenient times and places. This development is also dependent on behavioural learning and can be influenced by toilet training, which in turn depends on cognitive perception of the maturing urinary tract.

It is understandable that this series of complex events is highly susceptible to malfunction. Various functional derangements of the bladder-sphincter-perineal complex may occur during this sophisticated course of early development of normal micturition control mechanisms. These acquired "functional" disorders overlap with other types of bladder functional disturbances that may have a more organic underlying pathophysiological basis.

2. NORMAL VALUES

2.1. Normal bladder capacity

Bladder capacity increases during the first 8 years of life roughly with 30 ml per year, so with an average capacity of 30 ml in the neonatal period, a child's bladder volume can be calculated as Y = 30 + 30 X, where Y = capacity in ml and X = age in years (Fig 1) (11).

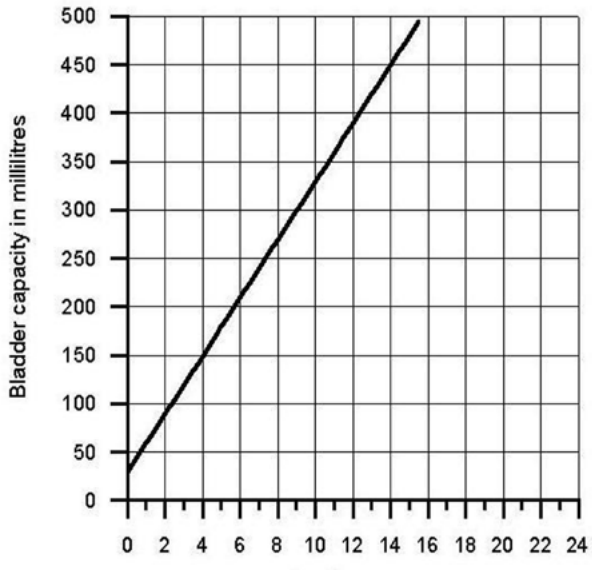

Fig 1. Bladder capacity using the formula Y = 30 + 30 X (Y= capacity in ml, X = age in years)

Hjälmås described a linear correlation that could be used up to 12 years of age: in boys, Y = 24.8 X + 31.6, in girls Y = 22.6 X + 37.4, where Y is capacity in ml, and X is age in years (12).

It should be noted that these data were obtained during cystometric investigations. Cystometric capacity is generally less than normal bladder volumes. Obviously, the relation between age and bladder capacity is not linear for all ages, nor is the relation between body weight and bladder capacity (15).

Another formula to calculate bladder capacity in infants is: bladder capacity (ml) = 38 + (2.5 x age (mo)) (13).

Kaefer and co-workers demonstrated that a non-linear model was the most accurate for the relation between age and bladder capacity, and they determined two practical linear equations:

Y = 2 X + 2 for children less than 2 years old, and Y = X/2+6 for those 2 years old or older; Y = capacity in ounces, X = age in years (Fig. 2) (14).

Normal urinary flow rates

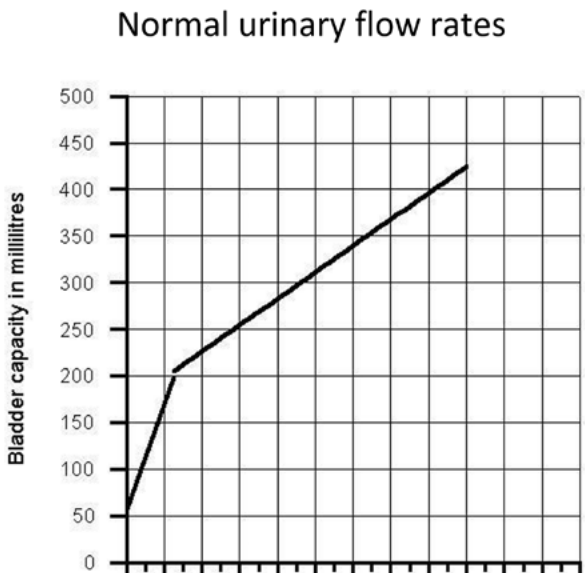

Fig 2. Bladder capacity using the formula
Y = (2 X + 2) x 28.35 ml < 2 years
Y = (X/2+6) x 28.35 ml > 2 years
(Y = capacity in ml, X is age in years)

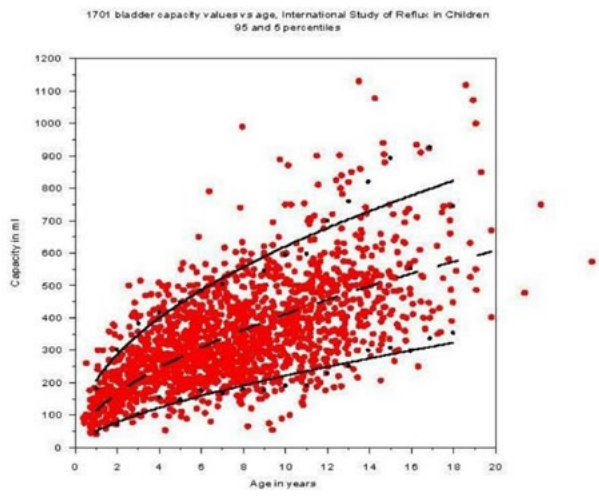

Fig 3. Bladder capacities determined by VCUG in the International Reflux Study

None of these formulas have been derived from a population based study and do not reflect normal bladder capacity. Normal bladder capacity should be regarded as the maximum voided volume of urine and shows huge variation. Recent work of Rittig et al looked at Maximum Voided Volumes (MVV). The Koff Formula showed a reasonably good correlation with 2836 daytime voids, if first morning voids were neglected (15). Girls were found to have a larger capacity than boys, but the rate of increase with age was not significantly different between them. Data on 'normal' bladder capacity have been obtained in continent children undergoing cystography, with retrograde filling of the bladder. Data obtained from the International Reflux Study indicate that there is not a linear relation between age and capacity and that there is a huge variability. (Fig. 3) (16).

2.2. Normal Voiding

The micturition frequency of the fetus during the last trimester is approximately 30 per 24 hours. It decreases to 12 during the first year of life, and after that it is gradually reduced to an average of 5±1 voidings per day (9, 13). The normal range for micturition frequency at age seven is 3 to 7. By age 12, the daily pattern of voiding includes 4-6 voids per day (17,18). Mattson and Lindström emphasize the enormous variability of voiding frequencies in children: also in individual children, the weight-corrected diuresis could vary up to 10-fold (19).

2.3. Normal voiding pressures

Bladder dynamics in children have demonstrated developmental changes with age. Detrusor pressures at voiding in children after the age of 2 years are similar to adults, with a mean maximum pressure of 66 cm H2O in boys, and 57 cm H2O in girls (20).

These pressures are lower than those reported in infancy by Yeung et al, who found boys having pressures of 118 cm H2O and girls 75 cm H2O (7).

2.4. Normal urinary flow rates

Urinary flow rates in normal children have been only minimally described. Szabo et al published nomograms for flow rates vs. age in normal children (21). Flow rates do increase with age.

As in adults, flow rates are clearly dependent upon voided volume, and normal values can only be applied to flow rates that have been registered when voiding at a bladder volume approximating the normal capacity for age (3,22).

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II. EVALUATION IN CHILDREN WHO WET

The first steps in the evaluation of the child that wets are a thorough history and physical examination. It is not uncommon that the complaint leading to the referral is only part of the issues that need to be addressed. Thus, a systematic and structured approach is mandatory. The overall objective of history taking and physical examination is to identify symptoms of bladder and bowel dysfunction, investigate for underlying pathology, establish habits regarding fluid intake and toilet visits, and appreciate the effect of previous treatment attempts if any. The combination of structured interviews, validated questionnaires and home recordings (frequency volume charts, bowel-movement charts, recordings of night-time urine production) often suffices to successfully treat the majority of patients with daytime incontinence and enuresis. When anatomical or neurological issues are suspected, urodynamic studies, non-invasive or invasive as well as imaging studies are typically warranted. That said, imaging studies may be helpful in children suffering daytime symptoms but are seldomly required in children with monosymptomatic enuresis.

The International Children's Continence Society (ICCS) has produced standardization documents covering the diagnostic evaluation of children with daytime incontinence as well as the diagnostics and treatment in children with enuresis. According to these documents evaluation and treatment is advised from the age of 6 years in the enuretic child and from the age of 5 years in children suffering daytime urinary incontinence at least once a month for a period of at least 3 months.

In case of refractory patients, diagnostic re-evaluation may be necessary and may reveal additional or overlooked issues that need to be addressed before a breakthrough in treatment efficacy is seen. Since home recordings with charts require time and effort, families need to be well informed about the reasons as well as the clinical value of these recordings in order to improve adherence and the quality of the data received.

1. HISTORY TAKING

History taking is the first and most important step when diagnosing children with incontinence. The young patients should be addressed directly when possible but even for the trained physician it can be equally difficult to connect with a 5-year-old as well as with the teenager with bladder and bowel complains. Establishing a trusting relationship is mandatory in order to be able to discuss issues that are considered a taboo. Sociocultural aspects and psychomotor development have to be taken into account. History taking needs to be detailed and structured [1]. The ICCS has provided standardization documents on the diagnostic evaluation of children with daytime incontinence, dysfunctional voiding, as well as on the evaluation of and treatment for enuresis [2, 3]. A number of validated questionnaires are at our disposal [4].

Conclusion: Validated questionnaires are an aid in history taking in children with enuresis and urinary incontinence (LoE 3)

Recommendation: the use of validated questionnaires is recommended in history taking in children with enuresis and urinary incontinence (GR:C)

The medical history should include questions regarding LUTS as well as bowel function and dysfunction, comorbidities and psychological assessment/behavioural problems. During history taking, the degree of motivation for both the parents and the child may become evident. An important task for the physician is to identify all the issues that need attention as often the initial complaints are not covering the entire spectrum of identified issues.

The following should be covered:
- Family history
- Birth history and development
- Past medical history, surgery, UTIs, medication
- Specify LUTS (daytime symptoms, enuresis)
- Bowel habits and dysfunction according to Rome IV criteria
- Toilet behaviour, toilet training and age of acquisition of bladder / bowel control
- Fluid intake habits
- Comorbidities, behavioural issues/psychosocial issues
- Sleep problems (signs of sleep disordered breathing)
- Previous treatment attempts
- Expectations of the parents/child

Specifically, for LUTS one can differentiate between storage symptoms (pollakisuria, voiding postponement, incontinence, urgency, nocturia, enuresis) and voiding symptoms (hesitancy, straining, dysuria, urine stream issues, intermittency, retention, post micturition dribble). In cases such as vaginal reflux, giggle incontinence etc. the diagnosis can be based solely on the history.

Warning signs suggesting an underlying pathology may include neurological issues, history of recurrent urinary tract infections and continuous incontinence.

Importantly, sexual abuse can be signalled first by symptoms of the lower urinary or gastrointestinal tract [5],[6]. However other symptoms may predominate.

2. SCREENING TOOLS

Self-reporting of symptoms is very often unreliable especially for the paediatric patient, therefore scoring systems and home recordings are of great value when evaluating bladder and bowel dysfunction in children. Not only can such tools help fully appreciate the symptoms, they can also be used in the follow-up, to assess the effect parameters.

A voiding diary is mandatory to determine the child's voiding frequency and voided volumes. A 48h frequency volume chart is advisable [2, 7] . For younger children 4-h void observations can be used [8]. Such charts can be filled in at home either on paper or through apps.

For the assessment of bowel function when desired 1-2 week diaries can be used registering frequency, stool consistency according to Bristol Scale [9], straining, pain and bleeding.

There is a well-documented high rate of behavioural disorders in children with bowel and bladder dysfunction (BBD) [10]. The ICCS recommends behavioural screening of all children with incontinence with validated questionnaire forms such as the Child Behaviour Checklist (CBCL Achenbach) or Strengths and Difficulties Questionnaire (SDQ) of the Behaviour Assessment of children (BASC) [11].

A short screening instrument for psychological problems in enuresis (SSIPPE) derived from CBCL [12] and a disease specific quality of life questionnaire for children with LUTD (PinQ) [13] are also available. If a clinically relevant behavioural or emotional disorder is suspected, a full child psychological or psychiatric assessment is recommended [14].

When sleep disordered breathing is suspected validated questionnaires can be used to identify patients in need for sleep studies [15]. This is particularly important in children who habitually snore, are overweight or have other risk factors for obstructive sleep apnoeas [16].

Conclusion: The use of validated questionnaires on behavioural screening and on sleep disorders in children with bowel and bladder dysfunction is effective to determine which patients needs further specified investigations (LoE:4)

Recommendation: Validated questionnaires on behavioural screening and on sleep disorders are recommended to determine which patients need further specified investigations (GR:C)

3. PHYSICAL EXAMINATION

Physical examination should be systematic with special focus on the genital region, pelvic region and lower back. Bedside ultrasound can be used for evaluation of bladder wall thickness and rectal diameter when needed.

The physical examination should include the assessment of perineal sensation and reflexes supplied by the sacral segments S1-S4 (standing on toes, bulbocavernosus reflex) and anal sphincter tone and control. The genital region should be thoroughly inspected as well as the positioning and characteristics of the urethral meatus. Asymmetry of buttocks, legs or feet, as well as other signs of spinal dysraphism in the lumbosacral area (subcutaneous lipoma, skin discoloration, hair growth and abnormal gait) should not be missed [17].

Palpation of the abdomen may reveal the presence of a full bladder, or a palpable mass on the left side representing a full sigmoid or descending colon. Although uncommon, it is also important to exclude other palpable masses.

When possible, direct observation of the child's voiding is advisable. Toilet posture should be evaluated and corrected if needed [18] (Figure 1). This can be done during uroflowmetry.

Once history is established and physical examination performed, further evaluation may include imaging studies, uroflowmetry and post void residual measurements, urine dipstick, transabdominal rectal US, pelvic floor US, and home recordings (frequency volume charts, stool calendar, recordings of night-time urine output).

Figure 1. Improper position for voiding: the feet are not supported (unbalanced position) and the boy is bent forward. Support of the feet will correct this and will allow the pelvic floor muscles to relax properly.

In selected cases invasive urodynamic studies, cystoscopy or further imaging may be warranted depending on the suspected diagnosis [1].

4. NON-INVASIVE DIAGNOSTIC TECHNIQUES

4.1. Urinalysis

Physical examination should include urinalysis to identify patients with urinary tract infection, proteinuria or haematuria. Further biochemical measurements in urine can be performed when needed to exclude hypercalciuria, tubular dysfunction, diabetes insipidus

Conclusion: urinalysis is essential to evaluate for UTI in patients with urinary incontinence (LoE:3)

Recommendation: urinalysis is recommended to evaluate for UTI in patients with urinary incontinence (GR:B)

4.2. Bladder diaries

The frequency/volume chart is a detailed diary recording each void by time and urine output over preferably four and a minimum of two 24-hour periods [7]. The chart gives objective information on the number of voids, the distribution of day and night voids, along with the voided volumes and episodes of urgency, leakage, or dribbling. In order to obtain a complete picture, defecation frequency and type according to Bristol scale and/or soiling episodes can also be recorded [19].

The frequency volume (FV) chart provides the maximum storage capacity as the maximal voided volume (MVV) [14]. First morning void reflects the nocturnal bladder capacity and should be excluded from the evaluation of MVV. MVV can be compared to the expected bladder capacity for age as calculated by the formula 30 x age +30 [3]. ICCS definition of normality is an MVV between 65% and 130% of the expected MVV. Normal voiding frequency is 4-7 voids per day on a normal fluid intake.

Whenever possible, filling out the chart should be the responsibility of the child with the parents providing assistance and support. The frequency volume charts can also be used to follow the progress. One has to bear in mind that for children on standard urotherapy on timed voids, FV charts can be misleading in evaluating MVV. Moreover, there may be differences between weekdays and weekends in toilet visits and fluid intake habits.

Registrations of fluid intake are of major importance both for evaluation of the total fluid intake per day but also the distribution throughout the day and of course any consumption of bladder irritants such as caffeine, carbonated drinks etc.

For nocturnal enuresis, patient's registrations of urine production during bedtime can identify the exact pathophysiology and can be used for tailoring treatment in the individual patient. Commonly seven nights of registrations as a minimum can provide a clear picture. Nocturnal urine production can be measured by weighing the diaper adding the first morning void. According to the ICCS a nocturnal urine production exceeding 130% of the expected MVV classifies for nocturnal polyuria. Such registrations of nocturnal urine output are of great importance especially in the patient refractory to first line treatments [3, 7].

Conclusion: a bladder diary is an effective tool to objectively assess the fluid intake and voiding habits of the incontinent child (LoE3)

Recommendation: The use of a bladder diary is recommended in the evaluation of every child suffering urinary incontinence or enuresis (GR:B)

4.3. Bowel diaries and evaluation of constipation

The high prevalence of constipation in children with bladder dysfunction dictates that all children attending incontinence clinics should be evaluated for constipation [20]. The physician will often find that an exact delineation of a child's bowel habits is not possible without a bowel diary. A 2-week bowel diary is advisable. The diagnosis of functional constipation should be based on the Rome IV criteria (https://theromefoundation.org/rome-iv/rome-iv-questionnaire/).

At least 2 of the following present at least once per week for at least 1 month:

- 2 or fewer defecations in the toilet per week
- At least 1 episode of faecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large faecal mass in the rectum
- History of large-diameter stools that may obstruct the toilet

The symptoms should not be fully explained by another medical condition.

Transabdominal rectal ultrasound may be useful not only in the diagnostics but also the follow-up of children with constipation [21, 22]. Using a full bladder as a window one can visualize and measure the diameter of the rectum. A rectal diameter of more than 3 cm predicts faecal impaction and has been validated against palpable mass in rectal examination, one of the criteria of functional constipation. This result was not age dependent.

To investigate for and adequately treat constipation is important in all children with urinary incontinence as this may improve the outcome [23].

Conclusion: constipation does influence the outcome of the treatment of incontinence (LoE:3)

Recommendation: Quantification of constipation is necessary in the diagnostic evaluation of the enuretic or urinary incontinent child (GR B)

4.4. Quantification of urine loss

Subjective grading of incontinence may not reliably indicate the degree of dysfunction. For objective grading a 12-h pad test and frequency/volume charts are validated instruments [24-26]. The dry pie is an alternative to the pad test when exact evaluation of the severity of the incontinence episode is the objective [27].This dry pie is a colorful and interesting home recording sheet designed to quantify the worst incontinence episodes during the day. The chart is very useful in following the progress of the symptoms. One should be aware that home recordings and diaries filled during weekends at home may deviate from what usually happens during school days.

The amount of urine lost during sleep (enuresis volume) can be determined by weighing diapers or absorbent pads, before and after sleep [7]. Although registrations of nocturnal urine output are of importance in the treatment of enuresis, especially the refractory type [3], the value of enuresis volumes remains in the research setting.

4.5. Scoring systems

At present three scoring systems, based on validated questionnaires have been described. Specific scores correlated with lower urinary tract dysfunction with a specificity and sensitivity of about 90% [28-30].

The value of these scoring systems to determine the cause of incontinence seems to be limited for the individual patient, but can be very useful in research studies to determine and compare treatment outcomes.

Conclusion: scoring systems are effective to define lower urinary tract dysfunction (LoE 3)

Recommendation. Scoring systems can be useful especially in research studies (GR: B)

5. URINARY FLOW

Voiding should be analysed in detail in all incontinent children, with the exception of monosymptomatic bedwetting, where voiding is usually normal. Graphic registration of the urinary flow rate (i.e., uroflowmetry) during voiding is a standard office procedure. Flow patterns and rates should be repeated to allow for evaluation, and several recordings are needed to obtain consistency. Afterwards, parents are asked if their child's flowmetry pattern was representative of their ordinary voiding.

In infants, there are features of micturition that can be observed in healthy normal infants. This includes arousal, which is detected in 90% of micturitions in healthy term infants, whereas they are only detected in 60% of pre-term infant micturitions. Parameters such as voided volume, bladder capacity, and flow rates increase with

age, whereas voiding frequency, post-void residual urine (PVR), and interrupted voiding tend to decrease with age [31]. It was previously thought that constant bladder volume would promote bladder voiding in neonates without significant brain involvement. However, investigation using video-electroencephalography showed that bladder voiding during quiet sleep is associated with cortical arousal, suggestive of bladder sensory maturation over time.

Measurement of urinary flow is performed as a solitary procedure, with bladder filling by diuresis (spontaneous or forced), or as part of a pressure/flow study, with bladder filling by catheter. Patterns and rates should be consistent to allow for evaluation, and several recordings are needed to obtain consistency [14, 32-34].

The same parameters used to characterise continuous flow may be applicable, if care is exercised, in children with intermittent, or staccato flow patterns. In measuring flow time, the time intervals between flow episodes are disregarded. Voiding time is the total duration of micturition, including interruptions. Flow time is the total duration of flow, excluding the interval between voiding flow.

When possible, uroflowmetry should be performed with optimal bladder volume. ICCS has recommended 50ml as the lower limit of interpreting uroflowmetry [14]. Flow recordings with a voided volume of less than 50% of the functional capacity are not consistent: they represent voiding on command, and many children will try to comply by using abdominal pressure. On the other hand, overdistension of the bladder can result in abnormal uroflow recordings also [35]. A recent study evaluating children 4-9 years of age, suggested that the best reproducibility and reliability was found when bladder volumes are optimized to between the lowest accepted value of bladder capacity, defined as (age in years x 5 + 50mL), and upper boundary of 115% of expected bladder capacity, defined as (age in years x 30 + 30mL)[36].

A helpful tool to ensure optimal bladder volume is the use of transabdominal ultrasound (e.g. bladder scan) before micturition in order to assess the bladder volume [33, 37]. If the bladder is still nearly empty, the child should be asked to drink some water until the bladder is full enough for a reliable flow.

Urinary flow may be described in terms of rate and pattern and may be continuous, intermittent (in fractions), or staccato (fluctuating) (Fig. 2). An intermittent flow pattern shows an interrupted flow, whereas in staccato voiding the flow does not stop completely but fluctuates due to incomplete relaxation of the sphincter. The continuous smooth flow can be bell, tower or plateau. Only the bell shaped uroflowmetry curves are regarded as normal.

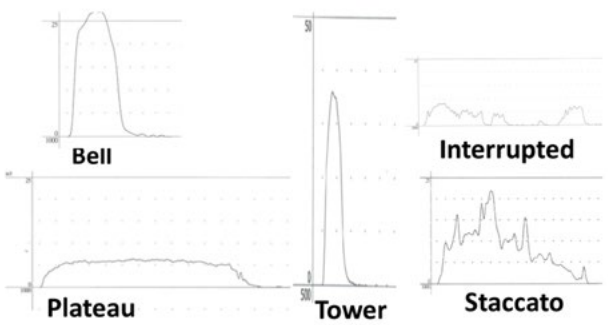
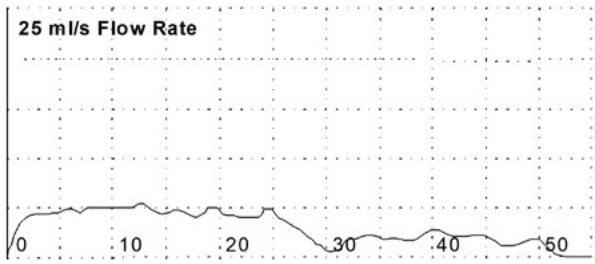


Figure 2. Typical uroflowmetry patterns

Under optimal bladder volume, approximately 1% of school children have voiding that can be labelled abnormal with flattened or intermittent flow curves. The remaining 99% have a bell-shaped flow curve [33, 38]. It should be noted that a normal flow does not exclude a voiding disturbance, nor does an abnormal flow pattern automatically means a bladder or voiding dysfunction, as in asymptomatic normal school children abnormal patterns were also found [39-41].

As current interpretations of uroflowmetry are descriptive (e.g. "bell-shaped"), there are low interrater agreements. Hence, objective criteria were suggested and may be beneficial to improve agreements between different professionals. Flow index (FI) is derived using the actual Qmax and the estimated Qmax. FI > 1.25 is suggestive of tower, FI 0.71-1.25 is suggestive of bell, and FI <0.71 is suggestive of plateau. FI may be a useful method to distinguish flow patterns with continuous curves [42, 43]. Figure 3 depicts typical plateau pattern with a low flow index. Other criteria that was suggested included Angle of Qmax (Angle_Qmax), which objectively relates the intuitive interpretation of flow patterns (Figure 4). Angle_Qmax ≥ 80° is suggestive of tower, Angle_Qmax 60-79° is suggestive of bell, and Angle_Qmax <60° are related to plateau curves[44, 45].

To better define interrupted flow, if the voided volume of a major curve is ≥80% of total volume of a uroflow curve, it is not an interrupted curve (figure 4a & 5a). In this way, one may avoid terminal dribbling as interrupted flow. A typical interrupted flow is shown in figure 6. There is no major curve, i.e., no single curve has a volume >60% of total volume in the voiding curves. Staccato flow pattern has less agreement. Some experts defined one deep drop as staccato. Since one deep drop can be common in healthy children (Fig. 5b), we recommend at least three deep drops of a curve to justify staccato pattern (Fig. 7)[44, 45].



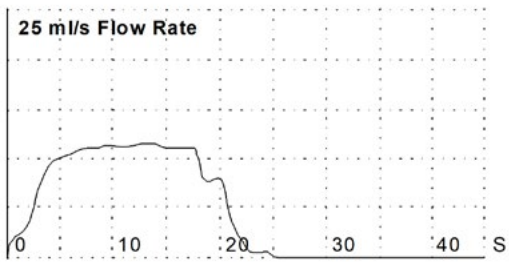


Figure 3: flow curves of 2 children with a static, anatomic obstruction; the curve is continuous but the flow is lower than normal and extended in time.

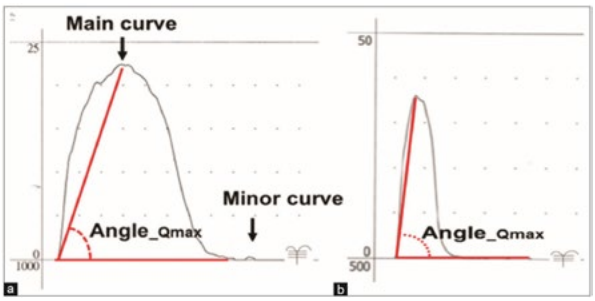


Figure 4. Typical bell (a) and tower (b) uroflowmetry curves show angle at Qmax (Angle_Qmax), and main and minor curves (a) (Shei-Dei Yang, S. and S.-J. Chang, Differentiating tower from bell curves in smooth continuous uroflowmetry curves of healthy adolescents. Urological Science, 2019. 30(2): p. 74.)

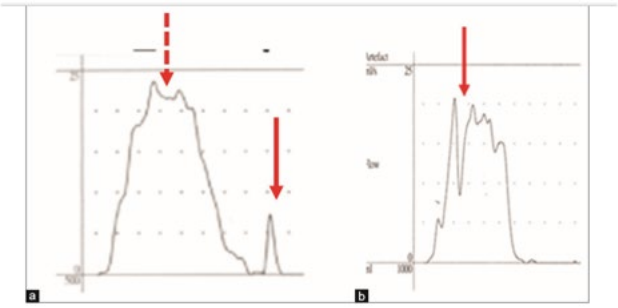


Figure 5. A "bell" curve with drop > 2 ml/s (broken arrow) and terminal minor curve (solid arrow) (a), and a "bell" curve with one deep drop >√ peak floe rate (arrow) and several significant drops > 2 ml/s (b). Both curves were record of healthy adolescents. (Shei-Dei Yang, S. and S.-J. Chang, Differentiating tower from bell curves in smooth continuous uroflowmetry curves of healthy adolescents. Urological Science, 2019. 30(2): p. 74.)

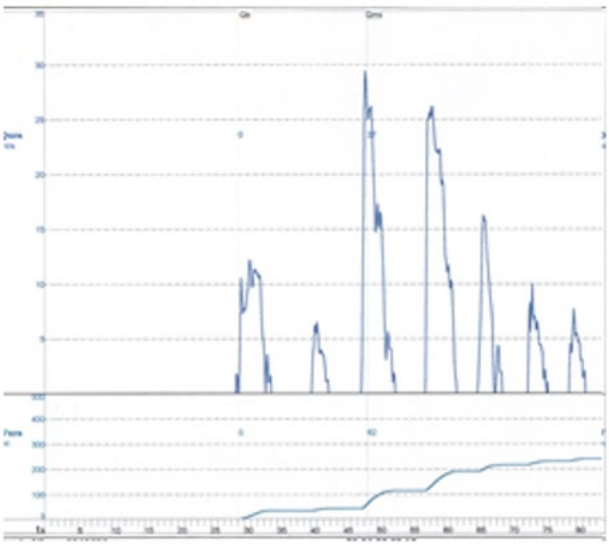


Figure 6: intermittent flow curve in a child voiding with abdominal straining

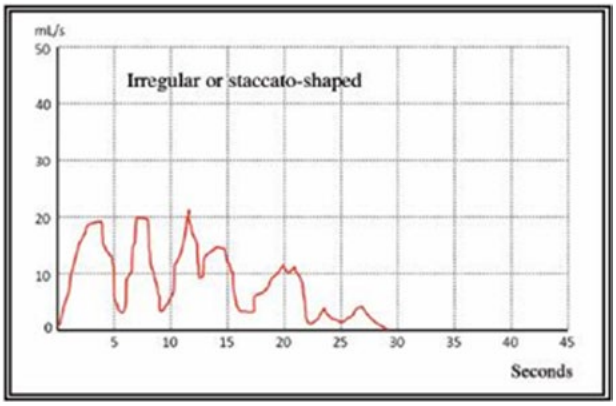


Figure 7: Staccato voiding in a child

Diagnoses based on uroflow pattern appearance without simultaneous electromyography (EMG) to support them can be misleading, and reliance on uroflow pattern alone can lead to overdiagnoses of dysfunctional voiding and detrusor underactivity. Hence, accompaniment of uroflowmetry with simultaneous pelvic floor electromyography is suggested to improve diagnostic accuracy and to provide the most appropriate management[46]. Nonetheless, uroflow-EMG has a low interrater agreement[47] and simultaneous use of uroflowmetry and EMG may require further studies to develop definitions that can be consistently used.

For children with MNE, both 48-hour frequency/volume charts and triplicate urine flow measurement with PVR evaluation are reliable methods of maximum bladder capacity evaluation. For children with OAB or DV, both methods may be necessary for accurate evaluation of decreased bladder capacity, as F/V chart and uroflow results may not be comparable. [48]

Conclusion: uroflowmetry is an adequate tool to analyse the voiding pattern of the incontinent child, although there exists high interrater variability in the descriptive interpretation of such studies. (LoE:3)

Recommendation: Uroflow is indicated in the evaluation of all incontinent children except those suffering mono-symptomatic enuresis. Adequate bladder filling is necessary for a reliable result. (GR: B)

6. ULTRASOUND IMAGING OF UPPER AND LOWER URINARY TRACT

In most clinical settings, ultrasound-imaging techniques are routinely used in children with incontinence. Upper tract abnormalities such as duplex kidney, dilatation of the collecting system, and gross reflux nephropathy can be readily detected, but detection of the more subtle expressions of these abnormalities requires urological expertise on the part of the ultrasound operator [49]. Most children with non-neurogenic lower urinary tract dysfunction (LUTD) have normal upper tracts. Therefore, routine ultrasound of upper tracts is not recommended for work up of primary nocturnal enuresis [14, 50]. Obtaining ultrasounds for PVR are helpful adjuncts in evaluating infants and children with LUTD and is recommended. These

can also provide additional information about bladder volume and thickness that can suggest neurogenic LUTD.

6.1. Post-void residual volume (PVR)

Except in small infants, the normal bladder will empty completely at every micturition [51].The identification or exclusion of elevated PVR is therefore an integral part of the study of micturition. However, an uneasy child voiding in unfamiliar surroundings may yield unrepresentative results, as may voiding on command with a partially filled or overfilled bladder. When estimating PVR, voided volume and the time interval between voiding and estimation of PVR should be recorded. This is of particular importance if the patient is in a diuretic phase. In patients with gross vesicoureteral reflux, urine from the ureters may enter the bladder immediately after micturition and may falsely be interpreted as residual urine. The absence of residual urine is an observation of clinical value, but does not exclude bladder outlet obstruction or sphincter / pelvic floor overactivity with absolute certainty. An isolated finding of residual urine requires confirmation before being considered significant, especially in infants and young children. Therefore, a single elevated age-specific PVR should prompt a confirmatory second PVR.

Sonographic estimation of PVR, instead of urethral catheterization, is recommended. Increased PVR is associated with prognosis and should be performed after uroflowmetry[52]. In children aged 4-6 years, a repetitive PVR of >20 ml or >10% bladder capacity is considered elevated. In children aged ≥7 years, repetitive PVR>10ml or 6% bladder capacity is regarded as elevated[53]. Ideally 3 uroflows are representative, but 2 will suffice as this maintains accuracy and consistency. First morning uroflows should be avoided as they may exceed normal voided volumes.

Dysfunctional voiding symptoms scores (DVSS), a numerical grading of voiding behaviors of children, is a non-invasive method of evaluating adherence to behavioural modification in pediatric patients with dysfunctional voiding. [30] However, an elevated PVR may mean lower likelihood of responding to treatment, regardless of their DVSS score. Hence, there may be benefit in serial uroflowmetry and PVR measurements in children with primary nocturnal enuresis[54].

6.2. Bladder wall thickness

Lower urinary tract abnormalities are even more difficult to assess for the inexperienced, aside from bladder wall thickness: a bladder wall cross-section of more than 3-4 millimetres, measured at 50% of expected bladder capacity, is suspicious of detrusor overactivity [55, 56]. Because only a few studies have been conducted to compare bladder wall thickness in normal children without complaints and in children with LUTD, more studies need to be performed to validate these non-invasive techniques[57, 58].

Another possibility is to assess bladder volume and bladder wall thickness to calculate the Bladder Volume/ Bladder Wall Thickness index. In children with nocturnal enuresis this index correlated well with response to treatment [59].

Bladder wall thickness and uroflow curve shape are related to the recovery period of pediatric overactive bladder (OAB). The bladder wall thickness, when measured within 5 minutes of voiding (or immediately after voiding if voiding time was greater than 5 minutes), was predictive of patients with shorter time to significant improvement (daytime incontinence less than once a month and no relapse for >6 months after cessation of treatment) following management of OAB. This may be due to strong detrusor overactivity associated with the bladder wall thickness, which will respond better to treatment with medications such as antimuscarinics. This may be the reason why patients who have a tower-shaped uroflowmetry curve may also have a shorter time to improvement compared to those with bell-shaped curve, since a tower-shaped curve may suggest bladder overactivity that may be more responsive to treatments.[60]

6.3. Ultrasound-flow-ultrasound

This combination of imaging and non-invasive urodynamics is a standardised procedure used to obtain representative data on flow rate and flow pattern, as well as PVR. With ultrasound, bladder filling is assessed and when the bladder capacity is equal to the functional or expected bladder capacity for age, the child is asked to void into the flowmeter. After recording the flow, PVR is assessed again. This procedure avoids the registration of flow rates at unrealistic bladder volumes.

Alternatively, children can be asked to use a flowmeter at home: a special flowmeter has been designed to use at home[61]. For those children who have difficulty voiding in a strange environment, this option can be useful.

Overall, non-invasive tests such as uroflowmetry, EMG, kidney and bladder ultrasounds, post-void residuals, and pelvic ultrasounds can all provide additional diagnostic information for children with LUTD. While invasive tests such as pressure flow urodynamics testing and voiding cystourethrograms can provide accurate diagnostic measures for selected patients, non-invasive tests can be considered as surrogate investigations that can provide similar information. Non-invasive diagnostic tests may guide us to select the most appropriate invasive investigations that may lead to the actual diagnosis that clinicians can target treatment for. This in turn, may improve patient and family satisfaction, as well as patient outcomes[62].

Conclusion: the combination of bladder ultrasound and uroflow is an important tool in the evaluation of voiding pattern in the incontinent child (LoE: 3)

Recommendation: Ultrasound and uroflow should be performed in the diagnostic evaluation of the incontinent child except for those with monosymptomatic enuresis, (GR/ B)

7. INVASIVE DIAGNOSTIC TECHNIQUES

The important question (for the incontinent child) “whether invasive diagnostic procedures are necessary” is decided by the results of the non-invasive procedures. At present, there are no studies indicating that a voiding cystourethrogram (VCUG) is useful in children with incontinence, without urinary tract infections.

Urodynamic studies may provide information that may change clinical decision making. However, they do not necessarily lead to improved incontinence outcomes. Hence, it is unclear whether routine use of urodynamics will benefit children who present with incontinence. In general, urodynamic studies will only be done if the outcome will alter the management, and this will also depend on whether the possible treatments being considered are invasive. The diagnostic information needed is that which is necessary to find the correct treatment. Indicators include straining or manual expression during voiding, a weak urinary stream, previous febrile UTI, continuous dribbling incontinence or pronounced apparent

stress incontinence, or previously identified dilating vesicoureteral reflux.

The finding of genitourinary abnormalities or signs of occult spinal dysraphism at physical examination also indicate the need for further diagnostics. Urinary flow registration will detect the plateau-shaped flow curve typical for structural bladder outlet obstruction, and an intermittent flow suggesting detrusor –sphincter- pelvic floor dyscoordination[14].

A clinically significant PVR on repeated occasions clearly points to incomplete bladder emptying. The pad test will detect the cases with obvious stress and urgency incontinence, or continuous dribbling. Ultrasound imaging will raise suspicion of an ectopic ureter, which can sometimes be confirmed on a well conducted physical examination as well. In short, invasive diagnostics are indicated when the non-invasive testing raises suspicion of neurogenic detrusor-sphincter dysfunction (occult spinal dysraphism), obstruction (especially posterior urethral valves), genitourinary abnormalities (e.g. epispadias), advanced non-neurogenic detrusor-sphincter-pelvic floor dysfunction (as in children with vesicoureteral reflux and upper tract dilatation and/or febrile urinary tract infections), or significant PVR.

To diagnose the complex of non-neurogenic detrusor-sphincter dysfunction, recurrent UTI and vesicoureteral reflux, urodynamic studies are needed in only a minority of all children.

7.1. Voiding Cystourethrogram

Technique of VCUG

To improve patient safety and to standardize the data obtained when a VCUG is performed, the American Academy of Paediatrics (AAP) Section on Radiology and the AAP Section on Urology have created a consensus on VCUG protocols to standardize the test [63]. The described technique is summarized below.

Cleanse and rinse the external genitalia with lukewarm water: do not use detergents. Use a feeding tube with side holes and a rounded tip (Ch 06-08), balloon catheter is not recommended; check the urine for infection. Empty the bladder completely before filling. Use a radio-opaque dye of maximum 30% concentration, at body temperature, and fill the bladder by slow-drip infusion, with a hydrostatic pressure of not more than 40 cm H2O. Note the volume of the contrast medium instilled. Use fluoroscopy during filling at regular intervals.

Take spot-films (70mm or 90mm camera) with the child in supine position, with partial filling and at the end of filling, in AP projection. Upper and lower tract should be visible.

When voiding is imminent, change the position of the child, so that spot films of bladder and urethra in 3/4 projection can be taken during voiding. Also take a spot film of the upper urinary tract during voiding, as the degree of vesicoureteral reflux (VUR) may change with the pressure generated by the detrusor muscle during voiding. Post-void residual volumes vary considerably with VCUG. The voiding phase is critically important to VCUG, both for reflux detection and for assessment of voiding dynamics. Without a voiding phase the VCUG is incomplete.

Prophylactic antibiotics are indicated in all children, to minimise the risk for post-VCUG UTI especially in children with history of febrile UTI or an anatomic abnormality.

Indications for VCUG

A VCUG is an invasive procedure and should only be done if the outcome will influence the management. It is indicated in children with recurrent UTIs to detect reflux, in children with a dilated system on ultrasound and in children with an abnormal flow pattern to detect bladder outlet abnormalities (like valves, strictures or a syringocele).

In children with incontinence the lateral projection during voiding is the most important part of the study. Especially in children with stress incontinence or a neurogenic bladder the position and configuration of the bladder neck during filling and voiding should be noted.

In children with non-neurogenic detrusor-sphincter- pelvic floor dysfunction (dysfunctional voiding) as well as in children with neurogenic detrusor-sphincter dyssynergia, the proximal urethra may show the so-called ‘spinning top’ configuration, during filling and during voiding. With detrusor and pelvic floor muscles contracting at the same time, the force of the detrusor contraction will dilate the proximal urethra down to the level of the forcefully closed striated external sphincter. The resulting ‘spinning top’ configuration was previously viewed as a sure sign of distal urethral stenosis, a concept held responsible for recurrent UTIs in girls, with urethral dilatation or blind urethrotomy as the obvious therapy. However, urodynamics has made it clear that the ‘spinning top’ will only appear when the detrusor and pelvic floor contract synchronously, which makes it a functional anomaly, not an anatomical one[64, 66].

Women often recall their experience with VCUG as young girls in terms bordering on abuse. The use of VCUG in children should be limited to those situations where it is absolutely necessary.

7.2. (Video)-Urodynamics

Urodynamic studies have become a major tool in evaluating lower urinary tract dysfunction (LUTD) in children [65]. It is indicated in children suspected of neurogenic or non-neurogenic LUTD refractory to empirical treatments based on non-invasive studies.

International Consultation on Incontinence-Research Society nocturia think tank (NTT) has recommended that standardized ALARA (“As Low As Reasonably Achievable”) principles should be adopted for videourodynamics in children. The risks of radiation related to x-ray images should be balanced with the benefits of the diagnostic test, and only the standardized and minimum necessary images should be obtained to correlate the pressure changes. Moreover, the pelvic muscle surface electromyography technique and its diagnostic relevance should be standardized and further investigated in the future [63].

In children, urodynamic investigations should only be performed if the outcome will have consequences for treatment [67-69]. Furthermore, like VCUG it may be considered when invasive or surgical interventions are planned. The main question is whether the urodynamic study will provide new information that cannot be obtained otherwise and will influence the further management. From the few studies that have addressed this issue it can be concluded that urodynamic studies in the majority of cases do not provide significant additional information to justify this type of investigation as a routine procedure in non-neurogenic children [70-72].

Both children and parents need careful preparation and adequate information before the study is done. It is an invasive procedure and artifacts may occur. Because of the invasiveness of the investigations all children are anxious and this may be reflected in the out-

come of the study. Especially during the first filling cycle, when the child does not know what to expect, detrusor overactivity may be seen and the voiding phase can be incomplete due to contraction or incomplete relaxation of the pelvic floor muscles during voiding. Once the child knows that filling and voiding are not painful a subsequent filling and voiding cycle may show a completely different pattern. The study should be repeated at least 2 or 3 times. Only if during the first filling cycle, no detrusor contractions are seen and also the voiding phase is in accordance with history and uroflow, it is probably sufficient to do only one complete filling and voiding cycle [73]. Still the results may not always be reproducible, and it should be stressed that the primary objective is to treat the child and not a "urodynamic abnormality" per se.

Special attention should be given to a pleasant surrounding for the child: one or both parents should be present and young children may be given a bottle. Older children may be distracted by watching a video movie. The child should be awake, non-anaesthetised and neither sedated nor taking any drugs that affect bladder function. Intranasal midazolam may be administered in certain situations where high anxiety levels cannot be mollified, as this drug appears to be innocuous regarding outcome of the study [74].

During the study the investigator has the opportunity to observe the child and discuss various findings and correlate them to what the child feels and/or normally would do in such circumstances. Because UDS is an invasive procedure artifacts may influence accurate interpretation of results [75].

In children, the transition from filling phase to voiding phase is not as marked as in adults. To avoid missing this important transition, cystometry and pressure-flow/EMG measurements are performed as one continuous study in paediatric urodynamics.

Electromyography of the pelvic floor muscles is assumed to evaluate the activity of the striated urethral sphincter, in the filling phase and in the voiding phase. Surface skin electrodes are usually used to record the EMG. In children the pelvic floor EMG is probably of much more importance than in adults as it helps to differentiate the different voiding disorders.

Filling the bladder can be achieved by diuresis (natural fill cystometry) or retrograde by catheter. For retrograde filling by catheter, saline 0.9% or contrast medium at body temperature is recommended in children. Especially in young children some urodynamic parameters, such as capacity and detrusor activity are influenced by the temperature of the filling fluid. Although the clinical relevance is as yet unknown, it is recommended to fill the bladder with fluid of body temperature [76]. When filling by catheter, slow fill cystometry (5 – 10 percent of expected bladder capacity per minute (based on the voiding diary), or < 10ml/min) is recommended in children.

Involuntary detrusor contractions may be provoked by rapid filling, alterations of posture, coughing, walking, jumping, and other triggering procedures. The presence of these contractions does not necessarily imply a neurological disorder. In infants, detrusor contractions often occur throughout the filling phase (Figure 8).

Bladder sensation is difficult to evaluate in children. Only in toilet-trained cooperative children it is a relevant parameter. Normal desire to void is not relevant in the infant, but can be used as a guideline in children of 4 years and older. Normal desire to void should be considered the volume at which some unrest is noted, e.g., wriggling the toes; this usually indicates voiding is imminent. In the older child, the volume may be small with the first cystometry,

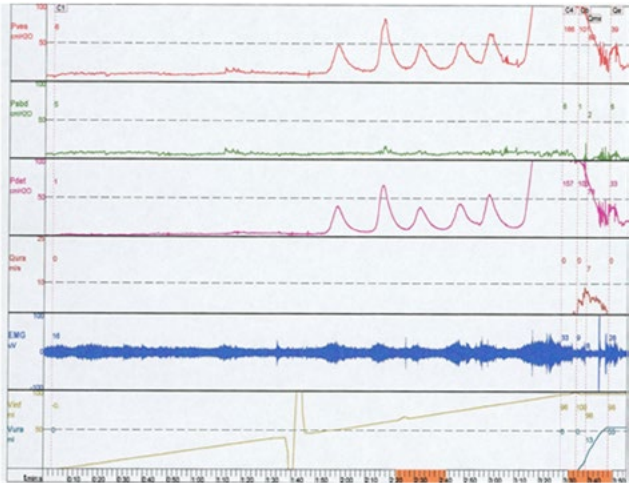


Fig. 8. Urodynamic study illustrating involuntary detrusor contractions, counter action of pelvic floor muscles (guarding reflex) and incomplete pelvic floor relaxation during voiding resulting in post void residual urine (detrusor overactivity + dysfunctional voiding) [77].

for fear of discomfort. Also, involuntary detrusor contractions occur more often during the first filling cycle [76]. This is the reason that in paediatric urodynamics at least two cycles of filling are recommended.

Maximum cystometric capacity (MCC) is the volume in the bladder at which the infant or child starts voiding. The value for maximum cystometric capacity is derived from volume voided plus residual volume. Values for MCC should be interpreted in relation to normal values for age.

Compliance indicates the change in volume for a change in pressure. For children with neurogenic detrusor-sphincter dysfunction, data are available relating poor compliance to the risk of upper urinary tract damage[78].

The usual notation for compliance is a single value, but a full characterisation of compliance may be helpful, as some children have varying compliance factors throughout filling [80]. This variability depends on several factors: rate of filling, which part of the curve is used for compliance calculation, shape (configuration) of the bladder, thickness, and mechanical properties of the bladder wall, contractility, relaxability of the detrusor, and degree of bladder outlet resistance [73]. To calculate the compliance ΔP represents the change in detrusor pressure from the onset of filling until just before the initiation of voiding or the pressure at the end of filling.

The urethral closure mechanism during storage may be normal or incompetent. The normal urethral closure mechanism maintains a positive urethral closure pressure during filling, even in the presence of increased abdominal pressure or during detrusor overactivity (guarding reflex) [77]. An incompetent closure mechanism is defined as one that allows leakage of urine in the absence of a detrusor contraction.

In urodynamic stress incontinence, leakage occurs when Pves exceeds Purethra (intraurethral resistance) as a result of an increase in intraabdominal pressure, often in conjunction with low Purethra [77]. Although common in multiparous females, it is exceedingly rare in paediatrics but may be noted in athletically active teenage

girls [83]. Immediately prior to micturition the normal closure pressure decreases to allow flow.

Bladder outlet obstruction, recorded with a pressure / flow study, may be anatomical or functional in nature. An anatomical obstruction may be present at the bladder neck or in the urethra as a stenosis or a stricture when there is a small and fixed urethral diameter that does not dilate during voiding. As a result, the flow pattern is plateau shaped, with a low and constant maximum flow rate, despite high detrusor pressure and complete relaxation of the urethral sphincter. In a functional obstruction, it is the active contraction of the urethral sphincter or pelvic floor during passage of urine, that creates the narrow urethral segment as a constant or intermittent obstruction. To differentiate anatomical from functional obstruction, information is needed about the activity of the urethral sphincter during voiding. This information can be obtained, and recorded together with pressure and flow, by monitoring the urethral pressure at the level of the urethral sphincter, or by recording a continuous electromyogram of the pelvic floor, as in clinical practice the urethral sphincter is not readily accessible, and the electromyogram of the external anal sphincter is often used to monitor activity of the striated urethral sphincter. This corresponds to activity of the pelvic floor muscles. Also, the use of video urodynamics can be very helpful in this respect, as contractions of the pelvic floor muscles can actually be seen during the voiding phase (Fig 6 and 7).

In infants and small children, pelvic floor muscle overactivity during voiding (with post-void residuals) is not uncommon: in all probability, it may be a normal developmental feature [79, 81].

Recently, the role of ambulatory urodynamics monitoring (AUM) in children with refractory monosymptomatic nocturnal enuresis has been investigated. AUM may overcome some of the limitations of traditional urodynamics as it allows physiological antegrade filling compared to rapid retrograde filling. AUM was shown to be more accurate compared to conventional urodynamics in evaluating bladder capacity, maximum detrusor pressure, detrusor overactivity, and PVR. For children with refractory monosymptomatic enuresis, AUM may help clarify its aetiology, although further studies validating these findings are required [82].

Conclusion: Video-urodynamic studies in children with non-neurogenic urinary incontinence are only indicated in rare cases (LoE:3)

Recommendation: Video-urodynamic studies should not be routinely performed in the evaluation of the child with non-neurogenic urinary incontinence unless significant additional information is expected from the study. (GR:B)

7.3. Cystoscopy

In the majority of children cystoscopy is not indicated. In boys with therapy resistant LUTS, an abnormal flow pattern, especially in combination with a history of (recurrent) UTI, is suspicious of infra-vesical obstruction such as bladder neck obstruction, urethral valves, syringocele etc. A VCUG may not always show these abnormalities and pressure flow curves may be equivocal [86].

For boys with mild posterior urethral valve type I at the anterior urethral wall, there was an association with refractory urinary incontinence and/or nocturnal enuresis [84]. Hence, for boys presenting with symptoms without success in management, a diagnosis of posterior urethral valve should be considered as cystoscopic ablation of these valves may improve incontinence with low uroflow rates[85].

In girls the flow may be directed upward, indicating an abnormal meatal position or stenosis. A dorsal meatotomy generally solves this problem. It has been postulated that in girls the abnormal direction of the stream triggers the bulbocavernosus reflex resulting in dysfunctional voiding [87].

Conclusion: Cystoscopy is not indicated in the majority of children suffering from urinary incontinence (LE:3)

Recommendation: Cystoscopy should only be performed if there is suspicion of infra-vesical obstruction in boys and in girls with clear anterior deviation of the flow. (Gr: B)

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III. CHILDREN WITH NOCTURNAL ENURESIS

Nocturnal enuresis (bedwetting) is a complex, heterogeneous disorder, with multiple pathogenetic factors treated by multiple disciplines. Progressive unravelling of the complexity has led to different terminology papers (ICI & ICCS, versus DMS IV)[1-7] in the past decades, adding confusion to the topic. This panoply of terminology publications is a major barrier to integrate the existing literature, since different authors are referring to different standardisation papers, even within the same decade. This ICI update largely tries to keep as much as possible the same definitions and structure of the chapter of the previous ICI consultations to avoid further confusion, [8], integrating recent ICCS standardisation papers [5]. The DMS III-IV derived standardisation papers on enuresis should be disregarded because they add more confusion to literature, as they overemphasize certain psychiatric characteristics, and do not adequately consider a multidisciplinary approach[9].

1. DEFINITION

Nocturnal enuresis (NE) is involuntary loss of urine during sleep in children over 5 years of age in the absence of congenital or acquired defects of the central nervous system [5, 10].Parental concern and child distress affect the clinical significance of the problem, as well as the urgency for initiation of therapy [7, 11]. This is certainly time, country and culture dependent ([12, 13]. Most children who wet at night after age five are nowadays considered as patients with enuresis[5]. The decision to initiate a diagnostic and therapeutic approach for an individual with NE has to take into account that several factors including the child's development level may play a role. The age criterion of five is not only epidemiology driven, but reflects the natural course of achieving bladder control[9, 13, 14], as well the maturation of the circadian rhythm of diuresis [15-22]. Epidemiology demonstrates that girls acquire earlier continence than boys, a gender difference that disappears after the age of 10 years [14, 23, 24]. Research on pathophysiologic characteristics has demonstrated that both nocturnal diuresis volume and bladder dysfunction might play a role in this gender difference [15, 16].

Conventionally enuresis patients are classified into

- **Monosymptomatic NE:** bedwetting without daytime symptoms.
- **Non-monosymptomatic or polysymptomatic NE:** describes children not only with both day and nighttime wetting [25], but also, according to the latest ICCS and ICI standardisation, patients with nighttime wetting and daytime symptoms other than daytime incontinence (LUTS) [4, 5, 7].

This subtyping is widely accepted to be essential for appropriate diagnostic and therapeutic approach in first line[26], but suffers from

some limitations. There is a large overlap in pathogenesis between the two archetypes. All patients with NMNE have apparent underlying bladder dysfunction, but this does not exclude other factors involved in pathogenesis of the individual patient. Identifying LUTS is largely dependent on the quality of the intake questionnaire, and the added value of a voiding diary, as well if screening was done during normalized fluid intake or not. This has led to a shift in literature, where 2 decades ago, it was widely accepted that NMNE was only present in a minority of patients; it has become evident in the more recent studies that NMNE has the higher prevalence.

2. SEVERITY

Nocturnal enuretic patients vary in wetting frequency. Variations are even seen per week and per season. Although fifteen percent wet each night, most children wet less frequently [5, 27] . Devlin described the frequency in an Irish population : 33 % < once per week in, 11% once per week and 25 % 2 to 4 times per month [28]. Some children and parents are concerned about an occasional wet bed, while others accept regular wetting. We advise to follow consequently . the ICCS definition to qualify the severity of enuresis as frequent (>4 per week) or infrequent (<4 per week), to homogenize literature and future studies[5]. Severe bedwetters at the age of 5 years have a poor prognosis, with a spontaneous regression-rate of only 50-60% [24]

3. PREVALENCE

Bedwetting is common. Prevalence data on MNE, or MNE versus NMNE are not known since most epidemiologic studies are in fact only delivering data on enuresis, and all fail to be in line with the recent ICCS- ICI definitions on MNE/NMNE. Historical data estimated that in the United Kingdom approximately 750,000 children and young people over 7 years regularly wet their bed and in the United States 5 to 7 million children regularly experience primary NE [29-31]. If prevalence has decreased remains questionable, since only few quality epidemiologic studies are recent [32].The prevalence of bedwetting might vary regionally[33, 34]. We should be aware that self-reporting in online surveys will always underestimate the real problem, because it is considered taboo in the majority of cultures[32, 33].

In China, where parents take children out of diapers earlier, bedwetting seems to resolve more quickly. The proportion of children attaining nocturnal urinary control before age 2 was 7.7%, by age 3 this had increased to 53%, and by age 5 to 93%.The overall prevalence of NE was 4.3%, with a significantly higher prevalence in boys than girls. [35] This suggests that structured awakening and toileting is effective prevention for monosymptomatic NE, even in small children. [23, 24, 36].

Bedwetting becomes less common with advancing age. In the West, 15 per cent of children each year develop nocturnal bladder control[10]. By adulthood, bedwetting is rare. Hirasing et al sampled over 13,000 adults [18-64 years] and found only two decades ago an overall prevalence rate of NE at 0.5%[37]. Of these, 12 percent of men and 29 percent of women had daytime incontinence. Despite persistence of wetting into adulthood, 50 % of men and 35% of the women never seek help for their problem. The enuresis prevalence of 0.5% in otherwise healthy adults in Hirasing's study refers to a largely untreated population. Fifty percent of the men had primary enuresis and had never been consistently dry at night. Assuming a prevalence of enuresis of 8 percent in 7-year-old boys, the risk for an enuretic boy to remain so for the rest of his life is 3 percent.[28, 38, 39] CK Yeung documented that the severe cases had only a spontaneous regression-rate of 50-60 % [36]

Adults with enuresis represent a "hard core" group with worse symptoms[24, 37, 40, 41]. These individuals are likely to have associated LUTS during daytime. Goessaert documented that in patients with long-term follow-up, up to one third of the patients persisted to have symptoms into adulthood, especially in a subgroup with nocturia ($p<0.01$) [42]

4. INHERITANCE

Bedwetting runs in the family of many children who suffer from bedwetting. In one study, a positive family history was found in 94 families (23%) of 411 probands with PNE, including 49% of fathers, 9% of mothers, 6% of both parents, 6% of the siblings and 30% of grandfathers or grandmothers. Among the probands the ratio of male to female was 1.3:1 excluding sex-linked inheritance. Family studies indicated autosomal dominant inheritance in 15%, and autosomal recessive inheritance consistent in 1.5% of families (19). Thus, the mode of inheritance is usually autosomal dominant. If both parents were nocturnal enuretics as child, the risk for their children to be enuretic is between 65 to 85 % .[10, 43] If only one parent has NE the risk is about 45 percent [44], Molecular studies have clearly shown that NE is a complex disease with locus heterogeneity and no clear genotype-phenotype association.

Linkage studies to determine the location of the genetic changes have suggested foci on several genes. Linkage studies to markers on chromosomes 4p, 8q, 12q , 13q and 22s demonstrate both clinical, as well as genetic heterogeneity in nocturnal enuresis [45-49]. So far, there has been no reported association of the genotype with a particular phenotype of enuresis [49]. The weak indications from genetic studies might indicate only autosomal monogenetic inheritance in a minority of cases, where in many families the predisposition might be multifactorial.

In the last decade several associations were found with renal transporters and or circadian rhythm genes[50-53]. The clinical relevance in the idiopathic enuresis patient has still to be demonstrated. Recently a Danish genome-wide association study documented common genetic variants contributing considerably to enuresis, and identified potential risk genes to play a role in sleep, urine production and bladder dysfunction[54]. The majority of genetic studies, were not appropriately subtyping into MNE/NME according to the new ICCS-ICI standardisation papers, so it remains questionable if the genetic findings really concentrate on the MNE group.

5. GENDER AND MONOSYMPTOMATIC NE

Boys suffer nocturnal enuresis more frequently [55]. Surveys of monosymptomatic NE undertaken in Great Britain, Holland, New Zealand and Ireland suggest that the prevalence for boys is 13-19% at 5 years, 15-22% at 7 years, 9-13% at 9 years and 1-2% at 16 years. For girls the prevalence rates are reported to be about half that rate: 9-16% at 5 years, 7-15% at 7 years, 5-10% at 9 years and 1- 2% in the late teenage years [9, 14, 28,56,57].. Although monosymptomatic NE is more common in young boys, by adolescence the incidence in males is the same as in females [24, 58]. This might be explained by gender difference in maturation of the

bladder, but also in renal sensitivity to vasopressin, not only in the elderly but also in children[15] [59].[60, 61]. In adults with nocturia and nocturnal polyuria gender differences are documented,however, in children with nocturnal polyuria this is not the case

6. CLASSIFICATION

6.1. Primary versus secondary nocturnal enuresis

Children who have never been free of bedwetting for 6 months have **primary NE**. **Secondary NE** is the re-emergence of wetting after a period of being dry for at least six months. A birth cohort of 1265 New Zealand children studied over 10 years by Fergusson et al found an increased risk of secondary nocturnal enuresis with age [62] . The proportion of children who developed secondary enuresis was 3.3 percent at 5 years up to 8 percent at 10 years. But all studies failed to document how many patients with secondary enuresis had absence of any daytime LUTS and/or nocturia.

In the past major attention was given to the psychological factors involved in pathogenesis [7, 63]. Secondary NE is associated with a higher incidence of stressful events particularly parental separation, disharmony between parents, birth of a sibling, early separation of the child from parents and psychiatric disturbance in a parent. Patents with secondary NE suffer more behavioural problems [44, 62, 64] [8, 65, 66]. Nowadays authors do consider the psychopathology rather as comorbidities but not as underlying primary pathogenetic factors. Both Jarvelin and Fergusson et al argue that primary and secondary enuresis are similar[62, 67]. They believe the two share a common organic etiological basis.

Other sources of secondary enuresis must be excluded prior to proceeding with treatment for enuresis. These include sleep apnoea from obstructive airway disease, obesity, constipation and infrequent or dysfunctional voiding. Treatment of sleep apnoea from obstructive airway has been shown to improve or eliminate NE in some children following surgery or medical management [68, 69]. Obesity has been associated with nocturnal enuresis both independently [70-74] 4]and in the context of sleep apnoea.[75-78]

6.2. Momo-symptomatic versus non-mono-symptomatic NE

Mono-symptomatic NE refers to those children who report no other bladder storage or voiding problems associated with wetting. Non-mono-symptomatic NE refers to bedwetting, that is associated with overt detrusor overactivity or voiding problems such as urgency, frequency and bladder holding during the day [79, 80]. This definition does not include bladder volume for age, nor OAB only overnight, neither differences in fluid intake.

This classification is widely considered to guide the clinician to the most appropriate treatment intervention in primary care. Many parents are unaware of daytime symptoms when seeking help for bedwetting and when identified these symptoms should be treated prior to intervention for the NE. 10-28% of children with NE have associated daytime wetting, and were considered according to the old ICCS standardisation[1] as NMNE . If so, these children should be considered day and night incontinent. In these cases, night time incontinence is not any longer an isolated phenomenon but part of the symptomatology of day and night time incontinence. These children are more resistant to treatment and more vulnerable to relapse [81]. These boys and girls are more appropriately managed in the context of the primary bladder problem.

7. PATHOPHYSIOLOGY OF MONOSYMPTOMATIC NE

NE stems from a mismatch of functional bladder volume overnight, nocturnal urine output and the ability of the child to arouse during sleep. Night wetting is considered normal/ acceptable until age 5. In the past 2 decades delayed maturation in one or more of the following systems resulting in a lack of stability in bladder function (OAB), or a decreased arginine vasopressin (AVP) release, were considered to play a major role in NE. It remains questionable if this can be considered as a real maturation defect. In desmopressin refractory nocturnal polyuria, more complex pathogenetic mechanisms are involved, such as abnormal circadian rhythm of different renal functions resulting in a relative increased solute excretion during the night [82-86] The third parameter is an inability to wake from sleep due to full bladder sensations [87, 88]. Combinations of all three problems may be present.

A unifying and simplistic concept with important clinical implications, is that NE is caused by a mismatch between nocturnal bladder capacity and the amount of urine produced during the night, combined with delayed or incomplete arousal response to the afferent neurological stimulus of the full bladder (Fig. 1).

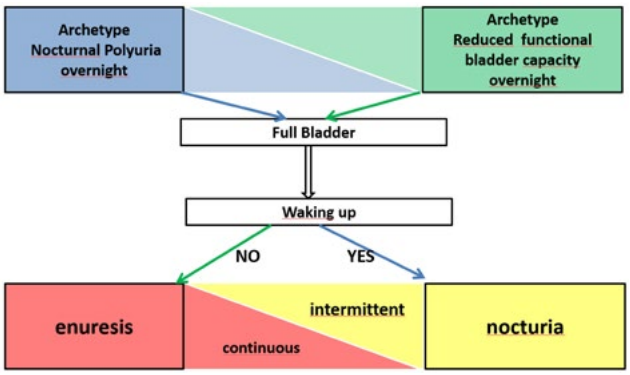

Fig. 1. Basic pathophysiology of NE or nocturia. When the bladder is full because of (relative) polyuria and/or a reduced bladder capacity, the child either wakes up to void (nocturia) or voids while sleeping (NE) . The two archetypes nocturnal polyuria and overactive bladder are well defined, but combination of both factors might be present. Additionally, it is important to stress that the enuresis and/or nocturia might be continuous ore intermittent

7.1. Increased nocturnal urine output

In normal children, the circadian rhythm of urine production results in a nocturnal reduction in diuresis to approximately 50% of daytime levels[55, 89] . In children this is the result of nocturnal release of hormones that regulate free water excretion (arginine vasopressin, (AVP)[90, 91] or solute excretion (angiotensin II and aldosterone, ANP) [92, 93] as well as hemodynamic homeostasis [94] and may result from circadian changes in glomerular filtration [95-97]. In the normal child, this results in increased urine concentration and reduced urine volume during sleep, in presence of decreased osmotic excretion. This is why children who are not enuretic sleep through the night without being wet and do not need to rise to void.

Two thirds of patients with mono-symptomatic NE [5] have been found to have a lack of circadian rhythm of vasopressin, resulting

in high nocturnal urine production, which exceeds bladder capacity [90, 98, 99]. Rittig et .l and Norgaard et al demonstrated abnormalities in the circadian rhythm of AVP secretion resulting in increased nocturnal urine output that exceeded bladder capacity in children with nocturnal enuresis [90,91, 98] .These children make more urine at night, and often overcome their bladder capacity and wet early in the night. Abnormalities can also be intrinsic, related to reduced nocturnal circadian changes in glomerular filtration rate (GFR)[95, 97]) or in sodium and calcium excretion [85, 100-103].

Detection of low plasma vasopressin levels, GFR assessments or specific sodium and calcium excretion are too difficult to measure in first line. Instead, we look for clinical signs of low vasopressin during the assessment interview. Weighing the diapers and adding the first morning void provides the total nocturnal urine output. If this total exceeds the child's functional bladder capacity this may indicate nocturnal polyuria. Nocturnal polyuria is defined as nocturnal diuresis >130% of expected bladder capacity for age, which is based on expert opinion. [104] However, the diuresis volume that might predict desmopressin response has been suggested to be >100% EBV (Expected Bladder Volume for age)[105]. Nocturnal urine output varies appreciably from night to night [61, 106], but seems larger in children with NE who respond best to desmopressin (dDAVP)[107].

By the time the child becomes an adolescent, the circadian rhythm is less prominent. In adolescents and adults with nocturnal enuresis, there is no diurnal rhythm of plasma vasopressin concentration. The changes in urine production at night occur from a decrease in the urinary sodium excretion that is not due to differences in concentration of AVP but due to a lack of sensitivity to AVP[89, 109] with resultant increased urine output[82, 110]

There may be a small sub-group of children with impaired renal sensitivity to vasopressin or desmopressin [83, 106, 111]. Recent work by Devitt et al suggests that 18 percent of children have 'normal' levels of plasma vasopressin release but remain enuretic [99, 112]. These children all failed to respond to a therapeutic dosage of desmopressin. This finding could indicate renal insensitivity to vasopressin but could also be indicative of detrusor overactivity or a small functional bladder capacity. Total urine output during the night could be helpful in differentiating between the two conditions. The archetype of patients with NE and increased nocturnal urine output generally has a favourable response to dDAVP if functional bladder capacity is normal. [4, 105, 107,113]. The archetypical patient with OAB will reduce fluid intake as a compensatory mechanism and has low diuresis volumes overnight. The combination of both also exists.

7.2. Detrusor overactivity during the night

The detrusor needs to be relaxed and accommodate to increasing volumes during filling to function appropriately. Detrusor overactivity usually causes small voided volumes resulting in a decreased functional bladder capacity [114-118].

Functional bladder capacity – defined as the largest daytime void on a frequency- volume (F/V) chart, after excluding the first morning void, may give a reasonably accurate assessment of daytime functional bladder capacity (FBC). [21] Reduced functional bladder capacity, when below 70% of the predicted FBC for age, is likely to result in a poor response to dDAVP treatment [105, 119]. Daytime bladder capacity is smaller than night time capacity in children without NE[120] .

The pattern may be different at night. Yeung et al reported that 44 percent of treatment failures [with desmopressin or the enuresis alarm] have normal daytime bladder function but marked detrusor overactivity during sleep resulting in enuresis [121]. Almost none of these children had nocturnal polyuria. Ultrasound studies of the bladder furthermore revealed an increased bladder wall thickness in these children[122,123]

Increased bladder wall thickness and bladder volume are predictive factors for the response to therapy in children with primary nocturnal enuresis. In one study, Yeung, et al[123], correlated ultrasound measured parameters and urodynamic findings. All the children with a normal bladder volume and bladder wall thickness index (BWWI%) either had a complete or good response to conventional treatment for nocturnal enuresis, whereas 62% of those with an index less than 70 % did not respond to treatment. The bladder dysfunction persisted in the 63% of children who had partial or no response to treatment. What this means is that ultrasound measured bladder parameters may segregate children, prior to management of primary nocturnal enuresis, into groups that have a favourable outcome and those that don't, following conventional treatment. These studies will become more and more important in helping to predict response of various treatment regiments in the future.

This approach may be even more important in adults with refractory monosymptomatic nocturnal enuresis. Bower, et al. [124] found that in 56 consecutive adolescents and adults compared with 293 normal adults, there were significantly higher childhood scores of urgency, frequency, urgency incontinence, infrequent voiding and small volume voids than their normal non-enuretic counterparts. This suggests that adolescents and adults with persistent nocturnal enuresis may have a more significant bladder component, particularly since the majority of patients with adult type nocturnal enuresis do not seem to exhibit the nocturnal polyuria problem seen more commonly in the smaller children.

7.3. Lack of arousal

The fundamental mechanism resulting in nocturia or NE is that the bladder fills to its capacity during sleep and needs to empty (figure 1). Bladder fullness is due to nocturnal polyuria and/or a reduction of the bladder capacity due to detrusor overactivity during sleep. Arousability differentiates patients with diuresis/ bladder volume mismatch into enuresis versus nocturia, but does not reflect underlying/ associated sleep disturbances or CNS disfunctions.

From an adult patient point of view these factors do not fully explain why the enuretic child does not wake up during the night to the sensation of a full or contracting bladder. Regardless of whether the child has detrusor overactivity or nocturnal polyuria, the enuresis event results from the child's inability to awaken from sleep to empty prior to the wetting episode. However it is important to stress that the majority of children eventually become dry, without nocturia, and this might indicate that nocturia is a defence against diuresis/mismatch, but is only present in children with high arousability. For decades enuresis was considered as synonymous with deep sleep, and lack of arousal. There was a widely held belief amongst parents and some clinicians that enuretics are deep sleepers. Many of the children exposed to alarm therapy sleep through the alarm while family members awaken. Neveus reviewed by questionnaire study in 1413 schoolchildren between the ages of six and ten and noted that enuresis was associated with subjectively high threshold arousal and significant confusion upon awakening from sleep [125]. Wolfish in a study of 15 enuretic and 18 control boys and girls found that enuretics wet most frequently during the first two-thirds of the night and that arousal attempts were less successful in

enuretics than in normals [126, 127]. This might explain why the most heavily endorsed view of both children and parents, regarding the aetiology of NE is a belief in deep sleep[128] . Recent findings suggest that the issue of decreased arousability is not the same as deep sleep[129-131], and that many patients have disrupted sleep, rather than a deep sleep [129, 130, 132-136].

7.4. Comorbidities

There is an increasing interest in comorbidities, not only coinciding with enuresis, but with common pathways in pathogenesis and/or interfering with therapy response.

7.4.1. Sleep

Sleep is more than arousal, and there is increasing evidence that sleep disturbances alone , or in combination with disrupted homeostasis play a role in the pathogenesis of nocturnal enuresis.

Enuretic episodes occur during all stages of sleep in proportion to the amount of time spent in that stage and appear to occur independent of sleep stage but occur when the bladder is at a volume equivalent to the maximal daytime functional capacity[137-140] . Bedwetting children have normal sleep but are unable to suppress nocturnal detrusor contractions or awaken in response to them or to bladder fullness.

Waking up becomes easier as the night progresses. Several authors have found that children with NE are also more likely to wet in the first third of the night, often in the first two hours following sleep [126, 127, 139, 141-145], Thus the point of bladder fullness for most enuretic children coincides with a time of night where they find it most difficult to wake from sleep, and not always when there is already an apparent diuresis / bladder mismatch . Maybe the high filling rate (diuresis rate) is more important than the absolute diuresis volume overnight as a reason to induce OAB overnight.[20]

Recently it was documented that enuretic children did not exhibit deep sleep, but rather a disturbed sleep with increased PLMS, cortical arousals, and awakenings [130, 133-136] both in patients with refractory enuresis as in children with monosymptomatic + nocturnal polyuria.. Polysomnography studies documented a significant difference in PLMS index, arousal index, and awakening index compared with healthy control subjects. The presence of sleep fragmentation does not exclude a high sleep pressure or high arousal threshold. The role of sleep fragmentation in children with NE was earlier emphasised using sleep actigraphy [146]. There is evidence that superficial sleep, was coinciding with neurocognitive dysfunctions[147-149], thereby undermining earlier opinions that sleep patterns of children with NE are not different from controls. [133, 136] . These neurocognitive dysfunctions were already documented in the past. In patients with enuresis treatment of enuresis resulted in amelioration of sleep quality and neurocognitive functioning[136].

Obstructive airway syndrome (OSAS) causes nocturnal polyuria in both children and adults, eventually resulting in enuresis[75, 150]. The prevalence of this NE subtype in patients primarily presenting for enuresis is not known, but the anti-enuretic response to OSAS therapy suggests that in refractory cases this might be considered[68, 75-78, 151, 152]. However there seems to be no indication for this therapy in children without clinical apparent OSAS.

In conclusion, albeit there is little doubt that sleep and/or arousal plays a role in the pathophysiology of NE the clinical relevance and possible implications are still unclear and so far sleep investigation is not part of the routine evaluation of enuretic children.

Conclusion: The clinical implication of sleep investigation in the screening of children with NE is not yet proven in prospective clinical trials. In children with refractory NE investigation of sleep is advocated (LoE: 3)

Recommendation: Investigation of sleep disorders is recommended in children with refractory NE (GR:C)

7.4.2. Neurocognitive comorbidities

Several neurocognitive comorbidities, coincide with nocturnal enuresis and might play a role, not only in pathogenesis but certainly in therapy resistance, such as psychological/behavioural problems, attention deficit disorders, and neurocognitive dysfunctions.

Psychological comorbidity among children with functional urinary incontinence is high: 20-30% of children with nocturnal enuresis (NE), 20-40% of children with daytime urinary incontinence (DUI), and 30-50% of children with fecal incontinence (FI) have clinically relevant comorbid disorders[8, 153-165] Both internalizing and externalizing characteristics are represented [162, 166-168]. The best documented comorbidity conditions are attention deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) [169]. Attention deficit disorders coincide with higher prevalence of enuresis (both MNE and NMNE), where the prevalence of ADHD in the enuresis population is up to 4 times higher than the background population[170]. The association of abnormal prepulse inhibition (Startle reflex) in both ADHD and enuresis patients, might suggest a common central nervous pathogenic pathway but is far from fully understood.[171-174] The observation that interpeak latencies of the brainstem evoked potentials were increased in children with nocturnal enuresis, suggests a maturational deficit of the brainstem present in children with nocturnal enuresis. Differences in visually evoked potential latencies might point to a reason behind functional cortical differences in children with a family history of nocturnal enuresis [175]. Freitag's study would suggest that a maturational effect is present;[176] however, overnight studies in enuretic children with simultaneous sleep electroencephalographic and cystometry have revealed marked detrusor overactivity, only occurring after sleep at night and not during wakeful periods during the day [176] Because this pattern has not been observed in normal non-enuretic subjects, even during the newborn period, one may hypothesize that this could be due to a small neurologic lesion affecting a tiny area in the vicinity of the pontine micturition centre, the posterior hypothalamus (responsible for secretion of antidiuretic hormone) or the locus coeruleus which may be the cortical arousal centre [177,178]

Baeyens et al.[171] documented significant differences between children with enuresis and control groups, including the startled eye blink reflex which improved with maturation but did not seem to correlate with resolution of enuresis.

But these research lines were stopped and replaced by FMRI-imaging studies[179-181], without conclusive observations at this moment.

7.4.3. Constipation

The coexistence of LUT symptoms and functional constipation and/or faecal incontinence in children is not uncommon and was previously identified as 'Dysfunctional Elimination Syndrome' (DES) [164-166,182-184] and 'Bladder and Bowel Dysfunction' (BBD) in the ICCS paper[182]. Although the association with dysfunctional voiding, decreased voiding frequency and underactivity is obvious, there is also a clear comorbidity between bladder overactivity (urge), increased voiding frequency, bladder underactivity and con-

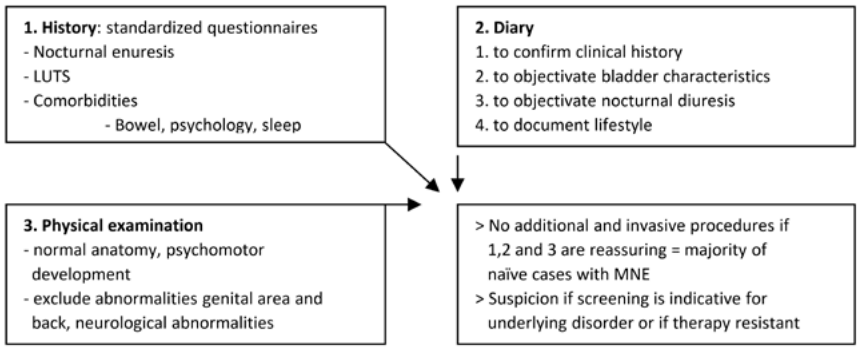

Fig. 2 : Schematic work-up in patients presenting with night-time wetting

stipation. It is well-established in clinical practice that treatment of defecation problems in children with BBD enhances successful management of lower urinary tract disturbances such as daytime urinary incontinence (DUI), enuresis, and urinary tract infections (UTIs) [66, 183, 185, 186]. Treatment of the bowel dysfunction often results in amelioration of the voiding disorder and should be first line treatment[187]. It is less obvious from the literature if there is a difference in enuresis response between MNE, and patients with OAB with and without dysfunctional voiding, since in the majority of studies the new standardisations were not used.

Conclusion: treatment of constipation is effective in the therapy of NE (LoE:3)

Recommendation: constipation should be treated primarily in children with NE.(GR:C)

7.4.4. Mentally and motor disabled

Enuresis has a higher prevalence in mentally and motor disabled patients. Von Gontard studied a variety of syndromes and subpopulations[155, 158, 161, 188-193]. Such comorbidities might have common pathways in the pathogenesis of enuresis including abnormalities of circadian rhythms, sleep disorders, and bladder dysfunction, and might predispose to therapy resistance. Still initial diagnostic and therapeutic approach does not differ from normal developed children suffering enuresis. Many of these children have underlying or associated bladder dysfunctions , but some may suffer classical nocturnal enuresis . As maturation level and cooperation is retarded, initiation of appropriate therapy might be postponed [19].

8. MANAGEMENT OF NOCTURNAL ENURESIS

The age at which the child and his or her parent begins to be concerned about bedwetting varies. Hjalmas, et al. noted that, “for successful treatment of nocturnal enuresis, the child must be brought to the physician by the parents who are concerned and the physician must have the necessary knowledge about the condition and be motivated to start treatment” [55] . In order to fulfil the requirements, parents, teachers, and nurses in primary care need to understand nocturnal enuresis and be ready to treat the child, regardless of age according EBM based guidelines, and not based on the often misleading information found on the internet. Demystification remains a big hurdle not only for patients/parents but also for caregivers in primary care. In such settings, it is important to ask the right questions and be compliant with LUTS questionnaires and diaries.

Nocturnal enuresis is thought of as a social problem and less as a medical problem. Since the majority of children stop wetting as they mature and as there are no persisting health problems associated with enuresis, there is a tendency for many practitioners to take a “wait and see” approach. Too many parents and medical caregivers underestimate the problem for the child. [194] .

The actual timing of treatment for nocturnal enuresis may vary depending on the needs of the child and the parent. It is essential that both the child and his or her parents understand bedwetting pathophysiology and treatment philosophy. The clinician should give the child general advice on proper dietary and fluid behaviours, as well as instructions to void regularly during the day, abstain from drinking too much during the late afternoon and evening and have relaxed routines at bedtime. The clinician should stress that NE is common and usually represents a delay in maturation without any psychopathological undertones. Up to 19 percent of children will become dry within 8 weeks following the initial consultation without any further treatment besides good counselling [55, 195, 196].

8.1. Evaluation and intake

This paragraph has some overlap with the previous chapter, that was drafted for all LUTS symptoms, but we concentrate here on patients primarily consulting for bedwetting and not for daytime incontinence. In the past decades several attempts have been made to standardize the qualitative intake of patients, although there has been limited uptake into primary care. Hjalmas recommended a careful history which we will summarize in these next few paragraphs. (Fig 2, Table 1). This approach, which has been recommended by the International Children’s Continence Society, provides an excellent guide toward the taking of a history for a child with nocturnal enuresis, with few adaptations over time[4, 55, 197-199].

8.1.1. Frequency volume chart (FVC)

Parents are asked to record a two-day three-night record. This includes recording the child’s fluid intake and urine output, frequency of micturition and the frequency and pattern of voiding. The largest single micturition is considered the functional bladder capacity. This chart can be performed beginning on a Friday evening and concluding on Sunday on any weekend[4].

8.1.2. History: Symptoms of nocturnal enuresis[4, 80, 199].

A careful history should include questions about the age of onset of nocturnal enuresis, length and circumstances of dry spells, number and time of episodes of nocturnal enuresis or nocturia, presence of

Table 1. Clinical management tool for diagnostic workup of nocturnal enuresis

	history	diary
Enuresis nocturna		
night time episodes only	Y/N n = /w	Y/N n = /w
nocturia	Y/N n = /w	Y/N n = /w
Exclusion daytime symptoms		
Daytime incontinence: timing before or after void? Very wet pants? Frequency of leakage, Intermittent versus continuous leakage	Y/N Y/N Y/N Y/N n = /w Interm /cont.	Y/N Y/N Y/N Y/N n = /w Interm /cont.
Urgency	Y/N	
Frequency >8 or < 3 x/day	 Y/N Y/N	 Y/N Y/N
Voiding postponement	Y/N	Y/N
Interrupted stream	Y/N	Y/N
Urinary tract infections	Y/N	Y/N
History uropathy	Y/N	Y/N
Comorbidities		
Sleep disorders: restless legs, arousals, sleepwalking, snoring	Y/N	Y/N
Psychological comorbidity	Y/N	
ADHD, ADD, autism	Y/N	
Mentally and motoric disabled	Y/N	
Constipation, soiling	Y/N	Y/N
Lifestyle		
Sleep hygiene: Hours + timing of sleep + waking up Voiding prior to bedtime Once in bed immediately sleeping	 / Y/N Y/N	 / Y/N Y/N
Fluid intake Enough, spread over the day No drinking before sleeping time or overnight	Y/N Y/N Y/N	Y/N Y/N Y/N

daytime voiding symptoms or urinary tract infection, posture while voiding, daytime and evening fluid intake, sleep habits, frequency and consistency of bowel movements and psychosocial situation. One must establish whether or not symptoms represent primary or secondary nocturnal enuresis. It is critical to search for new psychological problems that might cause secondary nocturnal enuresis, particularly when the child presents with nocturnal enuresis after a prolonged period of dryness. The personality of the child, family situation, school environment, and presence of alternate care givers might have an appreciable impact on voiding habits and will influence management options[55] . Children may drink large volumes of fluid in the hours before sleep and this may result in nocturnal enuresis or nocturia.

It is helpful to determine the number of hours of sleep and to compare this to standard charts of average duration of sleep by age. Morning fatigue may be the result of obstructive sleep apnoea or restless legs syndrome. Other symptoms of sleep apnoea include mouth breathing, snoring, and restless sleep [4, 55]. More attention should be given to sleep hygiene: Is the child drinking, eating prior to sleep?. Is the child voiding just before bedtime? Is the light turned off immediately after going to bed? Is the child afraid to go to the toilet alone at night?

It is important to rule out symptoms of anatomical or physiologic urologic conditions that may lead to nocturnal enuresis. Many of these conditions are covered in other parts of this section, and include a failure to store urine or failure to empty urine. Storage symptoms include increased frequency, urgency, and urgency incontinence including squatting behaviour, daytime incontinence and the sensation or need to void again. The clinician must carefully assess daytime wetting, particularly in older children. In many cases, the child may hide these symptoms from the clinician and the family.

Children void four to seven times a day or about every two to three hours[4, 105, 200] . If the child is voiding significantly more frequently than eight or more times a day, this may suggest incomplete emptying or overactive bladder symptoms. Urgency is present in many children and posturing, including squeezing or crossing the legs, squirming while standing or sitting, or physically compressing

the genital area with a hand are all suggestive of overactive bladder due to detrusor overactivity which may or may not be associated with dysfunctional voiding. Other causes include urinary tract infection, polyuria from diabetes mellitus or diabetes insipidus, which can also cause more frequent voiding [55]. Treatment for these symptoms is covered in other sections within this chapter.

Additional symptoms during the daytime include continuous dribbling between voids that can come from an ectopic ureter bypassing sphincter mechanisms, or from failing to empty the bladder or from sphincter incompetence. Also continuous leakage can result from neurologic causes or anatomical causes such as epispadias, or a closed bladder exstrophy or urogenital sinus.

Children may have incomplete emptying from true dysfunctional voiding which results from the sphincter or pelvic floor contracting at the same time as the detrusor contracts during micturition. In addition, detrusor underactivity may result from neuropathy from diabetes mellitus and in some cases conditions such as prune belly syndrome will result in detrusor underactivity. Lastly, urethral strictures may result in incontinence due to detrusor overactivity with poor bladder emptying. Boys with posterior urethral valves or Cobb's collar may also have incomplete emptying. The clinician should be alert for symptoms of constipation and faecal incontinence[201]. It is a common misconception that if a child is stooling once per day then he or she is not constipated. In fact, the most specific symptom of constipation is the infrequent or painful passage of small, hard pellet-like stools. Faecal incontinence may also be present, the principal sign of this being faecal material in the underwear. Excessive stool retention may result in bladder dysfunction. In these cases[202] , this may result in increased urethral sphincter and pelvic floor activity and explain the association of voiding dysfunction with incomplete voiding. Treatment of constipation may result in improvement in enuresis [187].

Several guidelines have tried to standardize clinical management tools (CMT). All CMTs have their benefits and their limitations. It is always a balance between feasibility (short) and optimization (long CMT's). The one described in the previous ICI-consultancy is still up to date to differentiate NMNE from MNE. (table 1.)

8.1.3. Physical examination

Anatomic and behavioural causes for enuresis may be identified through a careful physical examination. Evidence of improper gait, spinal deformities, and foot abnormalities including asymmetry, high-arched feet, or hammer toes are signs of sacral neuropathy. Physical signs of occult spinal abnormalities such as dimples, tufts of hair, skin discoloration, lipoma, asymmetrical buttocks and gluteal clefts are also important. A careful abdominal examination with particular emphasis on the left lower quadrant may identify the colon full of firm stool. In most cases, a rectal examination is not performed but in some cases this may also be indicated. Occult fecal impaction, poor perineal sensation and reduced anal sphincter tone can be indicative of neuropathy.

In boys, marked narrowing of the urethral meatus (when the meatal lips are separated and no mucosa is seen), must be identified and carefully noted. If these signs are present, the boy should be asked to void so the clinician can witness and record the flow rate and residual urine. Narrowed or displaced urinary stream is suggestive of meatal stenosis.

In girls, the introitus should be identified for the position of the urethra and the existence of labial adhesions and meatal web, which can be a cause of vaginal voiding. Evidence of wetting or irritation of the labia or vagina should be identified, as this could be suggestive of post-void dribbling or incomplete emptying with incontinence due to either detrusor overactivity or sphincter weakness [5, 182].

8.1.4. Laboratory examination

There is very little laboratory examination that is required in patients with nocturnal enuresis other than a urinalysis to rule out UTI and evidence of glucosuria and a urine culture if the urinalysis is suggestive of infection[55].

8.1.5. Urodynamics and imaging

Urodynamics and imaging have no place in the initial intake and therapeutic approach of a child with monosymptomatic nocturnal enuresis. If there is any suggestion, however, that daytime wetting is occurring, a full evaluation of the daytime problem should precede the evaluation for nocturnal enuresis.(see later discussion)

Conclusion: Urodynamics and imaging are not indicated in the diagnostic evaluation of monosymptomatic nocturnal enuresis (LoE:3)

Recommendation: Urodynamics and imaging are not recommended in the diagnostic evaluation of monosymptomatic nocturnal enuresis (GR:B)

9. THERAPY

The management of NE depends on:

- the child's motivation to participate in treatment
- exclusion of confounding psychosocial factors
- providing information and instruction about daily habits, underlining the importance of having regular fluid intake, regular voiding's, and relaxed routines at bedtime
- regular review of the new intervention

The therapist should convey a sense of understanding and compassion to both the child and the family. Education about the problem and a realistic discussion about the prognosis will help instil confidence in the treatment offered which may improve both compliance and outcome [78,107, 203-205]

9.1. Evidence based recommendations for treatment

First line treatment and preliminary steps: primary and secondary forms of nocturnal enuresis are treated the same. If faecal incontinence, constipation or daytime wetting are present, they should be treated first [182, 187, 202].

Urotherapy: All guidelines advocate urotherapy (for definition see chapter 4) as first line therapy, although the evidence in children with NMNE is low, and has been recently questioned[199, 206]. (Level of evidence: 4). However it remains rational to initially attempt to normalise the child's life-style including healthy food intake, normalized intake of healthy fluid well spread during the day , and normal toilet habits as well as initially provide urotherapy-advice.

Treatment modalities such as lifting (waking up the child during the night to void), fluid restriction, dry-bed training, retention control training, psychotherapy, acupuncture, and hypnosis are not currently recommended because of insufficient data in the literature [93-100] However, non-invasive behavioural modifications such as resisting over-hydration in the evening is an appropriate recommendation at the initiation of therapy. Normal fluid intake, well spread over the day should be advocated, to reduce osmotic ex-

cretion overnight [85]. The child must void before going to bed. Excessive protein or sodium intake should be avoided in the evening, since it will result in osmotic diuresis [85, 100, 101, 103] .

During the day the child should be instructed to void regularly, not to hold urine until the last minute, to relax during voiding and to take time to completely empty the bladder. If deemed important by the parents, a letter should be sent to the school to explain this.

Timing of treatment for the child who wets is dependent on the family's desire and the child's desire. As a good rule of thumb, children should be six to eight years of age at the initiation of therapy. Some children and families, however, may want to delay the initiation of therapy until later. Others may be ready closer to age six. It is important for the parents to know that relapses can occur. The successful treatment of children with nocturnal enuresis has a foundation consisting of realistic expectations and a motivated family [55] .

Before starting treatment, a "baseline" meeting with counselling, provision of information, positive reinforcement including reassurance that 15% of children with mild enuresis ("mild" defined as NE <4/7d per week) resolve each year, and assessing and optimizing motivation should occur first. Children are asked to fill out a calendar or chart depicting the wet and dry nights. Children became significantly drier in two non-randomized trials associated with fewer wet nights simply by focusing them more on record keeping and true reward charts [146].

Realistic expectations also include the next steps of EBM (Evidence Based Medicine), the alarm and desmopressin, where relapse free success-rates after 1 year often do not exceed 60%.

Conclusion: Urotherapy is effective in the treatment of NE (LoE:3)

Recommendation: Urotherapy is recommended in the treatment of NE (GR:C)

9.2. Alarm

The underlying mechanism of action of the alarm as a treatment for MNE remains uncertain[207],. It is presumed to cure NE by conditioning arousal and/or by reducing nocturnal bladder volume.[209, 210] [211]Furthermore, historical interpretation of the data in the literature is difficult as the new ICCS definitions, do not often allow differentiation of MNE from NMNE, according to the new standards [1, 5, 55, 104, 208].

The enuresis alarm is the most effective means of facilitating arousal from sleep and remains the most effective way to treat NE In unselected or poorly subtyped patients with enuresis [3, 212-214]. There is an average success rate of nearly 68% with efficacy increasing with the duration of therapy. Relapse rates in the 6 month period following treatment are on the order of 15 - 30 %, which is significantly lower than that for desmopressin in populations not subtyped for +/- LUTS and/or nocturnal polyuria. Alarm therapy has been shown in several reports and meta-analysis to have a 43 % lasting cure rate[34, 215-217] . .

Better results occur with optimal motivation of the child and family and higher frequency of wet nights. Reduced efficacy is associated with the lack of concern shown by the child, lack of supervision, inconsistent use, family stress, abnormal scores on behaviour system checklists, a psychiatric disorder of the child, failure to awaken in response to the alarm, unsatisfactory housing conditions and more than one wetting episode per night. Enuresis alarms require several months of continuous use and are, therefore, unsuitable for some families [4, 218, 219], because of the large burden associated with their use . Alarm therapy requires high motivation, high cooperation of the child and his family.

For optimal results, alarm therapy should be individualized; it requires a motivated family and child with significant commitment to time and effort. The impact on other family members should be considered. In some families, alarm therapy may wake other members of the family and may increase parental annoyance and place a child at increased risk for physical or emotional abuse. The caregiver and family should be aware of the burden if the alarm is activated early in the night or several times/night, especially because these are predictive to be parameters of resistance. Close follow-up is important to sustain motivation, troubleshoot technical problems and otherwise monitor the therapy [55], and identify the burden..

The exact mechanisms underlying the efficacy of alarm treatment are not known. The effects are not due to classical conditioning as stimulus awakening occurs after and not before wetting. Instead it is clearly an operant type of behavioural approach, i.e. a learning program with positive reinforcement that includes aversive elements. Dryness is reached either by waking up leading to "nocturia" in 35% of children or by sleeping through the night with a full bladder in 65%. Body worn (vibrating) alarms are at least as effective as bedside alarms [146]. The family should continue alarm therapy for at least 14 consecutive dry nights – or a maximum of 16 weeks before discarding it as ineffective[4] Compliance remains a problem and dropout rates are rarely disclosed in reported studies. Proper guidance and instructions are mandatory.

The key to success is not the stimulus intensity of the alarm triggering, but the child's preparedness to awake and respond to the signal. Comparison of the different types of alarms did not show significantly different outcomes. In general it can be stated that alarm treatment is more effective than other forms of treatment and the lasting cure rate is about twice as high .

In some cases, alarm therapy can be enhanced using the alarm in addition to other behavioural components. Overlearning (giving extra fluids at bedtime after successfully becoming dry using an alarm) and avoiding penalties may further reduce the relapse rate. [212,220, 221]

Conclusion: alarm therapy is an effective first line treatment in NE (LoE:1)

Recommendation: alarm therapy is highly recommended in children with NE (GR:A)

9.3. Dry bed training

Dry bed training is a package of behavioural procedures used in conjunction with the enuresis alarm first described by Azrin et al[222, 223] . It incorporates:

- the enuresis alarm
- cleanliness training (encouraging the child to take responsibility for removing of wet night clothes and sheets, re-making the bed and resetting the alarm),
- waking schedules – to ease arousability from sleep as described above and involving:

1. For the first night, waking the child each hour, praising a dry bed, encouraging the child to decide at the toilet door whether

he or she needs to void, and on returning to bed the child is encouraged to have a further drink
2. On the second night the child is awakened and taken to the toilet 3 hours after going to sleep. For each dry night, the waking time is advanced by 30 minutes. If the child is wet on any night, the waking time stays at the time of the previous evening. The waking schedule is restarted if the child begins wetting twice or more in any week, stating again 3 hours after sleep.

High success rates and low drop out rates have been reported although relapse rates are not different from enuresis alarm treatment alone [224, 225]. Modifications are advocated to remove some of the more punitive elements of the programme. Success-rates with group administered dry bed training is 80%. Girls respond better than boys[226] . Factors not related to success were the child's age, bedwetting frequency, secondary enuresis or family history. In another study a positive effect on behavioural problems was noted[227] .

Conclusion: Dry bed training is effective in the treatment of NE (LoE:2)

Recommendation: Dry bed training is recommended in the treatment of NE (Gr:C)

9.4. Arousal training

Arousal training entails reinforcing appropriate behaviour [waking and toileting] in response to alarm triggering. The aim is to reinforce the child's rapid response to the alarm triggering, not on 'learning to keep the bed dry'[228].

The instructions involve:
- setting up the alarm before sleep
- when the alarm is triggered the child must respond by turning it off within 3 minutes
- the child completes voiding in the toilet, returns to bed and resets the alarm
- when the child reacts in this fashion he is rewarded with 2 stickers
- when the child fails to respond in this way the child pays back one sticker

The initial study by Van London demonstrated significantly higher success-rates than in single alarm therapy., The authors conclude that arousal training is 'definitely the treatment of choice for enuretic children between 6 and 12 years'. Compared with other studies, and considering the experience of daily practice, one may question the very high success rate in this particular group of unselected patients. The study was not confirmed in study populations where categorisation into MNE and NMNE, according to the new standardisation, was performed.

Conclusion: Arousal training is effective in the treatment of NE (LoE:3)

Recommendation: Arousal training is recommended in the treatment of NE (GR:C)

9.5. Pharmacological therapy

Based on the three main causes of enuresis, namely nocturnal polyuria, detrusor overactivity, and a disorder of arousal, pharmacological treatment can be directed towards each of these three areas.

9.5.1. Desmopressin therapy [107, 229-239]

Arginine vasopressin (AVP) or antidiuretic hormone (ADH) is normally produced in the hypothalamus and released in the pituitary in response to hyperosmolality or hypovolemic conditions. Vasopressin acts on the collecting ducts and distal tubules to enhance water absorption. AVP, by virtue of an independent vasoconstrictor effect is also a potent vasopressor. Desmopressin (or dDAVP) is an analogue of vasopressin created by deaminating the cystine residue at position 1 and substituting D-arginine for L -arginine at position 8. These changes result in significantly increased antidiuretic activity but loss of vasopressor activity. The PK half-life of Desmopressin is 1.5 to 3.5 hours, but the duration of action is longer, and there is a certain hysteresis time to activity [236, 240-242]. In the majority of children with monosymptomatic nocturnal enuresis, the normal circadian variation in urine production is disturbed if vasopressin is absent resuting in a rise in nocturnal urine production[91]. In these cases, dDAVP would seem to be particularly appropriate.

Several formulations are on the market,: rhino nasal solution, desmopressin nasal spray, desmopressin oral tablet and the desmopressin oral lyophilizate (sublingual), all characterized by rather low bioavailability, with large intra-individual variability (0.08-0.16% in adults). Only the last 2 formulations (oral tablets and lyophilized) are labelled for the indication of enuresis in children [235, 236].The intranasal form is no longer recommended for nocturnal enuresis, because of concern for water-intoxication, due to unpredictable nasal reabsorption in children.

The low bioavailability is largely related to the peptide structure, making oral /intestinal reabsorption very difficult, although the pharmacodynamic effects remain very predictable, and when used as directed, is rarely associated with serious adverse effects. It is available for the indication of enuresis as a tablet (dosage, 0.1–0.6 mg) or a fast-melting oral lyophilizate (Melt- dosage, 120–240 µg) [243]. The latter is a recommended formulation for all children and is preferred by children from 6 to 12 years [236, 244-246]. It is not affected by nasal congestion or gastrointestinal transit and does not require fluid intake. Since tablets require up to 200 ml of fluid intake, which is ~25% of a 7-year-old's bladder capacity, the Melt formulation is more suited to the antidiuretic indication of desmopressin. Good pharmacokinetic and -dynamic data are available for the Melt and its dosing in children with enuresis [236, 247][58].

Recently PK/PD studies in young children documented different PK/PD characteristics in children and that size-dependent dosing might be necessary in younger age groups.[240]

Some patients have a delayed response and a small group of children who do not respond to desmopressin in ordinary dosages will become dry when the dose is increased. It is recommended that such off label dosing be limited to expert centres [248, 249]. Desmopressin may be particularly beneficial in the child with limited numbers of wet episodes per week. Some clinicians suggest the administration of desmopressin in particular situations such as added security on special nights during a sleepover, etc. However, there is no sound medical evidence for this practice as intermittent regimens have never been proven to be beneficial. [105]

Children with nocturnal polyuria respond the best to desmopressin [82, 105, 250]. ICCS defines nocturnal polyuria >130% of expected bladder capacity for age, but the DRIP study showed that diuresis lower than 60% of EBV is likely desmopressin resistant, where diuresis >100% of EBV has a 60% response-rate[5, 105, 136].[245]

The efficacy of desmopressin in the treatment of enuresis is well documented[83, 231, 232, 251]. In a Cochrane Library analysis 17 controlled trials all showed superiority of desmopressin compared to placebo regardless of the route of administration [233, 252] Up to 70% of the MNE enuresis population might have full or partial response to the drug [136]. The response to desmopressin is highly dependent on factors such as nocturnal urine production and bladder capacity. The few studies that have tried to compare different doses of the drug reveal comparable efficacies[230, 253-255] Several key issues should be taken in consideration when the drug is prescribed. 200 to 400 mg tablets are considered bioequivalent to 120-240 µg melt and are the therapeutic range for children between with MNE from 7 to 18 years. The recently documented size relationship to dosing could mean that higher doses may be needed in larger children [240, 245]

Optimal response is expected if desmopressin is taken 1 h before the last void before bedtime to allow for the timely enhanced concentration of urine to occur. Fluid intake should be reduced from 1 h before desmopressin administration and for 8 h subsequently to encourage optimal concentrating capacity and treatment response, as well as to reduce the risk of hyponatremia/ water intoxication[107, 233, 236, 244]

Desmopressin is only effective on the night of administration; therefore, it must be taken on a daily basis. Full adherence is required to avoid wet nights. Desmopressin acts immediately, but in our expert opinion, the initial duration of treatment should be for 2–6 weeks, to ascertain its anti-enuretic effect [4]. If a sufficient degree of improvement is experienced, treatment can be continued for an additional 3 months—where appropriate. Country-specific regulations regarding treatment breaks should be followed. If patients are dry on treatment after this initial period, breaks are recommended to ascertain whether the problem has resolved and therapy is no longer necessary. If the child does not achieve complete dryness, or if wetting resumes once treatment is withdrawn, it should be continued or resumed. There is some evidence that structured withdrawal of medication may reduce relapse rates following its discontinuation[256, 257] . Desmopressin is well tolerated, but clinicians should be aware that it is a potent antidiuretic and families must be educated regarding the rare possibility of patients developing hyponatremia/water intoxication with symptoms including headache, nausea, and vomiting [235]. Self-titration of medication should be avoided (opinion).

Adherence to the management plan, especially for a drug whose action covers only the night after intake, is important. It is estimated that ~30% of non-responders are not taking medication correctly [204, 205, 258]. Non-adherence to recommendations regarding timing of medication, voiding before bed time, and limitation of evening fluids can decrease treatment success[259] . Moreover, compliance is often overestimated, both by patients and clinicians; therefore, it should be documented in a diary. Regular contacts between caregiver and patient are necessary to keep up compliance. Patients who appear treatment-resistant should be advised of the importance of full adherence and asked if they have had any difficulty with complying with recommendations. It is important that in divorced families, information has to be given to both parents, so that the treatment is appropriately given on daily basis

Desmopressin has higher success rates in children with large bladder capacity and nocturnal polyuria [60, 105, 260]. Initial studies reported response rates of >70%, but subsequent more recent studies suggest that the response rates are lower, in the 20-30% range. The earlier studies may have included occult OAB patients with small bladder volume and low nocturnal diuresis volumes. [261]

Still, there remains several unanswered questions regarding desmopressin therapy. It is unclear whether desmopressin treatment leads to better long-term outcome than the spontaneous resolution rate. Nevertheless, some studies have shown that the long-term cure rate of 15- 30% annually with desmopressin is higher than the spontaneous resolution rate [232, 251, 262]. Long-term follow up has shown persistent LUTs symptoms in the patients with NMNE but not in the MNE patients[42]. Finally, the notion that tapering of the dose and a structured withdrawal program should be beneficial is still unproven[256, 263] .

Desmopressin: Tolerability and Safety :
Considering the world wide prescription-rate, desmopressin is an extremely safe product, if correctly dosed and fluid intake is withheld after administration.[235, 264]. It is clear that dDAVP is a potent antidiuretic drug and that there have been reports of severe water retention with hyponatremia and convulsions, but these are infrequent [249, 253, 265-274]. Since the withdrawal of the nasal spray from many markets, reports of water-intoxication with desmopressin as the melt or tablet form, at correct doses, have been rare, it is important to stress that the drug should be correctly administered near bedtime as noted above, since every year there are reports of children taking it inappropriately in the morning.

Furthermore, earlier ICI-advice regarding a fairly rigid regimen of water restriction must be enforced for the two hours prior to bedtime and to allow one eight-ounce (300 ml) glass of water at dinner and nothing for the two hours prior to bedtime. [266, 271, 275].

The results of numerous clinical trials have shown that desmopressin is well tolerated even during long-term treatment and associated with a low risk of adverse events. [235]

Predictors of Response:
The highest response rate is in older children, with less severe bedwetting, nocturnal polyuria and larger functional bladder volumes. A low diuresis-volume, <60% of EBV overnight is highly predictive of desmopressin resistance. This is logical, since low diuresis-volume coincides with the presence of maximal concentrating activity of the kidney, where desmopressin is unlikely to have additional physiological value. [79,105,246, 251, 253, 264, 276].

However, relapse after short-term treatment is common. [251]. This suggests that desmopressin, by reducing the urine output overnight, reduces nocturnal enuresis but does not significantly affect the resolution rate over time above the spontaneous cure rate. Tapering during withdrawal might decrease relapse rates [263, 277]

Conclusion: Desmopressine treatment with the melt and tablet formula is a safe first line treatment of NE (LoE:1)

Recommendation:Desmopressine melt and tablet formula are recommended in the treatment of NE in children (GR:A)

9.5.2. Combined treatment with alarm and desmopressin

Combined treatment may be superior to the use of the alarm alone , especially for non-responders of each individual treatment. In this approach, treatments are started at the same time: the rapid action of dDAVP is believed to facilitate the child's adaptation to the alarm [278-283]. After 6 weeks the dDAVP is discontinued while the alarm treatment is continued until the child becomes completely dry.

Compared with either therapy alone, the combination is particularly effective in children with high wetting frequencies and behavioural problems.

Full-spectrum therapy, a combination of alarm, bladder training, motivational therapy and pelvic floor muscle training may even yield higher success rates[278, 284-287]. Since alarm plus Desmopressin was not more successful in the long-term, combination therapy cannot be recommended as a primary strategy in the vast majority of MNE patients. [288].

Conclusion: Combination therapy is effective in the treatment of NE (LoE:3)

Recommendation: Combination therapy is recommended in the treatment of NE in children (GR:C)

9.5.3. Anticholinergic / antimuscarinic drugs for OAB

Anticholinergic drugs are widely prescribed in monotherapy as well as in combination therapy. Oxybutynin, propiverine, tolterodine, and solifenacin have sufficient PK/PD data to be prescribed safely in children, while some others are under study. Paediatric labelling is mainly restricted to OAB in neurogenic and non- neurogenic bladder dysfunction and are often country dependent. None of the current OAB medications fulfills the criteria for evidence as first line therapy for nocturnal wetting in children, although there is some evidence for the treatment of daytime symptoms.

Since antimuscarinic drugs can in theory only be efficacious in children with monosymptomatic nocturnal enuresis, with underlying overactivity of the bladder, they cannot be considered as first line therapy. The observed responses might be related to considerable underdiagnosis of LUTS and non monosymptomatic nocturnal enuresis or isolated overactive bladder at night. [289]. Antimuscarinics are also indicated as treatment for combined day- and night-time incontinence [111, 290, 291] .

In general, antimuscarinic drugs are well tolerated but there are some side effects, namely vasodilation, dryness of the mouth, constipation, vertigo (rare), and symptoms of hyperactivity and concentration disorders, especially in children with ADHD. These side-effects are more predominant with oxybutynin than with the more contemporary anticholinergics. Use of antimuscarinics may lead to constipation that may aggravate detrusor overactivity and thus counteract the beneficial effects of the drug. Antimuscarinics may also result in increased residual urine volumes which may make it difficult for the child to empty prior to bedtime. Although there is no evidence in MNE populations, it is important to monitor post void residual and constipation in such patients following initiation of therapy with these agents.[7, 292]

The combination of alarm and anticholinergics should be considered if overactive bladder is suspected. If the alarm is set off several times per night, indicative of overactive bladder, this combination has been proven to be successful.

Conclusion: combination of an alarm and anticholinergics are effective in the treatment of children with NE with suspected bladder overactivity (LoE:3)

Recommendation: the combination of an alarm and anticholinergics is recommended in children with NE and suspected bladder overactivity (GR: C)

In those children who have NE due to isolated nocturnal detrusor overactivity, treatment with an antimuscarinic drug should be considered. Because it is impractical to perform cystometry at night in these children to make the diagnosis of detrusor overactivity/OAB, the clinical evidence for such a diagnosis is generally considered to be 1-2 wetting episodes per night , in the presence of desmo-

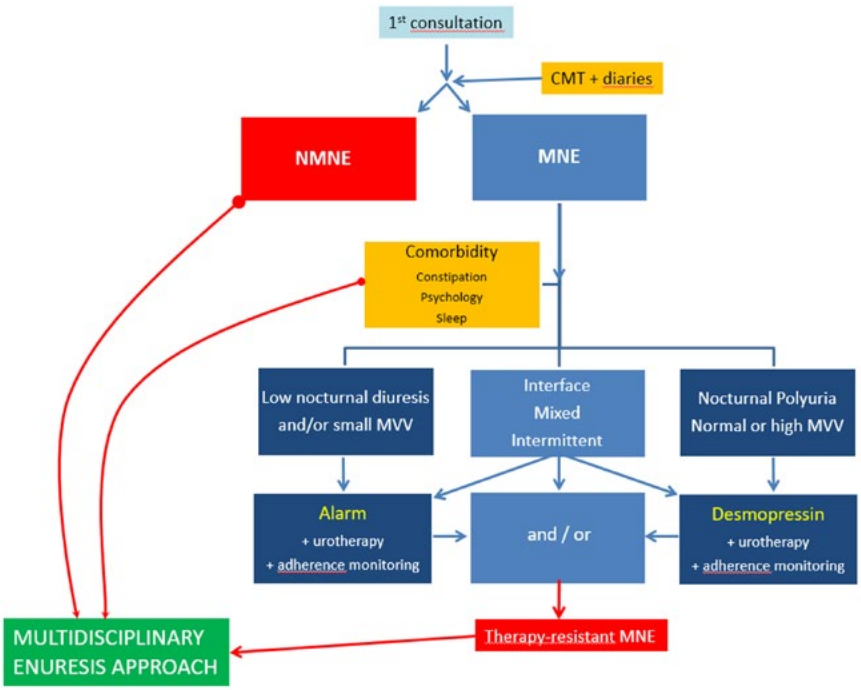

Fig. 3: Treatment algorithm for enuresis.

pressin therapeutic failure and/or the absence of nocturnal polyuria. [291,293]

Conclusion: single anticholinergic treatment is effective in children with NE and isolated nocturnal OAB (LoE:4)

Recommendation: single anticholinergic treatment is recommended in children with NE and isolated nocturnal OAD (GR:4)

9.5.4. Tricyclic antidepressants

Although tricyclic antidepressant drugs, imipramine in particular, have demonstrated efficacy in a number of children, most of the studies that recommend this drug are relatively old, and included patients that would be now likely be classified into both archetypes (NMNE/MNE). The major drawbacks to imipramine therapy are cardiotoxic side effects, in some cases even with therapeutic doses, and the possibility of death with overdose. [294].

Although treatment with tricyclic drugs is associated with a decrease of one wet night per week, the lasting cure rate is <20%[295] .

Only in selected cases (like adolescent boys with Attention Deficit Hyperactivity Disorder and persistent NE) or refractory cases should it be considered [296], but even in such circumstances, restriction to expert centres is recommended. Whether it is necessary to obtain a baseline ECG prior to the initiation of therapy remains debatable unless there is a family history of sudden death in which case it is mandatory.

Conclusion: tricyclic antidepressants are effective in the treatment of NE (LoE:1)

Recommendation: tricyclic antidepressants are recommended in the treatment of NE. Because of the potential cardiotoxicity their use should be limited to those cases refractory to all other therapy (GR:C)

9.5.5. Alternative regimens

Several other drugs, such as carbamazepine and NSAIDS (indomethacin, ibuprofen) have also been investigated. Based on study designs as well as on study outcomes, these drugs are not yet recommended for the treatment of MNE/NME [297-302] . Acupuncture, laser acupuncture and neuromodulation have also been suggested as treatment, but without sufficient evidence to be adequately assessed in the primary treatment of enuresis patients [303-308]

10. REFRACTORY MONOSYMPTOMATIC NE : [309]

About one third of children do not respond to treatment with alarm and/or dDAVP. The majority of these children are likely to have a small nocturnal bladder capacity and suffer from “detrusor dependent NE”. There are no large datasets using the latest ICCS standardisation to predict success-rates appropriately.

The majority of patients with MNE who are subsequently proven to be non- or partial responders are likely to have underlying bladder dysfunction, missed during the initial assessment, because 1) the intake evaluation was not performed appropriately, or 2) patients were classified according to the old ICCS standardisation, when according to the new ICCS-standardisation they would be considered as NME. In such refractory cases, a full intake screening should be redone. A history of diurnal incontinence, diurnal symptoms after the age of 3.5 years, too high or too low voiding frequency during the day, and postponing during normalized fluid intake are very suggestive for bladder dysfunction, as well as small enuresis volumes early in the night. Spontaneous low fluid intake is suggestive for a defence mechanism, and may mask OAB symptoms. These symptoms are often not mentioned by parents, and deserve repeated questioning or documentation in a bladder diary during a standardized fluid intake of 1.5ml/1.73m²/day. This provides additional information. Uroflow and bladder ultrasonography may also be useful. These children will benefit from a multidisciplinary approach and should no longer be treated exclusively by the primary care provider[310, 311].

In the absence of any bladder dysfunction we should concentrate on the desmopressin effect in differentiating different pathophysiologic characteristics that might be involved :

Anti-enuretic effect (= number of wet nights), the anti-diuretic effect (= nocturnal diuresis rate) and) concentrating capacity (= urinary osmolality) should all be evaluated.

Partial response to desmopressin in MNE (anti-enuretic effect) is related to persistent nocturnal polyuria on the wet nights[106]

Poor compliance should be excluded[205], including not taking the drug (consider letting the patient fill in a drug-diary and register the number of prescriptions /compliance)

In the diagnostic workup specific attention should be given to the following aspects:

-Does the child forget to void before sleeping, and already start the night with a filled bladder

-Can drinking overnight be excluded as a cause, as fluid intake overnight or even the hour before desmopressin administration reduces both the maximum and duration of anti-diuretic effect, as well as the concentrating capacity significantly. Intermittent polyuria might as well be related to the PK/PD characteristics of desmopressin [107, 244-247, 258]

The 3 formulations of DDAVP (tablet, melt and spray) have poor bioavailability, ranging respectively from 0,2-2%- 4%, but with a rather large SD resulting in high intra-individual variability. Only the melt has well established dose-response-data, proper pharmacodynamic and pharmacokinetic data in children. The melt showed superior PK and PD profile, better compliance and some indications of higher response rates. Before considering desmopressin resistance, a switch to the melt should be considered.

The child should take the drug just before sleeping time as the time to reach maximum concentrating capacity and anti-diuretic effect is 1-3 hours. Therefore, the drug should be taken at least one hour before the last void before sleeping) [110, 236, 244]

The tablet should not be taken at mealtime. DDAVP dosing should occur with an empty stomach , at least 2 hours after the last meal [110, 244, 245, 312]. However, such a dosing schedule (2 hours after the last meal, and 1 hour before sleep) is not realistic or practical in many children. This consideration favours the melt above the tablet. The melt study has demonstrated that, even in the therapeutic range of 120-240µg there are large standard deviations in maximal concentrating capacity and antidiuresis, as well as duration of

action. A better understanding of these PK/PD dynamics, can lead to more personalized approach to dosing. The PK/PD data demonstrate that at least 25% of patients might benefit from higher doses. Such patients can be identified by a pharmacodynamics test in an ambulatory setting in the individual patient (24h concentration-profile), especially in the older patients. Increasing the dose without this test is not recommended, because of the risk for toxicity.

In desmopressin refractory nocturnal polyuria with low urinary osmolality, diabetes insipidus (DI) should be excluded. X-linked DI in boys may not present with enuresis, but female carriers might have a more forme fruste pattern with enuresis as the predominant symptom. Many renal diseases (CKD, tubulopathies, renal dysplasia, uropathy, etc.) may present with enuresis. Hypertension, and especially nighttime hypertension coincides with nocturnal polyuria, and should be considered in refractory patients. Although there might be some anti-diuretic effect of desmopressin, these patients never reach maximum concentrating capacity. A desmopressin / vasopressin concentration test may be helpful if conventional diagnostic tools (ultrasound, lab) fail. It should be noted that the majority of studies on desmopressin in children with MNE, demonstrate that up to 25% of patients do not reach >850 mosmol/L after desmopressin. Although these patients do not fulfil the criteria of DI, there is a high prevalence of patients at the lower end of the normal range of concentrating capacity. Notably, a 20% decrease in concentrating capacity results in a 20% increase in diuresis and this may be the difference between continence and enuresis in many patients.

Desmopressin resistant nocturnal polyuria, with high urinary osmolality overnight might be correlated with high osmotic excretion overnight. This can be caused by an increased solute load only in the evening or during the preceding 24 hours [85, 86] . Sodium is the major osmotic agent [85, 97, 101, 313]. Although nutritional intake plays a major role, abnormalities of several circadian rhythms like prostaglandins [314-316], GFR [95, 97], blood pressure [94] and sleep pattern[129, 130, 134] have a significant impact in selected tertiary care patient populations. Extrapolation into the primary care enuresis patients remains premature. But these findings suggest a role for potential future treatment options. Some pilot studies evaluating the role of sodium restricted diet, diuretics (furosemide [101, 297, 317, 318]) , NSAID's and treatment of sleep disturbances (OSAS and melatonin) [75, 77, 319-322] have demonstrated some promising results. In the past, the role of calcium , and calcium restricted diet have been evaluated, [102, 103, 323], but other studies have suggested that such hypercalciuria might be a secondary phenomenon due to differences in diet[100, 109, 324].

Therapy resistance to conventional therapy can not only be related to underlying bladder dysfunction and/or renal response to desmopressin, but due to a number of other associated comorbidities (5). Identifying these, and addressing them if possible might increase the response rate. Constipation and faecal incontinence should be addressed before initiating other treatment for MNE but such conditions are often underestimated and underreported. Psychological comorbidities, as well internalizing as externalizing are more frequent in enuresis-patients. Attention deficit disorders, and autism are well studied and seem to have common pathways. A structured therapeutic approach is mandatory. Renal dysfunction, hypertension, diabetes mellitus and sleep disturbances have already been mentioned, but these should be treated appropriately. Many drugs interfere with the circadian rhythm of several biorhythms, including diuretics, steroids, cyclosporine A, neurotropic drugs and may be a possible trigger to set off enuresis in a sub-set of children.

Conclusion: individual analysis of the nocturnal diuresis parameters in refractory NE is necessary to optimise the treatment of the nocturnal polyuria (LoE:3)

Recommendation: in children with refractory NE, individual analysis of the nocturnal diuresis parameters is recommended (GR:C)

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IV. CHILDREN WITH BOTH DAY AND NIGHT TIME INCONTINENCE

Children with lower urinary tract dysfunction (LUTD) may present with urinary incontinence, irritative or obstructive symptoms (urgency, straining during voiding), urinary tract infection (UTI), vesicoureteral reflux (VUR), and bowel problems (constipation, soiling) alone or in combination. Lower urinary tract (LUT) symptoms in school-aged children can be noted in as high as 20% of individuals and may present with a wide spectrum of severity [1]. They may just be slightly disturbing without any need for seeking professional help or have significant social consequences and sometimes clinical morbidity like UTI and VUR. This condition may also be associated with psychiatric, developmental disorders, and obesity. The most common symptom is day and night-time incontinence. There is high prevalence of constipation (30-50 %) among these patients with LUTD symptoms (LUTS). Urinary incontinence in children may also be caused by a congenital anatomical or neurologic abnormality, such as ectopic ureter, bladder exstrophy or myelomeningocele (MMC) as such and they are not within the scope of this chapter. In many children, however, there is no such obvious cause for the incontinence and they are referred to as having “functional incontinence”. This lower urinary tract dysfunction is not considered to be of any organic aetiology, but is often attributed to a developmental delay or problem. The most recent International Children’s Continence Society (ICCS) document suggests using the term daytime lower urinary tract (LUT) conditions to group together all functional bladder problems in children [2].

Normal storage and emptying of the bladder at a socially acceptable place and time is mostly achieved by age three to four. Children with LUT conditions would most commonly present with being still wet after the age of four often in the form of urge incontinence with or without weak stream, hesitancy, frequency and accompanied UTIs. Isolated night-time wetting without any day-time symptoms is known as ‘enuresis’ and considered as a different entity.

Bladder control is believed to be under the influence of the central nervous system. The pontine region is considered to be responsible for detrusor sphincter coordination while the cortical area is responsible for inhibition of the micturition reflex and voluntary initiation of micturition (detrusor over activity control). Formerly it was believed that bladder maturation followed maturation of cortical inhibition processes. Current understanding is that there is a dialogue between the cortex and pons resulting in bi-directional maturation of both and the coordinating influence on the bladder and the pons is also involved. This indicates that a condition such as detrusor overactivity would be the result of loss of cortical control or of a deficiency in cortical control, while dysfunctional voiding would be the result of non-maturation of the coordination. Detrusor overactivity should not be considered as a sole bladder-based problem but more a symptom of a centrally located dysfunction affecting bladder, bowel and even mood and behaviour [3,4,5]. Indeed, many studies indicate that there exists a link between lower urinary tract dysfunction and behavioural disorders such as ADHD (attention deficit / hyperactivity disorder) [6,7].

In the first few years of life there is an ongoing development in lower urinary system from an initially involuntary voiding pattern to a more socially conscious type of voluntary micturition control. During this ongoing evolution which includes the increase of functional bladder capacity and maturation of the detrusor-sphincter coordination a progressive development of the voluntary control over the infantile voiding reflex takes place. It is no surprise that during this complex evolution various derangements of lower urinary tract function may occur resulting with various LUT conditions with variable severity. The desire to void is a sensation which, in the developing child, is incorporated into daily life so that voiding takes place at an appropriate time and place. Variations with toilet training, developmental differences or psychological difficulties possibly have an impact on the results of training [8,9]. The positive reinforcement that the child receives by voiding even a small amount may lead to the development of an abnormal voiding pattern. The same may be true when children receive negative feedback related to voiding [8-12]. The issue remains to be controversial and the evidence is poor.

Urinary incontinence in children may be due to disturbances of the filling phase, the voiding phase or a combination of both. In the ICCS terminology document, these conditions are termed functional bladder disorders or Lower Urinary tract (LUT) conditions [2].

Filling-phase (storage) dysfunctions

In filling-phase dysfunctions, the detrusor can be overactive, as in OAB, or underactive, as in underactive bladder (UAB). Overactivity of the bladder is the most common problem which may lead to disturbances characterised by urgency, frequency and at times urgency incontinence. Some children habitually postpone micturition leading to voiding postponement. Therefore, holding manoeuvres such as leg crossing and squatting can often be seen in this group [5]. If not accompanied with an emptying disorder and residual urine, recurrent UTIs are not common. Constipation can be an additional aetiological factor, which needs to be assessed. In children with an underactive detrusor, voiding occurs with reduced or minimal detrusor contractions with post-void residuals (PVR). Urinary tract infections, straining to void, constipation and incontinence is common. Incontinence often occurs when the bladder is over-distended in the form of overflow incontinence.

Voiding-phase (emptying) dysfunctions

In voiding-phase (emptying), incomplete relaxation or tightening of the sphincteric mechanism and pelvic floor muscles results in staccato voiding pattern (continuous urine flow with periodic reductions in flow rate precipitated by bursts of pelvic floor activity) or an interrupted voiding pattern (unsustained detrusor contractions resulting in infrequent and incomplete voiding, with micturition in fractions). The general term for this condition is “dysfunctional voiding” and is associated with elevated bladder pressures and PVRs and UTIs are more common. Symptoms will vary depending on the severity of dyscoordination between bladder and the sphincter. Staccato

voiding is in less severe forms, and interrupted voiding and straining is in more severe forms. Children with dysfunctional voiding are also prone to constipation and soiling [13].

In incomplete emptying, high voiding pressures generated by the bladder working against a functional obstruction caused by non-relaxing sphincter may induce not only UTIs but also vesico-ureteric reflux (VUR). It is been shown that LUTD is more significant for the occurrence of UTI than VUR itself [15]. In the majority of children with dysfunctional voiding the recurrent infections disappear following successful treatment, which confirms the hypothesis that dysfunctional voiding is the main factor responsible for the infections. Spontaneous resolution of VUR may also be seen after successful treatment of dysfunctional voiding.

Storage and emptying dysfunctions can of course coincide and one may even be causative of the other. No evidence exists however for this last assumption. It has been postulated that detrusor overactivity may eventually lead to poor bladder emptying due to underactivity of the detrusor or severe dyscoordination between detrusor, sphincter and pelvic floor. However, the natural history of many of these children does not confirm this hypothesis, nor the early onset of severe pathology in some of them. Hoebeke et al. found no evidence for this dysfunctional voiding sequence: children with functional incontinence have different primary diseases, but all have a common risk of incontinence, UTI, VUR (15%) and constipation (17%) [14].

1. PREVALENCE

For more detailed information on the prevalence of daytime incontinence the Chapter on Epidemiology should be consulted. The main problem is that it is impossible to draw any conclusions from the presented data as different studies have used different definitions and criteria. Furthermore, it is virtually impossible to identify the prevalence of detrusor overactivity or dysfunctional voiding as the studies tended to look primarily at daytime versus night-time incontinence and made no effort to evaluate the type of daytime incontinence.

Daytime or combined daytime and night-time incontinence at least once a week seems to occur in about 2-7 percent of 7-year-old children and is more common in girls than in boys [15,16]. There are many studies in the literature looking at the prevalence of this condition and overall, the rates of prevalence vary from 1 to 20 percent depending on how the condition is defined. In general, for 6 to 7-year-old children the prevalence is around 5-10 percent, and rapidly decreases during the following years [15-19].

Sureshkumar et al. in a population-based survey of over 2000 new entrant primary school children [age 4-6 years] in Australia, noted an overall prevalence of daytime wetting of 19.2% defined as at least one daytime wetting episode in the prior 6 months with 16.5% having experienced more than one wetting episode and only 0.7% experiencing wetting on a daily basis [20]. Multivariate analysis showed that recent stress, a history of daytime wetting along the paternal line, and a history of wetting among male siblings were independent risk factors for moderate to severe daytime wetting. Because this was a cross-sectional study, recall bias may have resulted in an overestimate of the risk of daytime wetting being caused by such factors as emotional stress and family history. In addition, urine cultures were not obtained so occult UTIs could not be identified.

In a similar study looking at primary school students voiding disorders were detected in 175 (19.2%) of 907 children. One hundred and fifty-two (16.8%) had daytime urinary incontinence, and 131 (14.5%) had night-time incontinence. Voiding disorders decreased as the age increased. There was a significant relationship between voiding disorder and positive family history [21].

In another cross-sectional study looking at 2750 children aged between 11-14 years the overall prevalence of urinary incontinence was 8.6% and decreased with age [23].

Chung finds the percentage of OAB (16,6%) in 19,240 Korean children. In this study OAB was differentiated in ‘dry’ OAB and ‘wet’ OAB: children with OAB do not always have incontinence [22].

In a questionnaire-based study, supplemented by telephone calls, Hellstrom assessed the prevalence of urinary incontinence in 7-year-old Swedish school entrants [24]. Diurnal incontinence was more frequent in girls than boys, 6.7% vs 3.8%, respectively. Wetting every week was reported in 3.1% girls and 2.1% of boys. The majority of children with diurnal incontinence had concomitant symptoms: urgency was reported in 4.7% girls and 1.3% boys. Nocturnal incontinence combined with daytime wetting was equally common in males versus females, 2.2% versus 2%, respectively. At the age of 17 years daytime wetting, at least once a week, was found in 0.2 % of boys and 0.7% of girls. A limitation of this study is its dependency on recall. Children with daytime or mixed wetting were found to suffer from urgency in 50.7%, with 79.1% wetting themselves at least once in 10 days [25]. Urgency symptoms seem to peak at age 6–9 years and diminish towards puberty, with an assumed spontaneous cure rate for daytime wetting of about 14% per year [26].

In a cross sectional sample of 594 individuals 4 to 26 years old, Kyrklund (2012) described 4% of respondents with frequent UI, most < 12 years. Prevalence decreases enormously with age [27].

Most children are toilet-trained by the age of 3 years, although the mean age may range from 0.75 to 5.25 years, with girls being trained earlier (2.25 years) than boys (2.56 years) [28]. A 2008 Turkish study reported day dryness at a mean age of 28 months (29). This is confirmed by a 2015 Turkish study in 1500 children whose mean age of dryness was 29 months [30]. The age of commencing toilet training has increased [31]. This is thought to be associated with higher education levels in parents and the popularity of the child-oriented approach rather than parent-initiated methods. Children who exhibited elimination signals for voiding became dry sooner than those who did not show such signs. There is huge social and cultural variation in toilet training practices with some of the implicated issues being, availability of inside toilet, washable versus disposable diapers, working or home-based mothers, rural or urban location and use or not of punishment methods [29]. It appeared that initiating toilet training after 24 months of age may be associated with problems attaining and maintaining bladder control and that early training is not associated with bladder dysfunction [31,32]. A prospective study in 112 patients published in 2014 however showed problems in early training (<2 years) and in late training (>3 years) alike [33]. Da Fonseca found no association between children with combined bladder and bowel dysfunction and the time of toilet training compared to healthy children [34].

Swithinbank et al. found a prevalence of day wetting [including also “occasional” wetting] in 12.5% in children age 10-11 years which decreases to 3.0% by age 15-16 years [35]. Based on these findings, it seems that the prevalence of all kinds of daytime inconti-

nence diminishes by 1-2% per year from age 10-11 to age 15-16 years, while daytime incontinence, at least once a week, seems to diminish by 0.2% per year from age 7 to age 17 years. Because of treatment interventions the studies may not recount the true natural history.

A cohort study of all school children in the first and fourth grades in the city of Eskilstuna (Sweden), published in 2004, daytime urinary incontinence (at least once a month) was reported in 6.3% of the first graders and 4.3% of the fourth graders, while bedwetting (at least once a month) was reported in 7.1% and 2.7% and faecal incontinence in 9.8% and 5.6%, respectively. This study demonstrates that soiling and daytime urinary incontinence often coexist [36].

There has been ample amount of literature examining toilet training and dysfunctional elimination association and suggesting that late toilet training with bladder overactivity may be a leading factor. Bowel and bladder dysfunction in children may be due to delayed toilet training in children; however, there is no clear explanation how this happens. Some hypothesise that changing attitudes and practices towards toilet training make the completion of toilet training at a later age compared to previous generations. Concomitantly, there has been an increase in the incidence of paediatric bladder bowel dysfunction. One other theory suggests that the symptoms of dysfunctional voiding are more common when toilet training early, as immature children may be less likely to empty in a timely manner, or when training late due to (or in association with) constipation.

A meta-analysis reports the comprehensive search of current literature investigating the association between age at initiation of toilet training, approach used for toilet training, and bladder bowel dysfunction. A total of 10 studies with 24,121 participants (aged 5-17) were included for pooled analysis. Overall, the odds ratio (OR) with 95% confidence interval (95%CI) of lower urinary tract dysfunction in children who initiated toilet training at a younger age when compared to those who initiated toilet training at an older age, was 0.71 (0.63-0.81), (P < 0.001), irrespective of the approach used for toilet training. Subgroup analysis for day-time incontinence (persistent daytime wetting) was 0.77 (0.62-0.95), P =0.014; although the outcomes for enuresis fluctuated, favourable results were still observed in the earlier training group (OR:0.63, 95% CI:0.43-0.94, P = 0.023). Subgroup analysis for age at initiating toilet training vs LUT dysfunction also showed favourable results in children who were trained earlier, i.e., before 24 months (OR:0.77, 95% CI 0.63-0.94, P Z=0.009). Sensitivity analysis confirmed that the results were strong [37].

This meta-analysis presents preliminary findings that show that the incidence of bowel and bladder dysfunction may be decreased by initiating toilet training in children at a younger age prior to the age of 24 months [37]. Although the definition about the age of initial toilet training varied greatly in studies, findings from the current study suggested that the optimal time for initiating toilet training may be prior to the age of 24 months; if toilet training was initiated after 24 months or later, it may result in increased prevalence of LUT dysfunction. Since no RCTs studies were included in the current meta-analysis, well-designed longitudinal studies with larger sample size and from different cultural background are needed to confirm these results.

The natural history of detrusor overactivity in children is not well understood. It is no longer held that detrusor overactivity in children is idiopathic or due to a maturational delay but more likely to be associated with feed forward loops from the generation of a high-pressure system during voiding or filling. Both the interplay of neural drive with motor control and the dynamic nature of the growing bladder could be causative. This is in contrast to the adult population, where detrusor overactivity is considered a chronic condition, whose origin is unrelated to functional use. There is no long-term data to determine if childhood detrusor overactivity predicts detrusor overactivity as an adult. There is evidence that genetic influences affect adult urinary symptoms and that suffering lower urinary tract conditions in childhood increases the risk for these conditions in adult woman [38-41].

By the age of 5 years, unless organic causes are present, the child is normally able to void at will and to postpone voiding in a socially acceptable manner. After this age, night-time and daytime involuntary wetting become a social problem and a cause for therapeutic intervention. In children who present with a change in voiding habits, such as a new onset of voiding dysfunction, one should consider the possibility of child sexual abuse [41]. A more recent study found no significant differences in the presence of lower urinary tract symptoms between children and adolescents who had experienced sexual abuse and controls [33]. Nevertheless, this should be kept in mind, especially when invasive diagnostic and therapeutic procedures are contemplated. One may want to simply ask the parent or caregiver if there were any precipitating events or concerns that they feel may have led to the changes in the child's voiding habits. The appropriate individuals should be contacted if there is a high index of suspicion. Of adult women with complex urinary symptoms, a significant proportion report sexual abuse as a child.

2. CLINICAL ASSESSMENT

The evaluation of LUT conditions includes medical and voiding history (bladder diaries and structured questionnaires), a physical examination, a urinalysis, and uroflowmetry with post void residual (see the algorithm in table 1).

The upper urinary tract needs to be evaluated in children with recurrent infections and dysfunctional voiding. Uroflowmetry can be combined with pelvic floor electromyography to demonstrate over activity of the pelvic floor muscles during voiding. Because urodynamic studies are invasive and most often outcome will not alter treatment plan; they are reserved for patients with therapy resistant dysfunctional voiding and/or those not responding to treatment who are being considered for invasive treatment [42-46].

In addition to a comprehensive medical history a detailed voiding diary provides documentation of voiding and defaecation habits, frequency of micturition, voided volumes, number and timing of incontinence episodes, and fluid intake. A voiding diary should be done for at least 2 days– better 3 days, although longer observation periods are preferred. A voiding diary provides information about storage function and incontinence frequency, while a pad test can help to quantify the urine loss. In the paediatric age group, where the history is taken from both the parents and child together, a structured approach is recommended using a questionnaire. Many signs and symptoms related to voiding and wetting will be unknown to the parents and should be specifically requested, using the questionnaire as a checklist. Symptom scorings have been developed and validated [46-49] Although the reliability of questionnaires is limited, they are practical in clinical setting to check the presence of the symptoms and also have been shown to be reliable to monitor the response to treatment. History-taking should also include assessment of bowel function. For evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool [50].

Urinalysis and urinary culture are essential to evaluate for urinary tract infection (UTI). On urinalysis, the specific gravity (concentration) of the urine is noted, as is any evidence of underlying voiding problems based on the presence of hematuria, proteinuria, or glucosuria. Since transient voiding symptoms are common in the presence of UTI, exclusion of UTI is essential before further management of symptoms.

During clinical examination, genital inspection to see any pathologies like meatal stenosis or congenital abnormalities of the urethra and observation of the lumbosacral spine and the lower extremities are necessary to exclude obvious uropathy and neuropathy.

Uroflowmetry with post-void residual evaluates the emptying ability, while an upper urinary tract US screens for secondary anatomical changes. A flow rate which reaches its maximum quickly and levels off ('tower shape') may be indicative of overactive bladder whereas interrupted or staccato voiding patterns may be seen in dysfunctional voiding. Plateau uroflowmetry patterns are usually seen in anatomic obstruction of flow. A single uroflowmetry test may not be representative of the clinical situation and more uroflowmetry tests, which are all giving a similar result, are more reliable. Uroflowmetry examination should be done when there is desire to empty the bladder and the voided volume should at least be 50% of the age expected capacity ((age in years) + 1] x30 mL). While testing the child in clinical environment impact of the stress and mood changes on bladder function should also be considered.

In the case of resistance to initial treatment, or in the case of former failed treatment, re-evaluation is warranted and further urodynamic studies may be considered. Sometimes, there are minor, underlying, urological or neurological problems, which can only be suspected using urodynamic studies. In these cases, structured psychological interviews to assess social stress should be added [51-54].

In cases of febrile urinary tract infections vesico-ureteric reflux needs to be excluded either by VCUG or video urodynamic studies. With video-urodynamic studies, reflux may be observed along with bladder dynamics.

In the case of suspected anatomical problems which may cause infravesical obstruction such as posterior urethral valves, syringocoeles, congenital obstructive posterior urethral membrane (COPUM) or Moormann's ring, it may be necessary to perform further cystoscopy with treatment. If neuropathic disease is suspected, MRI of the lumbosacral spine and medulla can help to exclude tethered cord, lipoma or other rare conditions.

3. CONFOUNDING FACTORS: LOWER URINARY TRACT DYSFUNCTION, RECURRENT URINARY TRACT INFECTION AND VESICO-URETERIC REFLUX (VUR)

The relationship between detrusor dysfunction and VUR associated with a urodynamic anomaly was first described by Allen and Koff and has been confirmed by several authors [55-58]. Koff demonstrated that treatment of detrusor overactivity reduced the incidence of infection and resulted in a 3-fold increase in the rate of reflux resolution. In a study by Sillen of children with gross bilateral reflux, extreme detrusor overactivity without signs of bladder outlet obstruction was found in boys. Infant girls with gross bilateral reflux did not show the same degree of detrusor overactivity [50]. Other investigators assessing high grade VUR in new-borns noted similar findings. Van Gool et al. noted that 40% of 93 girls and boys evaluated for urgency incontinence and recurrent UTIs had reflux [59].

These studies in infants and the association of combined bladder and bowel dysfunction with reflux and infection in older children support the suggestion that, in some individuals, vesicoureteral reflux is a secondary disorder related more to abnormal detrusor function than to a primary anatomical defect at the ureterovesical junction. It has been shown that increased intravesical pressure, without reflux, may be detrimental for the upper tracts: renal scarring without reflux was recently described by Vega et al. [60].

Generally, high pressure during both storage and emptying do not always generate reflux but can easily do that in case of slight ureterotrigonal anatomic deficiency. In support of this concept is the common finding of vesicoureteral reflux in children with neuropathic bladders and detrusor-sphincter dyssynergia. In such children, the institution of clean intermittent catheterisation and anticholinergic therapy leads to the resolution of VUR in a large number of cases. It is believed that the decrease of detrusor overactivity and restoration of functional capacity in combination with regular and complete emptying of the bladder are the responsible co-factors [61]. If reflux continues to be a problem despite proper management of bladder pressures, anatomic correction could be warranted.

Koff et al. evaluated the effects of antimuscarinic therapy in 62 children with a history of recurrent UTIs, VUR and detrusor overactivity, and compared these children with an age-matched control group with a normal urodynamic study [62]. The overall small sample size and the small number of compliant patients limit the study, however, it did demonstrate a statistically significant difference in the resolution rate of VUR between the treated group and the control group. The overall infection rate was lower in the treated group (16%) compared to the non-medically treated group (63%) and the age-matched control group (71%)]. Several authors have documented the relationship between detrusor overactivity and dysfunctional voiding with recurrent UTIs .

Proposed aetiologies for the increased incidence of UTIs in these patient populations include a milk back phenomenon whereby bacteria in the proximal urethra are "milked back" into the bladder during contraction of the pelvic floor muscles. Alternatively, decreased blood flow and relative hypoxia during periods of increased detrusor pressure such as during involuntary detrusor contractions and voiding against functional obstruction, may induce transient bladder mucosal injury.

Constipation is prevalent among children with bladder symptoms, but often poorly identified by parents [63]. It is a risk factor for recurrent UTIs. Contrary to expectations, findings from the European Bladder Dysfunction Study suggested that symptoms of disordered defaecation did not influence the cure rate of treatment for bladder symptoms [64]. In a prospective non-randomised clinical series of day wetting children, a strong correlation was found between recurrent urinary tract infections, detrusor overactivity and detrusor-sphincter dysfunction [65]. In a study by Hansson et al. symptoms of detrusor overactivity, such as urgency and daytime incontinence were found in a high percentage of girls with asymptomatic bacteriuria [66].

In the majority of children with dysfunctional voiding the recurrent infections disappeared following successful treatment of the voiding dysfunction. This finding confirms the hypothesis that dysfunctional voiding is the main factor responsible for the infections (and to a lesser extent vice versa) [67,68]. Additionally, since such children typically have coexistent constipation, attempts at restoring normal bowel habits will also contribute to decreasing the risk of UTIs. At present, current opinion is that vesicoureteral reflux as such does not predispose to UTI: however, it may facilitate renal involvement [causing pyelonephritis] once bacteriuria has been established in the bladder. This concept has not been scientifically validated and the incidence of renal scars as a consequence of pyelonephritis is reportedly the same, regardless of whether reflux has been documented or not [69]. Those children with VUR in association with detrusor overactivity and/or voiding dysfunction may be at increased risk for upper tract damage given their increased risk of developing UTIs. With this in mind, aggressive treatment of the underlying filling/voiding disorder, the addition of prophylactic antibiotics, and attention to their bowel habits should be given in an effort to decrease the risk of UTIs in this higher risk group [70-73].

In a recent retrospective study evaluating a large group of children with LUT conditions it was shown that in patients who had urinary tract infection the presence of reflux increased the rate of renal cortical abnormalities [74].

4. CLASSIFICATION

Numerous classifications have been used for children who present with varying degrees of 'functional' urinary symptoms, unrelated to apparent disease, injury or congenital malformation. In 2016, the International Children's Continence Society (ICCS) released a standardised terminology to provide guidelines for the classification and communication about LUTS in children [2].

Symptoms are classified according to their relation to the voiding and or storage phase of bladder function. Classification in a clinical setting may have its difficulties because of overlapping conditions and sometimes may not be really needed. Both invasive and non-invasive tools may be needed for better classification. Most often a non-invasive approach in the clinical setting will help classification, as such, use of invasive tools like video-urodynamics are rarely needed.

In addition to obtaining a comprehensive history, observing micturition and examining the child forms the basis of assessment: the information derived from a 48-hour bladder diary, stool record, voiding uroflowmetry and lower urinary tract ultrasonography is also essential in making the initial diagnostic classification [38,67].

Screening for psychological conditions with questionnaires is recommended, as 30-40% of children with daytime urinary incontinence are affected by comorbid emotional or behavioural disorders [75].

Urodynamic investigations elucidate the basis of clinical findings but are first line evaluation techniques only in tertiary referral centres where children have not responded to previous treatment or have symptoms suggestive of neurological involvement or anatomical anomalies.

The ICCS has classified daytime LUT conditions into groups that currently align with understanding of underlying pathophysiology.

The groups commonly overlap and allocation is based on the 4 symptoms of urinary incontinence, frequency of volitional voiding, micturition volumes and fluid intake.

- Overactive bladder (OAB) including urgency incontinence
- Dysfunctional voiding
- Underactive bladder

In general, classifying according to those 3 groups is essential for planning treatment.

The symptom-specific conditions as listed below are also important for planning specific treatment.

- Voiding postponement
- Vaginal reflux
- Giggle incontinence
- Extraordinary daytime urinary frequency
- Elimination syndrome, now called Bladder Bowel Dysfunction

The term 'non-neurogenic dysfunction' is commonly encountered in the literature and describes the whole spectrum, from simple bladder overactivity to severe cases with deterioration of the upper tracts. The fact that a neurologic deficit is not demonstrated at the time of evaluation, does not exclude the possibility that a neurological abnormality was present at the onset of the problem. It has been postulated that detrusor overactivity may eventually lead to poor bladder emptying due to underactivity of the detrusor or severe dyscoordination between detrusor, sphincter and pelvic floor. However, the natural history of many of these children does not confirm this hypothesis, nor the early onset of severe pathology in some of them. Hoebeke et al. found no evidence for this dysfunctional voiding sequence: children with functional incontinence have different primary diseases, but all have a common risk of incontinence, UTI, VUR [15%] and constipation [17%] [14].

4.1. Overactive bladder in children

The term overactive bladder (OAB) is used to describe the symptom complex of urinary urgency, which may or may not be associated with urgency incontinence and is not a direct result of known neurological damage in association with urinary frequency. Recent suggestions describe OAB as a symptom of corticocentral dysfunction that affects multiple systems rather than a dysfunction isolated to the urinary bladder [69]. Urgency syndrome is characterised clinically by frequent episodes of an urgent need to void, countered by contraction of the pelvic floor muscles (guarding reflex) and holding manoeuvres, such as squatting and the Vincent curtsey sign. The term urgency refers to a sudden compelling desire to void that is often difficult to defer, unlike the need to void which is experienced by all individuals and may be intense if one holds one's urine for a prolonged period. The symptoms are thought, at least in part, to arise from detrusor overactivity during the filling phase, causing urgency. These detrusor contractions are countered by voluntary contraction of the pelvic floor muscles to postpone voiding and minimise wetting. Where present, the detrusor contractions can often be demonstrated urodynamically, as can the increased activity of the pelvic floor muscles during each contraction.

The voiding phase is essentially normal, but detrusor contraction during voiding may be extremely powerful. The flow rate reaches its maximum quickly and may level off ('tower shape'). Such strong bladder and pelvic floor muscle contractions have been postulated to result in damage to the bladder mucosa increasing the risk of UTIs. In addition, these children may note suprapubic or perineal pain. A cohort of patients presenting with night-time pain syndromes based on pelvic floor spasms was described by Hoebeke et al. [77].

Overactive bladder should also be considered in “continent” children with recurrent UTIs and vesicoureteral reflux. Depending on fluid intake and urine production, the complaints of incontinence become worse towards the end of the day, due to loss of concentration and fatigue and may also occur during the night. Children usually diminish their fluid intake to minimise wetting, and therefore incontinence may not be the main complaint or symptom, but on careful questioning urgency becomes apparent.

Frequent voluntary contractions of the pelvic floor muscles may also lead to postponement of defaecation. Constipation and faecal incontinence (soiling) are often found in children with detrusor overactivity [78]. The constipation is aggravated by the decreased fluid intake. Constipation contributes to an increased risk of UTIs and may exacerbate the detrusor overactivity. An investigation of the natural history of combined emptying dysfunction of bladder and bowel, using an elimination score in women with and without urogynaecological problems, demonstrated that childhood lower urinary tract dysfunction may have a negative impact on bladder and bowel function in later life [80].

Urinary symptoms and faecal problems often go hand in hand, epidemiological data show that urinary incontinence is found more often in girls, where defaecation problems are more often found in boys. A clear explanation is not yet found.

A careful history, physical examination and scrutiny of the child’s bladder diary will identify symptoms of bladder overactivity. Urine flow rate registration and post-void residual urine measurement help to identify co-existing dysfunctional voiding. Thus, in most children, invasive studies such as urodynamic studies are not indicated as part of the initial evaluation. Such studies are reserved for those children with a question of an underlying neurological defect and those who fail to improve with medical and behavioural therapy, especially if invasive therapies are being considered. Those children with a history of recurrent UTIs should undergo assessment with a renal/bladder ultrasound and depending on the age of the child and the severity of the UTI(s), a voiding cystourethrogram (VCUG) to assess reflux. [81,82]. By adopting a structured approach to history and physical examination, the diagnosis can be made in most children without the need for invasive diagnostic procedures.

4.2. Dysfunctional voiding

Dysfunctional voiding refers to an inability to fully relax the urinary sphincter or pelvic floor muscles during voiding. There is no identified underlying neurologic abnormality. Children with dysfunctional voiding usually present with incontinence, urinary tract infections and constipation and demonstrate an intermittent, or fluctuating pattern referred to as staccato flow (by ICCS definition) during repeated uroflowmetry.

No clear data are available on the possible causes of dysfunctional voiding. It may be that bladder overactivity eventually leads to overactivity of the pelvic floor muscles, with subsequent insufficient relaxation during voiding [83]. Alternatively, poor relaxation of the pelvic floor muscles during voiding may be a learned condition during the toilet training years, adopted following episodes of dysuria due to UTI, or constipation or occurring secondary to sexual abuse [84]. The child’s environment, in particular toilet conditions and privacy issues, can trigger or exacerbate voiding anomalies [85]. In some girls, anatomical anomalies of the external urethral meatus seem to be associated with a higher incidence of dysfunctional voiding. The urine stream may be deflected anteriorly and cause stimulation of the clitoris with subsequent reflex activity of the bulbocavernosus muscle causing intermittent voiding [86]. Since no true structural obstruction can be identified the intermittent incomplete pelvic floor relaxation that occurs during abnormal voiding is termed a functional disorder.

Abnormal flow patterns seen in children with dysfunctional voiding:

- Fluctuating (Staccato) voiding: continuous urine flow with periodic reductions in flow rate precipitated by bursts of pelvic floor activity. Voids are commonly prolonged and incomplete.
- Interrupted voiding: characterised by unsustained detrusor contractions resulting in infrequent and incomplete voiding, with micturition in separate fractions. Bladder volume is usually larger than age-expected capacity. Residual urine is often present resulting in increased UTI incidence. Bladder overactivity commonly accompanies this but it may also be absent [79, 86]

Sustained alteration of voiding is associated with subsequent filling phase anomalies such as phasic bladder overactivity and inappropriate urethral relaxation [87]. Urinary tract infections and kidney damage are common sequelae [88]. Over time, routine incomplete bladder emptying may possibly progress to bladder over-distension associated with chronic urinary retention and poor bladder emptying due to bladder underactivity.

Urinary symptoms associated with dysfunctional voiding range from urgency to complex incontinence patterns during the day and night [84]. Children with dysfunctional voiding have a higher rate of recurrent urinary tract infections than children with no voiding abnormality and demonstrate increased incidence of higher grades of VUR [90]. Symptoms are significantly more common in children with Attention Deficit Disorder than in ‘normal’ children [91].

Signs of dysfunctional voiding reflect initial “compensatory” overactivity of the bladder along with poor emptying ability. They may include small bladder capacity, increased detrusor thickness, decreased detrusor contractility, impaired relaxation of the external urinary sphincter/ pelvic floor during voiding, weak or interrupted urinary stream and large post-void residual volumes of urine. There may also be ultrasound abnormalities, secondary vesicoureteric reflux, faecal incontinence or constipation [92-94].

4.3. Bladder underactivity

Children with bladder underactivity may demonstrate low voiding frequency and an inability to void to completion using detrusor pressure alone. Voiding is of long duration, low pressure, intermittent and often augmented with abdominal straining.

Children with this condition usually present with urinary tract infections and incontinence. Urodynamically, the bladder has a larger than normal capacity, a normal compliance and reduced or no detrusor contraction during voiding, and is then termed detrusor underactivity. Abdominal pressure is the driving force for voiding. The previously used term ‘lazy bladder’ is incorrect and is no longer used.

A correct diagnosis can only be made by urodynamic evaluation. Renal function studies, renal ultrasound and VCUG should be performed to assess the extent of renal damage and reflux. Long-standing overactivity of the pelvic floor may in some children be responsible for decompensation of the detrusor, leading to an acontractile detrusor. However, no data are available to support this theory.

4.4. Voiding postponement

Voiding postponement is a condition in which children habitually postpone imminent micturition until overwhelmed by urgency, resulting in urgency incontinence [94]. A study comparing children

with typical OAB to those with voiding postponement revealed a significantly higher frequency of clinically relevant behavioural symptoms in postponers than in children with OAB, suggesting that voiding postponement is an acquired or behavioural disorder [95]. The rates of Oppositional Defiant Disorder (ODD) are especially high. Some children with voiding postponement have abnormal uroflow patterns [96].

Voiding postponement can develop out of previous OAB, but can represent a separate disorder. Also, voiding postponement can induce OAB. Therefore, different aetiologies need to be considered.

Only 20% exhibit a fluctuating voiding pattern. It remains to be determined whether voiding postponement can develop in the setting of a perfectly normal urinary tract or whether OAB is a necessary precursor.

4.5. Giggle incontinence

In some children giggling can trigger partial to complete bladder emptying well into their teenage years, and intermittently into adulthood [97,98]. The condition occurs in girls and occasionally in boys and is generally self-limiting. The aetiology of giggle incontinence is not defined. Urodynamic studies fail to demonstrate any abnormalities, there is no anatomic dysfunction, the upper tracts appear normal on ultrasound, the urinalysis is normal and there are no neurological abnormalities [92,93]. It is postulated that laughter induces a generalised hypotonic state with urethral relaxation, thus predisposing an individual to incontinence, however the effect has not been demonstrated on either smooth or skeletal muscle. It has also been suggested that giggle incontinence is due to laughter triggering the micturition reflex and overriding central inhibitory mechanisms. One small study hinted at an association with cataplexy (associated involuntary truncal body movements) and narcolepsy (a state of excessive daytime sleepiness), suggesting involvement of central nervous structures, however with only 7 subjects in this study, further evidence is needed [98-104].

4.6. Vesicovaginal entrapment

Urinary leakage that occurs in girls a short time after voiding to completion, that is not associated with any strong desire to void, may be the result of vesicovaginal reflux [105]. Urine may become entrapped in the vagina during voiding due to labial adhesions, a funnel shaped hymen, or an inappropriate position on the toilet. The classic presentation is that of a girl who does not spread her legs apart during voiding and who is not sitting all the way back on the toilet seat, but who is rather sitting near the end of the toilet seat tilting forward. Obesity may be an associated risk factor.

4.7. Bladder and bowel dysfunction

This is a term used to describe the association of any bowel and bladder dysfunction (BBD) (11).

The genitourinary tract and the gastrointestinal system are interdependent, sharing the same embryologic origin, pelvic region and sacral innervation. Although children with voiding disturbances often present with bowel dysfunction, until recently this co-existence was considered coincidental. However, it is now accepted that dysfunction of both systems, in the absence of anatomical abnormality or neurological disease, is inter-related. The common neural pathways, or the mutual passage through the pelvic floor musculature, may provide a theoretical basis for this relationship, as may the acquisition of environmental and developmental learning. The latter can be influenced by episodes of urinary tract infection, constipation, anal pain or trauma, childhood stressors, reluctance to toilet and poor toilet facilities [106].

There is also evidence to suggest that in severe cases symptoms may have a neurological basis.

BBD is seen more frequently in girls than boys and is significantly associated with the presence of both VUR and UTI [107]. VUR is slower to resolve and breakthrough urinary tract infections are significantly more common in children with BBD when compared to those without the diagnosis. Infections do not ameliorate with antibacterial prophylaxis. Age of first febrile UTI does not appear to be an aetiological factor [97], however, recurrence of UTI in children older than 5 years is associated with the presence of BBD [108-110].

Abnormal recruitment of the external anal sphincter during defaecation or at call to stool is considered causative, in that it elicits concomitant urethral sphincter and pelvic floor co-contractions. Thus, in both systems a functional obstruction to emptying is generated. In the case of the urinary system, high pressures generated by the detrusor muscle to overcome a decrease in urethral diameter can stimulate detrusor hypertrophy, detrusor overactivity, and lead to incompetence of the vesicoureteric junctions. In the early stages of defaecation disorders, bowel emptying is incomplete, infrequent and poorly executed. As the dysfunction progresses stool quality becomes abnormal, the child develops distension of the rectum and descending colon, seems to lose normal sensation and develops faecal retentive incontinence. If constipation was not present as a predisposing factor, it rapidly develops [111].

Children with BBD commonly complain of daytime urinary incontinence, non-monosymptomatic nocturnal enuresis, recurrent urinary tract infections, imperative urgency to void (OAB) and exceptional urinary frequency. On investigation, they are often noted to have poor voiding efficiency, vesicoureteric reflux, constipation, faecal incontinence, no regular bowel routine and infrequent toileting. The incidence of children with elimination syndrome and sub-clinical signs and symptoms is unknown.

It is important to differentiate between functional constipation and non-retentive faecal incontinence, as the treatment differs. The ICCS has provided documents for both disorders [111,112].

Assessment follows the same process as for other aspects of paediatric bladder dysfunction, with the addition of a 2-week bowel diary and relevant symptom score. The inclusion of an ultrasound rectal diameter measurement when assessing the bladder, has been shown to be discriminative for children with constipation. Urinary flow curve, perineal EMG and post void residual urine estimate, when considered in isolation, are not conclusive for the diagnosis of BBD. There is no evidence to suggest that anorectal manometry is warranted as a first line investigation in these children. Recently a symptom scale for BBD has been developed providing objective assessment for diagnosis and quantification of severity [113-115].

Conclusion: In the evaluation of children over 5 years of age with LUTS voiding diary, stool pattern evaluation, thorough physical examination to exclude neurogenic pathology or anatomic problems, urinalysis and uroflowmetry combined with post void residual determination are essential.

5. MANAGEMENT

The treatment of LUTD involves a multimodal approach, utilizing strategies such as behavioural modification (urotherapy), anticho-

Table 1: **Management Algorithm: Children with LUTS over 5 years of age**

Diagnostic Work-up
Voiding diary 2 full days minimum
Bristol stool scale
Questionnaires (optional)
To evaluate voiding and bowel habits, wetting severity/frequency, fluid intake, quality of life
Physical exam
To exclude neurogenic pathology or anatomic problem (meatal stenosis, labial fusion)
Urinalysis
To exclude presence of UTI or any other pathology (DM, DI)
Uroflowmetry and PVR determination (USG or bladder scan)
To evaluate urine flow and emptying efficacy
USG (optional).
To determine bladder wall thickness, upper tract changes, signs of constipation
Urodynamic studies
Not required unless refractory to management
VCUG
Only required if recurrent febrile UTI is present
Management
If UTI is present treat UTI first
If constipated treat bowel first with dietary changes and laxatives.
Urotherapy is initial therapy in all cases to maintain controlled fluid intake, regular and efficient bladder emptying
Medical treatment (anticholinergics: if OAB symptoms dominate and persist despite urotherapy.
Antibiotic prophylaxis; in case of recurrent UTI
Biofeedback is optional as first line therapy as part of urotherapy program; otherwise it recommended use if refractory to urotherapy.
Neurostimulation or Botulinum toxin A injection to detrusor is suggested if refractory to urotherapy and medical treatment but still experimental.

linergic medication and physiotherapy; along with addressing underlying and potentially complicating conditions such as constipation and urinary tract infections. In a recent publication EAU-ESPU provided guideline recommendations for daytime lower urinary tract conditions in children [116].

Behavioural modification, mostly referred to as urotherapy, is a term, which covers all non-pharmacological and non-surgical treatment modalities. It consists of rehabilitation of lower urinary tract and aims to normalise micturition in order to prevent further functional disturbances. This includes standard instructions in proper hydration and bowel management; timed voiding and basic relaxed voiding education. The child and family are educated about normal bladder function and responses to urgency. Urotherapy may often need to be combined with medical treatment including anticholinergics and antibiotics. Voiding regimens are instituted and UTIs and any constipation are treated using antibiotics and laxatives. Treatment is aimed at optimising bladder emptying and inducing full relaxation of the urinary sphincter or pelvic floor prior to and during voiding.

Recurrent urinary infections and constipation should also be addressed and prevented during the treatment period. In the case of combined bladder and bowel dysfunction it is advised to treat the bowel dysfunction first [117] as LUTS may disappear after successful management of bowel dysfunction.

Additional strategies as below may be needed for cases which do not show satisfactory response to urotherapy and who have some conditions which may need specific treatment.

- Physiotherapy which includes pelvic floor muscle awareness practices with/without sessions of biofeedback, visualisation of uroflow curves and/or pelvic floor activity and relaxation.
- Clean intermittent self-catheterization for large post-void residual volumes of urine despite urotherapy and biofeedback.
- Antimuscarinic drug therapy if bladder overactivity is present.
- If the bladder neck is associated with increased resistance to voiding, alpha-blocker drugs may be introduced.

Most often these complex patients would need urodynamic studies to delineate the underlying problem that may need specific treatment.

Treatment efficacy can be evaluated by improvement in bladder emptying and resolution of associated symptoms. Controlled studies of the various interventions are needed. As with detrusor overactivity, the natural history of untreated dysfunctional voiding is not well delineated and optimum duration of therapy is poorly described. A high success rate has been described for urotherapy programs, independent of the components of the program [117-118]. However, the evidence level is low as most studies of urotherapy programs are retrospective and non-controlled. Some recent controlled studies show efficiency of urotherapy over pharmacologic treatment and suggests its use as the initial treatment [119].

Treatment strategies may vary according to subgroups as listed below.

5.1. Overactive bladder in children:

Treatment involves a multimodal approach, involving strategies such as behavioural modification, antimuscarinic medication and neurostimulation. Underlying and potentially complicating conditions such as constipation and UTI are managed prior to intervention.

Conclusion: multimodal approach is effective in the treatment of the overactive bladder in children (LoE:3)

Recommendation: it is recommended to treat children with overactive bladder with a multimodal approach (GR:C)

5.2. Dysfunctional voiding:

Symptoms are often refractory to standard therapy of hydration, bowel management, timed voiding and basic relaxed voiding education. Effective intervention requires combination therapy, generally with a sizeable investment of time over a long period. Treatment is aimed at optimising bladder emptying and inducing full relaxation of the urinary sphincter or pelvic floor prior to and during voiding. Strategies to achieve these goals include pelvic floor muscle awareness and timing training, repeated sessions of biofeedback, visualisation of uroflow curves and/or pelvic floor activity and relaxation, clean intermittent self-catheterisation for large post-void re-

sidual volumes of urine, and antimuscarinic drug therapy if detrusor overactivity is present. If the bladder neck is implicated in increased resistance to voiding, alpha-blocker drugs may be introduced. Recurrent urinary infections and constipation should be treated and prevented during the treatment period.

Treatment efficacy can be evaluated by improvement in bladder emptying and resolution of associated symptoms [94]. Controlled studies of the various interventions are needed. As with bladder overactivity, the natural history of untreated dysfunctional voiding is not well delineated and optimum duration of therapy is poorly described.

Conclusion: treatment focussing on the full relaxation of the urinary sphincter and the pelvic floor is effective in dysfunctional voiding (LoE:4)

Recommendation: in case of dysfunctional voiding relaxation treatment of the urinary sphincter and the pelvic floor are part of the treatment (GR:C)

5.3. Detrusor underactivity:
Treatment is aimed at optimising bladder emptying after each void. Clean intermittent (self) catheterisation is the procedure of choice to promote complete bladder emptying, in combination with treatment of infections and constipation [which may be extreme in these patients]. Intravesical electrostimulation has been described, but is not recommended as a routine procedure for children.

Conclusion: Clean intermittent catheterisation can be used effectively in the treatment of detrusor underactivity but the level of evidence is low (Lo4)

Recommendation: In cases of detrusor activity, intermittent catheterisation can be used as a treatment option (GR:C)

5.4. Voiding postponement:
Urotherapy focused on behaviour modification and timed voiding is the mainstay of treatment.

Conclusion: urotherapy is effective in the treatment of voiding postponement (LoE:4)

Recommendation: urotherapy is recommended in the child with voiding postponement (GR:C)

5.5. Giggle incontinence:
Positive results have been reported with conditioning training, methylphenidate and imipramine [98,104]. Others have tried antimuscarinic agents and alpha-sympathomimetics. There is no acceptable evidence that any form of treatment is superior to no intervention.

Conclusion: conditioning training, methylphenidate, imipramine, antimuscarinics and alpha-sympathomimetics are not superior to no intervention in the treatment of giggle incontinence (LoE: 3)

Recommendation: conditioning training, methylphenidate, imipramine, antimuscarinics and alpha-sympathomimetics can be used in the treatment of giggle incontinence but with limited results (GR:D)

5.6. Vesicovaginal entrapment:
Changes in voiding position and treatment of labial adhesions will usually lead to resolution of the urine leakage.

Conclusion: correction of the voiding position and treatment of labial adhesion are effective as a treatment for vesicovaginal entrapment (LoE:4)

Recommendation: in cases of vaginal entrapment, attention should be paid to correction of voiding position and treatment of labial adhesions (GR:C)

5.7. Bladder and bowel dysfunction:
Treatment aims at assisting a child to become clean and dry in the short term, by retraining appropriate bladder and bowel awareness and teaching optimal toileting skills. As bowel dysfunction is more socially isolating than urinary incontinence, and in the light of evidence that amelioration of underlying constipation can relieve bladder symptoms, most clinicians begin with treatment of the bowel. Strategies include disimpaction [if needed], prevention of stool reaccumulation, and post-prandial efforts to empty the bowel while maintaining optimal defecation dynamics [114]. Once stools are being passed regularly, treatment focuses on teaching awareness of age appropriate fullness in the bladder, and training unopposed emptying (without straining or pelvic floor muscle recruitment), at pre-scheduled times. Pelvic floor awareness training and biofeedback therapy are integral.

There are few studies of the efficacy of treatment in children with BBD. Several authors have evaluated the outcome of constipation management on bladder symptoms; however the baseline characteristics of subjects were not described adequately enough to allow a clear diagnosis of BBD [78, 113]. A review on the effectiveness of biofeedback for dysfunctional BBD reports that 80% of children benefited from biofeedback but that the level of evidence was low due to poor study designs [112, 115]

Despite early successful treatment of LUTD there is evidence that there is a high recurrence rate of symptoms in the long term which necessitates chronic follow-up [120] and thus many patients may present later in adulthood with different forms of LUTD [121].

Conclusion: biofeedback is effective in the treatment of bladder and bowel dysfunction (LoE: 3)

Recommendation: biofeedback is recommended in the treatment of bladder and bowel dysfunction (GR:C)

Treatment:
Treatment aims at assisting a child to become clean and dry in the short term, by retraining appropriate bladder and bowel awareness and teaching optimal toileting skills. It has been shown that a full rectum can result in bladder over- or under-activity [122], and the fuller the rectum the larger the post void residual urine [123]. Functional constipation can often be missed, but it is essential in the light of evidence that amelioration of underlying constipation can relieve bladder symptoms, beginning with treatment of the bowel. Strategies include disimpaction [if needed], prevention of stool re-accumulation, and post-prandial efforts to empty the bowel while maintaining optimal defaecation dynamics [124] The aim therefore is active and ongoing (as relapse is common) bowel management to optimise bowel evacuation and reduce any faecal incontinence. The next aim is optimising age-appropriate bladder storage, blad-

der sensation and awareness and unopposed, relaxed and complete bladder emptying. Strategies to do this are described below.

Conclusion: Amelioration of underlying constipation can relieve bladder symptoms (LoE:4)

Recommendation: constipation should be treated prior to bladder dysfunction treatment (GR:C)

6. PRINCIPLES OF NON-PHARMACOLOGICAL TREATMENT OF ALL DIFFERENT STATES

Urotherapy is the term for all non-surgical and non-pharmacological interventions and is the first-line therapy for children with bladder and bowel dysfunction. It is cognitive and behavioural in nature, and undertaken by a range of clinicians with different skill sets – doctors, nurses, physiotherapists and psychologists [125].

It is classified as standard or specific urotherapy [126]. Standard urotherapy involves age-appropriate information and demystification regarding urinary and gastrointestinal tract functions, instructions on how to resolve bladder and bowel symptoms, behavioural modifications including regular bladder and bowel habits, timed voiding, fluid and dietary choices, pelvic floor muscle awareness and posture for relaxed voiding and defaecation, family documentation of interventions and symptoms and clinical support and follow-up. Specific urotherapy involves pelvic floor muscle training, electrical neuromodulation, alarm therapy and clean intermittent catheterisation. Additional treatment involves pharmacotherapy, psychotherapy and cognitive behavioural therapy, either alone or in combination.

6.1. Standard urotherapy

Initial intervention for overactive bladder (OAB), voiding postponement (VP) and dysfunctional voiding (DV) uses a non-pharmacological approach. The main objectives of treatment are to normalise the bowel and defaecation pattern, normalise bladder storage and emptying and pelvic floor activity, and cure the incontinence, infections and constipation. Initial treatment for most children with LUTS includes a regular drinking and voiding regime. For many children who present with symptoms of OAB, as well as a voiding/drinking schedule, treatment focuses on both the involuntary bladder contractions and the child's awareness of these. Children learn to recognise the desire to void and to suppress this by normal central inhibition instead of resorting to holding manoeuvres to generate urethral compression. Children with DV learn to initiate voiding with a completely relaxed pelvic floor and to pass urine in association with a bladder contraction rather than via generation of increased abdominal pressure. Dietary changes and bowel regimens are used to treat the constipation. In children with OAB and DV, pelvic floor muscle relaxation can be impaired during voiding. Physiotherapy is concerned with re-training of specific muscle groups. Adjunctive physiotherapeutic input offers children different strategies to achieve pelvic floor relaxation during micturition.

Antibiotic prophylaxis may prevent recurrent UTIs, however, data to support this is limited. A combination of bladder training programmes and pharmacological treatment, aimed specifically at reducing detrusor contractions, is often useful and sometimes necessary also.

If children do not respond to these interventions, then specific urotherapy may be instituted (see below).

A Danish report of the outcome of standard urotherapy in 240 children with daytime incontinence noted achievement of dryness in 126 children (55%). Alarm therapy has traditionally been used for the treatment of nocturnal enuresis but has been used in management of daytime wetting. When a timer watch was utilised as a reminder to void at regular intervals 70% of children became dry. Predictors for dryness included a low voiding frequency, larger volumes voided in relation to age-expected storage and fewer incontinent episodes per week [127]. There is evidence that for children who are therapy-resistant, timed voiding assisted by a timer watch added to urotherapy is effective [128].

Another study found that following a 3-month training programme, 42.8% of day wetting children were cured at 1 month, 61.9% by 6 months, and 71.4% by 1 year [129]. Allen et al. [130] reported that urotherapy patients who had good compliance with timed voiding were significantly more likely to improve their continence than those with poor compliance. It has recently been highlighted however, that there is frequently conflict between school rules, routines and toilet facilities and the urotherapy programme components. Adaptive coping techniques added to urotherapy training may enhance gains in dryness.

Several centres offer intensive urotherapy called voiding schools or even inpatient rehabilitation. A prospective evaluation of 38 Belgian children who underwent this approach showed improvement in 90% of the children with 42% becoming dry, whilst no child on the waiting list improved during the 6 months [131]. Long-term follow-up of 75 incontinent children 16-22 years after they underwent intensive urotherapy showed a good result in 84% and the authors concluded that if the original outcomes of paediatric intensive inpatient urotherapy were good, they tend to remain so over time in most patients [132].

Although there are many studies reported in the literature assessing the effects of various forms of therapy on daytime incontinence and urinary symptoms, many of these are case series rather than being randomised or controlled trials. The paucity of studies evaluating standard urotherapy initiatives has precluded double-blinded trials of novel and multimodal interventions. Whilst clinically important benefits are commonly described, and there are some studies comparing urotherapy with or without pelvic floor muscles training, with or without anticholinergics, with or without voiding re-education and uroflowmetry, with or without timer watch and others, variations in design and delivery of interventions, patient numbers, objective outcome measures and length of follow-up are sub-optimal. A recent Cochrane review concluded that most of the evidence for these interventions was of very low or low certainty [133]. However, Schafer et al. reviewed studies and concluded that standard urotherapy is effective for treating daytime urinary incontinence [134]. Another recent review concluded that standard urotherapy applied as first line treatment in BBD in children resulted in positive outcomes in symptom reduction and improvement in uroflowmetry parameters [135]. Some authors contend that in less severely affected children a thorough explanation of the underlying causes and the expected progress of resolution is sufficient treatment [136]. Buckley et al. comment that treatment choices must take into account not only a comprehensive assessment, but also the child and carers' capaci-

ties and commitment, supports available to the child and family and the resources of the health setting the child attends [123].

Conclusion: Standard urotherapy is effective as a treatment of daytime incontinence (LoE:3)

Recommendation: Standard urotherapy is recommended as a first line treatment of daytime urinary incontinence (GR:C)

6.2. Specific urotherapy

6.2.1. Pelvic floor muscle training.

In contrast to adult incontinence, little is known about pelvic floor muscle (PFM) function and training interventions in children. There are many reasons for this, including the lack of a gold standard of measurement of PFM function, not being able to be invasive and therefore using surrogate measures, for example, superficial perineals to measure Levator Ani, or the external anal sphincter to represent urethral sphincter function. These may or may not be adequate. Furthermore, a range of clinicians, trained or not in muscle re-education, participate in this work and studies reflect poor methodology or report none at all [137].

In this arena, PFM awareness (contraction vs relaxation) is primarily used to facilitate defaecation and treat DV. In the latter, the aim is to achieve relaxed unobstructed voiding and complete bladder emptying. In most instances it is not difficult for a trained therapist to teach this and feedback about performance to the child is given immediately. The aim is for the child to internalize the sensation and have sufficient awareness to practice correctly, and to apply such techniques during initiation of the void and throughout voiding. How to teach PFM awareness to a particular child depends on the motor learning needs of that child which vary with many factors, including age, sensori-motor awareness and cognitive ability.

Biofeedback is a technique in which physiological activity is monitored, amplified and conveyed to the person as visual or acoustic signals, thereby providing the patient with information about unconscious physiological processes. It is a technique which may be used, in this case, to facilitate muscle training, not as a treatment in itself. Biofeedback is mainly utilised for the management of the voiding phase (DV due to pelvic floor muscle overactivity) [138]. This is often undertaken with electromyography (EMG). EMG needs to be used in trained hands as there are many pitfalls of its use and what is seen on one day cannot be measured again, or may not reflect what happens on another day [139].

Training with biofeedback can be used as a single treatment or in conjunction with a comprehensive rehabilitation program. To assist the child to recognise detrusor contractions it may be performed by a cystometrogram during which the child is taught to recognise and inhibit involuntary detrusor contractions by watching the pressure curve during cystometry. This is invasive and a time-consuming process with limited application as a routine treatment.

Real-time uroflow can also provide indirect/surrogate feedback of the child's ability. The child sits on a toilet with a flow transducer (with or without EMG), watching the flow curve, and attempts to empty completely in one relaxed void. In the absence of real-time uroflowmetry post-void feedback can be given by the shape of the uroflow or post void residual. Ultrasound may be used to determine the post-void residual and demonstrate complete emptying.

Transabdominal or transperineal ultrasound can also give direct feedback to the child as the movement of endopelvic fascia and the effect on the bladder neck can be seen as the child contracts and relaxes the pelvic floor. Its use for PFM measurement and training has been validated in adults and is applicable to children [140].

Rectal balloon training has repeatedly been shown not to be effective routine treatment in children with bladder dysfunction [141] or defaecation difficulty [142]. For constipation and defaecation dysfunction there are studies reporting that in addition to standard medical care, the success of a physiotherapeutic approach as adequate toilet posture, abdominal musculature (involved in increased intra-abdominal pressure), PFM/sphincter/abdominal muscle dyssynergia and defaecation dynamics, rectal sensation and perception are comprehensively re-trained [143, 144].

The results of biofeedback are commonly reported as case series rather than RCT, and often the interventions are multifactorial. Results are generally positive but overall may not be superior to high quality standard urotherapy, and whether it is biofeedback, the added input of a clinician, or the effect on the bladder/bowel or reinforcement of other urotherapy advice has not been elucidated.

Long duration follow-up, whilst desirable, confounds results of interventions in children who are continually growing and maturing. Hellstrom et al. reported results of a 6-week bladder rehabilitation programme inclusive of biofeedback [145] and noted that at 3 years, 71% of the children with detrusor overactivity, 70% of those with dysfunctional voiding and 73% of those with a combined disturbance had a normal micturition pattern. The potential for bias from intercurrent events and interventions precludes statements about the efficacy of biofeedback alone.

Buckley found in a recent Cochrane review that in 11 qualifying studies no clear evidence was available to suggest that biofeedback was effective in treating children with bladder or bowel dysfunctions with no differences being found at 3-, 6- and 12-months post intervention [133]. Janet Chase stated that "Without a complete published description of interventions, clinicians and patients cannot reliably implement interventions that are shown to be useful, and other researchers cannot replicate or build on research findings". For this reason the Template for Intervention Description and Replication (TIDieR) checklist and guide has been developed and future studies should adhere to the twelve items [146].

Conclusion: Pelvic Floor muscle training is an effective treatment of dysfunctional voiding (LoE:3)

Recommendation: Pelvic floor muscle training ie recommended to treat dysfunctional voiding in children (GR: C)

6.2.2. Clean intermittent (self) catheterisation

In children with an underactive detrusor, bladder emptying may be achieved with timed and double voiding. If this does not adequately empty the bladder clean intermittent self-catheterisation (CISC) may be tried. This requires careful guidance for both the child and the parents. Sometimes it is necessary to give the child a suprapubic catheter for a while and gradually prepare him/her to accept CISC. Once the infections have cleared and the child is continent it will become easier for both the parents and the child to accept. The frequency of CISC depends on the severity of the problem and may vary between four times a day and once a day before going to bed.

Conclusion: Clean intermittent catheterisation can be used effectively in the treatment of detrusor underactivity but the level of evidence is low (Lo4)

Recommendation: In cases of detrusor underactivity with significant PVR intermittent catheterisation can be used as a treatment option (GR:C)

6.2.3. Electroneurostimulation

Electroneurostimulation (ENS) has been used in adults for a variety of lower urinary tract symptoms and its use has been reported in children for many years also. ENS has been used to influence childhood bladder and bowel symptoms (both neurogenic and non-neurogenic) using surface or skin electrodes, anal electrodes, percutaneously with needle electrodes, intravesical and implanted electrodes. Current is delivered from different stimulation devices with varying waveforms, frequencies and intensities.

Electrical current directly stimulates nerves and muscles with an immediate effect, and use of electrical stimulation in this way is often referred to as functional electrostimulation (FES). For example, FES can be used to stimulate muscles to improve function or to increase awareness, including the pelvic floor or abdominal musculature. Once neural efficiency has improved, training is augmented by active muscle training.

Neuromodulation implies that the application of electrical current alters neurotransmission patterns over time and usually with a carry-over effect. Borch et al. found no immediate bladder effect of sacral TENS in a group of children with OAB [147]. However, Dombek et al. did find a significant immediate effect in 77% of a group of children with neurogenic bladder dysfunction [148]. In LUTS, ENS has been shown to enhance beta-adrenergic activity, reduce cholinergic activity in the bladder, alter other transmitters such as GABA, nitric oxide and serotonin and raise endorphins and enkephalins in cerebrospinal fluid [149]. Although the exact mechanisms are not fully understood changes in the brain have been demonstrated. There are therefore local, spinal and supraspinal effects. Recently, a functional MRI study on 10 healthy adults, comparing sacral versus thoracic TENS showed activity in anterior cingulate cortex (ACC) and the dorsal lateral prefrontal cortex (DLPFC) were significantly increased during sacral TENS compared to rest. Thoracic TENS did not increase connectivity between the ACC and DLPFC when compared to rest [150].

Looking at TENS with non-invasive transcutaneous electrodes, the majority of studies have been done to treat OAB with electrodes positioned over the second and/or third sacral foraminae. Initially this was used for treatment-resistant OAB with a 16.6% cure rate and a 43% improvement rate after 12 weeks [151], but now is used as first line treatment. A prospective study of 69 children where sacral neurostimulation was used as first-line treatment, showed 55.1% complete resolution of symptoms after 20 sessions [152]. Other good success rates have been demonstrated in many case series and also randomised controlled studies investigating BBD (see Table 2). A current review reports the overall success rate with sacral TENS as first line treatment was 1.92 times that of children undergoing standard urotherapy alone (RR: 1.92, 95% confidence interval [CI: 1.02, 3.61]) and 1.56 for those undergoing either urotherapy alone or with pharmacotherapy [153]. Reported changes in bladder function with neurostimulation include: significantly increased bladder capacity, decreased severity of urgency, improved continence, and decreased frequency of urinary tract infections. Significant improvement in urodynamic parameters of bladder compliance, number of involuntary contractions, and bladder volume at first detrusor contraction have also been noted.

Other administrations of current to treat OAB have been with different electrode placement or type, or different current waveform. Examples are posterior tibial nerve (PTNS) (ankle) or plantar nerves stimulation with non-invasive electrodes (sole of foot) [154, 155]. In one RCT when transcutaneous PTNS was compared to sham there was a 71.42%:12.5% complete incontinence improvement respectively and AVV, MVV and NE improved significantly in the test group only ($p < 0.001$) [154]. Abd El-Moghny used intra-anal stimulation to successfully treat refractory MNE [156]. Cultural differences may determine whether this is seen as invasive or not. Different current has also been used, usually as interferential therapy (IFT) to treat constipation ,and both bladder under- and over-activity (see Table 2).

Use of neurostimulation in children with neurogenic LUT dysfunction has been reported with varying results and in 2 RCT's using transcutaneous stimulation in children with myelomeningocele one showed no significant differences in incontinence (TENS compared to sham) [157], and one that did (IFT compared to sham) [158].

Four forms of invasive ENS techniques have been reported.

Percutaneous PTNS using a needle electrode close to the medial malleolus, usually performed once per week for 30 minutes has been reported since 2002 [159]. It is used to inhibit detrusor function although has been reported in group of children with a variety of neuropathic and non-neuropathic LUTD, with symptom improvement better in the non-neuropathic group ($p=0.002$) and with reportedly good tolerability by children [160]. Barrosso et al. carried out a prospective study comparing PTNS with sacral TENS for the treatment of OAB. Children having TENS had a 70% cure rate compared to 9% of the PTNS group ($p=0.02$) but there was no statistical difference on DVSS ($p=0.55$) [161]. There is one RCT using PTNS in refractory MNE in which there was a symptomatic and urodynamic improvement in the PTNS group of 78.6% (which fell to 42.9% at 3 months) versus 14.3% in the control group [162].

Recently a pilot study on percutaneous (needle) sacral stimulation has been carried out on eighteen children (aged 4- 14 years) with OAB who underwent weekly treatment for 20 weeks. There were significant reductions in urinary urgency, incontinence, urinary tract infection and enuresis [163].

Intravesical electrical stimulation (IVES) involves introducing a cathode on a catheter into the bladder and an anode over the abdominal wall. Initially this was done on an outpatient basis and then progressed to a home-based treatment as the children were catheterising anyway because of idiopathic or neuropathic detrusor underactivity. One NRCT showed normalising of voiding in the former group in 84% children and 40% in the latter [164]. Hagerty reported 22 years of experience in neuropathic IVES in 392 children. With a mean of 6.6 years follow-up, nearly 80% had a 20% increase in bladder capacity with a, bladder pressures less than 40 cm H_2O and 61% developed or sustained bladder sensation [165]. Choi reported on 10 years' experience on IVES and UD patterns in children with spina bifida [166]. Bladder capacity increased especially if IVES was started before 18 months, detrusor sphincter dyssynergia resolved in 55.66% and in the acontractile detrusor group, contraction ability increased in 48%. Intravesical stimulation is rarely indicated but more studies are needed as treatments for bladder underactivity are few.

A recent review states “Neuromodulation is a promising tool in the management of constipation refractory to medical treatment and faecal incontinence in children” [167]. One randomised placebo-controlled trial using interferential current transcutaneously 3 times weekly, showed significant improvements in colonic transit times, decreased soiling and abdominal pain and increased quality of life in children with severe constipation [168]. Daily home treatment showed further improvements [169, 170]. Follow up on these children for an average of 3.5 years has shown that these improvements were maintained [171]. Kajbafzadeh et al. treated 30 children aged 3-12 years with neurogenic bowel dysfunction randomising them into physiotherapy plus sham or physiotherapy plus real IFT. There was a significant improvement in anorectal manometry measurements ($p<0.05$) and increase defaecation frequency ($p< 0.005$) in the real IFT group [172]. Sharifi-Rad randomised children with constipation into receiving physiotherapy or physiotherapy plus IFT [173]. Both groups improved in defaecation frequency but the IFT group had better results at 6 months ($p=0.005$). Sacral TENS has been used to treat constipation and it was reported that after the treatment 85.7% of the children’s constipation symptoms had improved according to the Rome III criteria (174). Certainly, anecdotally many clinicians note an improvement in bowel function when treating OAB in this way. Lecompte reports a small study of children with congenital abnormalities and faecal incontinence treated with PTNS with some good results as well [175].

Different modes of application have been trialled in mostly small studies with in children. There is minimal standardisation of populations, application parameters or outcome measures, and short periods of follow up. Thus, evidence is largely drawn from low quality studies with considerable risk of bias. A recent Cochrane review found that comparing TENS vs sham more children with day wetting receiving active TENS may achieve continence but there is low-certainty evidence [133]. Clearly neurostimulation in children warrants larger, controlled and randomised studies. Despite the slow pace of research, the reviewers of the articles mentioned above agree that there is a positive role for neurostimulation in children with LUTD and bowel dysfunction, and that it is adjunctive to other interventions, with no known predictors of efficacy now, but also rare and minor adverse events.

Sacral nerve stimulation with implantable electrodes, although still not approved in children is gaining importance in the treatment of children with refractory non- neurogenic and neurogenic lower urinary tract dysfunction and bowel bladder dysfunction.

Different neuroanatomical pathways have been described as targets for invasive sacral neurostimulation. The third sacral (S3) nerve root remains the main access point used for neurostimulation treatment but also the stimulation of the pudendal nerve has been reported.

In a first step a tined quadripolar stimulator lead is placed under fluoroscopic guidance and under general anaesthesia and connected with an external pulse generator. Unilateral stimulation of S3 has to be achieved. After a successful trial period a pulse generator is implanted.

In 2004 Guys et al. reported a prospective randomised controlled study on the benefits of sacral neuromodulation in 32 patients suffering from neurogenic bladder dysfunction, mainly due to spina bifida. 21 patients received an implant. 9 patients reported improvement in intestinal transit, 5 had total disappearance of urinary infection and 6 had persistent sensation of a full bladder. No one in the control group reported improvement. Three cases needed revision surgery because of lead migration, faulty connection or wound infection [176].

The same group published in 2010 the results of a multicentre, open label, randomised, crossover study in 33 children older than 5 years with mainly neurogenic pathology, suffering mixed urinary and faecal incontinence in 19, urinary incontinence in 9 and faecal incontinence in 5. The only urodynamic parameter that showed a significant change was the cystometric bladder capacity.

A retrospective study by F. Sharifiaghdas on the other hand only showed significant decreased detrusor overactivity but no significant positive effect on maximum cystometric capacity. [177]. The overall clinical response rate was more than 75%. For urinary incontinence the response rate was 81% and for faecal incontinence it was 78% [178]

Nearly the same results were mentioned in a retrospective study by AL Groen et al. :18 patients, of which 5 with neurogenic bladder, showed a good short term (78%) and long term (73%) response . [179]

Neurostimulation has also been successfully used in the treatment of bowel bladder dysfunction and refractory faecal incontinence and constipation.

In a prospective study M. E. Dwyer followed up 105 children with BBD. Ninety-four percent of the patients experienced improvement of at least 1 symptom after implantation of a sacral neuromodulator. Ten percent showed complete resolution of all preoperative symptoms. Symptom resolution was observed in 41% of the children suffering incontinence and 40% of those who were constipated.[180]

In a prospective cohort study in 30 children and adolescents (10-20 year) suffering from refractory constipation, A.A van der Wilt et al. showed a positive test stimulation in 27. In these 27 who underwent a stimulator implantation 42.9% showed durable improvement of the symptoms [181].

A prospective study by M.D. Mason et al. in a group of 30 children with refractory bowel bladder dysfunction, showed that all patients had a significant improvement in quality of life and symptom scores, and those with detrusor overactivity on preoperative urodynamics had a significantly greater improvement in symptom scores.[182]

Schober et al. described a case of refractory bowel bladder dysfunction in a patient with caudal regression and partial sacral agenesis in which they used pudendal neuromodulation (PNM) They placed the quadripolar tined electrode into Alcock’s canal adjacent to the pudendal nerve. During the stimulation trial episodes, faecal incontinence decreased significantly and bladder spasms completely resolved. Two months after implantation of the Implantable Pulse generator urodynamic testing showed a good compliance, and no more bladder overactivity [183].

Although many studies report promising results the majority also report a high complication rate, especially infection, lead migration and fracture of the lead.

A systematic review by R. Iacona et al. illustrated that both non-invasive and invasive neurostimulation are effective in the treatment of constipation and faecal incontinence in children. The main disadvantage of invasive neurostimulation is the high complication rate of 17- 53% and a reoperation rate of 11-50% [184].

In a retrospective study by M.E. Fuchs et al. on 63 children who underwent SNM, 49% because of primarily bowel symptoms and 51% for primarily bladder symptoms the incidence of reoperation was studied. 25% needed reoperation because of infection, lead breakage or migration. According to this study there is no correlation between age, gender or BMI and the complications, in contrast to former studies on smaller groups [182, 185].

As mentioned, many patients with an implant will develop post-implant complications. Up to 53% will develop pain at the implant site and 3-38% will lose effective stimulation. C.R. Powell focussed on a standardised troubleshooting algorithms to overcome these problems and to avoid surgical intervention. Changes in stimulation effect often can be overcome by reprogramming the device. Even in cases of lead migration or a fractured lead, reprograming can offer, in some cases, a solution [186].

Another important issue is the fact that an implanted neurostimulator possibly interferes with the follow-up of patients with medullary or spinal pathology as an MRi may not be performed because of the metal components of the stimulator [184]. However, newer iterations of the device are now MRI compatible.

Table 2: Non invasive ENS in children with non-neurogenic or functional bladder or bowel dysfunction RCT"s since 2009
TENS transcutaneous electrical stimulation. IFT interferential therapy. OAB overactive bladder. MNE monosymptomatic nocturnal enuresis. PFMT pelvic floor muscle training. ES electrical stimulation. PT physiotherapy.

Author and year of publication	Population	Design	N	Mode of application	Outcome measure
Hagstroem 2009	5-14 years Day wetting	TENS vs sham TENS	25	Sacral	Sig decrease daily incontinence episodes in active group vs sham (p=0.05)
Clarke 2009	8-18 years severe refractory constipation	IFT vs sham IFT	42	Quadripolar anterior abdominal wall and T10-L2	Scintigraphic transit studies sig improved in real IFT group (p 0.0001)
Lordelo 2010	Over 4 years, mean 7 years OAB	TENS vs sham TENS	37	Sacral (real) Scapular (sham)	62% cured test group. None in control (p<0.001)
De Oliviera 2013	Over 6 years Primary MNE	Urotherapy vs urotherapy +TENS	45	Sacral	Sig > in in dry nights in TENS group 61.8% vs 37.3% controls (p=0.0038)
Sillen 2014	5-12 years Day wetting	TENS + urotherapy vs urotherapy alone	62	Sacral	Reduction in wetting episodes in both groups – no sig difference
Reis 2014	5-16 years Day wetting + enuresis	PFMT (EMG) +urotherapy vs TENS + urotherapy	78	Sacral	60.6% complete resolution symptoms TENS vs 54.9% PFMS group (p=0.483)
Kajbafzadi 2015/1	Children with underactive bladder	Physiotherapy + IFT vs Physiotherapy alone	36	IFT quadripolar symphysis pubis and ischial tuberosities	IFT vs control, sig >se in voiding freq (p<0.002), sig <se bladder capacity (p<0.01), >se in Qmax (p=<0.05)
Kajbafzadi 2015/2	6-14 years Primary NE	Urotherapy (standard) vs urotherapy (standard) + IFT	54	IFT quadripolar symphysis pubis and ischial tuberosities	Sig decrease in wet nights in IFT group compared to controls at 2 months and 1 year (P=0.003 and P=0.03, respectively
Quintiliano 2015	4-17 years Urinary urgency +/- day wetting	Anticholinergics + sham TENS vs TENS + placebo	28	Sacral (real) Scapular (sham)	Both groups sig improvement in symptoms. Real TENS no side effects and improved bowel function
Patidir 2015	Mean age 8 years Refractory OAB day wetting	TENS vs sham TENS (no stimulation)	40	Tibial (transcutaneous)	Test group vs sham 71.42%:12.5% complete incontinence improvement AVV, MVV and NV improved significantly in test group only (p < 0.001)
Borch 2017	5-14 years Urge incontinence	Anticholinergics + sham TENS vs TENS + placebo vs TENS + anticholinergics	66	Sacral	TENS+anticholinergic 83% >ed treatment response than either monotherapy (p+0.05). Combined also < wet days, < severity and < voiding frequency, and TENS < PVR risk compared to anticholinergics

Author and year of publication	Population	Design	N	Mode of application	Outcome measure
Jorgensen 2017	7-11 years MNE	TENS vs sham TENS	47	Sacral	No sig. changes in no of wet nights, nocturnal urine production, MVV or voiding frequency
Abd El-Moghny 2018	8–12 years refractory PMNE	behavioural therapy and PFM training alone or added intra-anal BFB or added intra-anal ES	90	Intra-anal	3 groups had sig. improvement in first void of am, reduced wet nights. Greater improvements in ES group.
De Paula 2018	3-18 years OAB day wetting and 7 with enuresis	Tens + urotherapy vs sham +urotherapy	16	Sacral (real) Scapular (sham)	Sacral TENS – sig. improvement urgency as well as an increase in dry (p = 0.03). No difference was noted regarding day wetting.
Sharifi-Rad 2018	5-13 years Constipation	Physiotherapy + IFT vs physiotherapy with sham IFT	90	IFT Quadripolar anterior abdominal wall and posterior paraspinalT10-L4	Frequency of defaecation >ed in both groups. At 6 months better in IFT group (P= 0.005)
Ladi-Seyedian 2019	5-13 years Non-neuropathic urinary incontinence	Standard urotherapy vs physiotherapy vs physiotherapy+ IFT	46	IFT Quadripolar anterior abdominal wall and paraspinal T12 and L4	At 6 and 12 months UI sig decreased in PT + IFT group (P<0.04 and P=0.05 respectively)
Ladi-Seyedian 2020	5-10years BBD	Physiotherapy vs physiotherapy + IFT	34	IFT Quadripolar anterior abdominal wall and paraspinal T12 and L4	Significant more children receiving PT+IF [11/17 (64.7%)] had full response versus PT: P= < 0.03.
Abdelhalim 2020	7-14 years PMNE	Sacral TENS vs IFT	52	Sacral TENS S3/4 IFT quadripolar pubic symphysis to ischial tuberosity	No of wet nights, reduced significantly (P < 0.05) in both groups, in favour of IFC group

The restricted lifespan of the battery, 3 to 9 years depending on the stimulation program, is another limiting factor, implicating necessity of multiple operations in future. However, new rechargeable implants have a much longer battery life, potentially up to 15-20 years.

Compared to other treatment modalities, the cost-effectiveness of sacral neuromodulation, certainly in children is an important consideration. A study by H.S. Harvey et al showed that in adult women suffering refractory urgency urinary incontinence, SNM and BTX 200 units are both effective treatment modalities but that cost-effectiveness of SNM is much lower than BTX 200 Units [187].

General limits of the evaluation of results for invasive SNS are the small number of patients in all series, the heterogeneity of the study populations, the general absence of RCTs, the different ways to evaluate results and different clinical protocols. For all these reasons SNM in children still needs further studies (controlled and randomised).

Due to the uncontrolled design the level of evidence is low. Experience from adults treated with SNM suggests future positive development in children, in well-defined cases, to be likely.

Conclusion: non-invasive ENS is effective in the treatment of children with non-neurogenic LUTS. It is also effective in the treatment of bowel and bowel-bladder dysfunction (LoE:3)

Recommendation: non-invasive ENS is recommended as a treatment option in children with non-neurogenic LUTS and in those suffering bowel and bowel-bladder dysfunction (GR:C)

6.2.4. Alarm therapy

Alarm therapy has traditionally been used for the treatment of nocturnal enuresis as it is the most effective treatment with the best long-term results with approximately two thirds of children becoming dry. When appropriate, the alarm is considered as first line treatment for enuresis. (See above) Alarm therapy can also be used for daytime wetting but not often. Only one randomised clinical trial has been published to establish the efficacy of this form of treatment. Halliday et al. compared a contingent alarm which sounded when the child wets with a noncontingent alarm system (which sounded at intermittent intervals to remind the child to void) [188]. Forty-four children participated in the study, 50% were assigned to each form of therapy for a 3-month period. Success was measured as 6 consecutive weeks without daytime wetting. Nine children in the non-contingent group and 6 children in the contingent group had persistent wetting. Although the risk of persistent wetting with the contingent alarm was 67% of the risk of persistent wetting with the noncontingent alarm, the difference in the reduction in wetting between the groups was not significant (RR 0.67, 95% CI 0.29 to 1.56). In a retrospective review by Van Laecke et al., a cure rate of 35% after the use of a daytime alarm was described [189]. Due to the retrospective design of the study the level of evidence is low.

Conclusion: alarm therapy is effective in the treatment of daytime incontinence in children (LoE:3)

Recommendation: alarm therapy can be used in the treatment of daytime incontinence (GR:3)

6.3. Group training

Group training programmes have been developed for children with treatment-resistant incontinence. The program includes provision of information, coaching regarding drinking and voiding habits, relaxation and stress-reduction techniques, as well as cognitive-behavioural therapy (CBT). The training proved to be effective in pre-post analyses [190].

6.4. Conclusion

Many clinical studies describe combinations of therapies rather than single interventions, which makes it difficult to evaluate the results. Most studies only state the clinical responses, and do not provide information on urodynamic parameters or muscle measurements before and after treatment. A 'normal' flow curve may not mean normal voiding if no information is provided on post-void residual urine. In most papers the inclusion and exclusion criteria are not clearly documented, and it may very well be that the more difficult patients with both storage and voiding dysfunction were included in the study population. Furthermore, different series may describe different groups of patients due to poor definitions and an inadequate classification system. Again, we recommend the Template for Intervention Description and Replication (TIDieR) checklist guide future studies [146].

7. PHARMACOLOGICAL TREATMENT

7.1. Antimuscarinic therapy

Antimuscarinic therapy remains one of the common forms of therapy for overactive bladder / detrusor overactivity. Its use is predicated on the concept that parasympathetic mediated stimulation of muscarinic receptors in the bladder causes detrusor overactivity, which is responsible for the symptoms of overactive bladder. Antimuscarinic agents have been demonstrated to increase bladder capacity, increase bladder compliance and decrease detrusor contractions in neurogenic detrusor overactivity. Detrusor overactivity is believed to play a role in many children with functional incontinence, vesicoureteral reflux and urinary tract infections [191]. More commonly, pharmacotherapy is instituted when behavioural therapy has failed to achieve a satisfactory outcome. Some clinicians use pharmacological therapy as first line in children with moderate to severe daytime incontinence [73].

Despite the frequent use of anticholinergic therapy, often in conjunction with a behavioural therapy regimen, the outcome of pharmacological therapy for daytime urinary incontinence is "unpredictable and inconsistent" and there are few randomised studies available to assess drug safety and efficacy in children.

The following antimuscarinics are briefly discussed:

- Oxybutynin: approved for use in children FDA EMA
- Propiverine: approved for use in children EMA
- Tolterodine: tested phase 3 clinical trials, not approved for use in children
- Solifenacin: tested phase 3 clinical trials, awaiting approval for use in children
- Terodiline: investigated in a randomised placebo controlled trial, withdrawn because of serious cardiac side effects.
- Trospium chloride: approved for use in children 2 years and older FDA EMA
- Fesoterodine: used in small series in children, but not approved for use in children

Oxybutynin

Currently the pharmacological therapy most widely used in children with detrusor overactivity is oxybutynin [192]. In 2002, a long-acting formulation, Oxbutynin XL, was approved by the FDA for use in children [193]. Historically, oxybutynin use has been limited by its adverse effect profile with such side effects as dry mouth, constipation, facial flushing and CNS effects. The incidence of side effects seems to be dose-related, both for oral and intravesical administration [194]. The CNS effects are related to the ability for oxybutynin and its metabolites to cross the blood brain barrier. Oxybutynin XL utilises a novel delivery system, which results in absorption in the large intestine, thereby bypassing the first pass metabolism in the liver. This leads to a decrease in the amount of active metabolite [produced in the liver]: resulting in a more favourable tolerability profile. The delivery system requires an intact tablet and thus it cannot be cut or crushed to facilitate swallowing. Another method of delivery of oxybutynin is intravesical therapy. This method of delivery also avoids the first pass effect and leads to increased amounts of oxybutynin available compared to immediate release oxybutynin. Its use in the neurologically intact patient is limited by the need for catheterisation [194].

Transdermal delivery of oxybutynin is another approach to avoid the first pass metabolism through the liver. Limited small studies have been reported with children and the localized skin irritation and continued adherence of the transdermal patch limit its utilisation.

There are only a few studies and only one randomised and double blinded, assessing the efficacy of oxybutynin in detrusor overactivity (DO) in children. In the European Bladder Dysfunction study, 97 children with DO on cystometrogram, received oxybutynin or placebo: the placebo effect of 45% was equal to the effect of oxybutynin chloride [195].

Curran et al. in a retrospective review of 60 patients assessed the efficacy of several agents, primarily oxybutynin in children with non-neurogenic detrusor overactivity, confirmed by urodynamics, who were refractory to behavioural therapy. Some children were treated with combination therapy. Eighty percent had complete resolution or a significant improvement in their urinary symptoms. The authors noted an average time to resolution of symptoms of 2.7 years (range 0.2 to 6.6), however patients were not followed frequently [196]. In a study by Van Hoeck et al. holding exercises with and without oxybutynin showed no beneficial effect on bladder volume. [197].

Conclusion: Oxybutynin is an effective treatment in children with incontinence due to detrusor overactivity (LoE:3)

Recommendation: Oxybutynin is recommended in the treatment of daytime incontince in children with bladder overactivity. Attention should be paid to adverse effects (GR:B)

Propiverine

Propiverine is the second antimuscarinic drug approved by the EMA for use in children. A randomised, double-blind, placebo-controlled phase 3 trial with propiverine in children aged 5-10 yr. was reported in 2008. Of 171 randomised children, 87 were treated with propiverine and 84 with placebo. The primary efficacy outcome, decrease in voiding frequency, was -2.0 episodes for propiverine versus -1.2 for placebo; p=0.0007. Superiority could also be demonstrated for increase in voided volume (31.4 vs. 5.1ml; p<0.0001) and reduction in incontinence episodes (-0.5 vs. -0.2) episodes per day; p=0.0005. This clinical trial showed superior efficacy of propiverine over placebo and good tolerability for the treatment of children suffering from DO and urinary incontinence. [198,199] This is the first study with level of evidence 1 that demonstrated a beneficial effect of anticholinergic therapy in children.

A retrospective study published in 2012 on 68 children with OAB, reported a response rate of 86.8% [200].

Conclusion: propiverine is effective in the treatment of daytime incontinence in children (LoE: 1)

Recommendation: propiverine is recommended as therapy for urinary daytime incontinence (GR: B/C)

The following antimuscarinics are not approved for use in children, and may only be used off-label.

Tolterodine

Tolterodine is a non-selective antimuscarinic used for the treatment of overactive bladder and detrusor overactivity in adults. It is the first antimuscarinic agent designed specifically for use in detrusor overactivity and is felt to be “bladder selective”. Its affinity for the bladder compared to other organ systems has been suggested to account for a favorable tolerability profile. The chemical nature of tolterodine makes it less likely to penetrate the blood brain barrier, which is supported by EEG studies [201]. The delivery system of the long acting preparation is such that the capsule may be cracked and “sprinkled” on food. Tolterodine has not been approved for use in children but there are several studies, which evaluated its safety and efficacy in children with detrusor overactivity. Hjålmas reported the results of an open label, dose escalation study using immediate release tolterodine in 33 children [202]. Doses ranged from 0.5 mg po BID to 2 mg po BID for 14 days. The results demonstrated a 21% (23% with 2 mg po BID) mean decrease from baseline in micturition frequency and a 44% mean decrease from baseline for the number of incontinence episodes in children treated with 1 mg and 2 mg po BID. Bolduc et al. reported on a prospective crossover study of 34 children followed for > 1 year who were crossed over from oxybutynin to tolterodine because of adverse effects with oxybutynin [203]. Detrusor overactivity was confirmed in 19/20 who had urodynamic studies performed prior to therapy. Children received either 1 mg or 2 mg po BID and the median treatment period was 11.5 months. Efficacy was assessed by a questionnaire and was comparable for oxybutynin and tolterodine. Sixty-eight percent noted a > 90% reduction in wetting episodes at 1 year and an additional 15% noted a > 50% reduction in wetting episodes. Fifty nine percent reported no side effects with tolterodine and 18% reported the same side effect as with oxybutynin, but felt it was less severe. Eight patients (24%) discontinued tolterodine.

Munding et al. reported on the use of tolterodine in children with “dysfunctional voiding” manifested as daytime wetting, frequency or urgency [204]. There was no documentation of uroflow studies to make the diagnosis of “dysfunctional voiding” and from the symptoms these children appeared to have detrusor overactivity. Children were started on behavioural modification for 4-6 weeks and pharmacological therapy was instituted if they failed or had only slight improvement with behavioural therapy. A minimum of 1 month’s follow-up was needed for inclusion, but the mean follow-up was only 5.2 months. Doses ranged from 1 mg po BID to 4 mg po BID. Assessment of results was made by telephone survey. Thirty-three percent had > 90% reduction in daytime and night-time wetting episodes and 60% had > 50% reduction. Four patients (13.3%) had side effects, constipation in 2, dry mouth in 1 and diarrhoea in 1.

Reinberg et al. performed an open label parallel group retrospective study of the efficacy and safety of immediate release and long acting tolterodine and extended release oxybutynin [205]. Children started out with the lowest possible dose, 2 mg tolterodine and 5 mg oxybutynin and titrated up according to response and side effects. Children were arbitrarily assigned to therapy based on the formulary restrictions of the health plan and there was an uneven distribution of patients in the treatment groups. Final dose and duration of treatment were not noted. Study nurses asked about side effects and a voiding diary was used to assess efficacy. The authors concluded that extended release tolterodine (p<0.05) and oxybutynin (p<0.01) were more effective than immediate release tolterodine in improving urinary incontinence symptoms and that extended release oxybutynin was more effective than extended release tolterodine in resolving diurnal incontinence (p<0.05) Long term tolerability of tolterodine extended release in a large paediatric population has been shown [206].

Conclusion: Tolterodine is effective and safe in the treatment of overactive bladder in children (LoE:3)

Recommendation: Tolterodine is recommended as a therapy for overactive bladder in children. The is off-label (GR:C)

Solifenacin

Solifenacin is an antimuscarinic agent used in children with OAB: Hoebeke et al. published results on 139 children with therapy resistant OAB, with favourable results, and few side effects, in 2009 [207].

Bolduc et al. conducted a prospective, open label study, and published their results in 2009: 72 children enrolled, 45 with non-neurogenic DO. Continence improved in all patients, including 24 who were dry, and 42 and 6 who were significantly and moderately improved, respectively [208].

Long term use showed that high subjective and objective success rates were maintained over a longer follow-up [209].

Conclusion: Solifenacin is effective in the treatment of overactive bladder in children (LoE:2)

Recommendation: Solifencin is recommended as treatment of overactive bladder in children . The use is off-label in non-neurogenic children(GR:B)

Terodiline

One of the drugs which has been investigated in a randomised placebo controlled trial was terodiline [210,211]. Because of serious cardiac side effects terodiline has been withdrawn from the market and is of only historical interest.

Trospium chloride
Trospium chloride has been used in small series in children. It is currently available in a twice a day dosing formulation that can be used in children. For adults a once daily preparation is available. In the adult population, there is a 16% intra-individual variability in bioavailability and 36% inter-individual variability. Absorption is affected by food intake. Trospium's chemical structure make it unlikely to penetrate the blood brain barrier as supported by EEG studies. Lopez Periera et al. evaluated the use of trospium in 62 children with documented detrusor overactivity and absence of 'detrusor sphincter dyssynergia' [212]. Children were randomly assigned to 10, 15, 20 or 25 mg of trospium administered in 2 divided doses or placebo. Fifty-eight children were evaluated. Response rates were assessed by incontinence episodes and urodynamic parameters. Overall, 32% had an excellent response, 42% a good response and 8% a fair response. Detrusor overactivity completely resolved in 35%. Four children had medication related adverse effects including headache, dizziness, abdominal cramps and dry mouth.

Conclusion: trospium chloride is effective as therapy for overactive detrusor in children (LoE:3)

Recommendation: trospium chloride is recommended for the treatment of overactive detrusor in children. The use is off-label in non-neurogenic children (GR:C)

Fesoterodine
Fesoterodine is approved for adults, and is reportedly safe and effective. A post marketing surveillance study in Korea with 2978 adults with OAB scored on efficacy showed amelioration in 91% [213]

Comparison with solifenacin showed no difference in efficacy, but more side effects with fesoterodine [214].

Expert opinion is that fesoterodine has a similar tolerability and side effect profile to other antimuscarinics and is, therefore, unlikely to revolutionise the treatment of the overactive bladder [215].

In children, the only study done is a dose-escalating study of the pharmacokinetics and tolerability, showing steady-state plasma 5-hydroxy-methyltolterodine exposures similar to those in adults. The doses given were well tolerated. Only 10 children with non-neurogenic bladder and OAB were included [216].

Darifenacin
Darifenacin is approved for use in adults as well. Although already mentioned in 2004 to be promising, in children, up to date no studies have published [217].

Combination therapy
Some authors have tried combinations of anticholinergics for refractory OAB: Bolduc et al. treated 33 children with a combination of oxybutynin and solifenacin or tolterodine with good success [218, 219].

Fahmy et al. enrolled 72 children in a prospective study where trospium chloride was added to oxybutynin in refractory OAB: 68% showed improvement, 22,2% were completely dry [220].

7.2. Beta3-adrenoceptor agonists
Mirabegron is the first of a new class of drugs for the treatment of OAB. Stimulation of β3-adrenoreceptors results in relaxation of the detrusor smooth muscle and improves bladder compliance and bladder capacity. Randomised controlled trials in adults show that mirabegron decreased the number of micturitions and incontinence episodes in a 24-hour period compared with placebo. Mirabegron is approved for use in adults [221,222].

A small number of studies have been published in children. A prospective off-label study in 58 children with refractory OAB or with significant side effects with at least two different antimuscarinic agents were recruited. Continence improved in 52 of 58, with 13 being completely dry. Eight patients reported mild or moderate side effects. Absence of a placebo group is a limitation of the study [223].

Phase 3 studies with mirabegron are currently ongoing in children with neurogenic bladder, but not yet in neurologically normal children. A recent study evaluating the pharmacokinetics (PK) of mirabegron in children demonstrated that single, weight-adjusted paediatric mirabegron doses were successfully predicted by population PK modeling to achieve drug exposures comparable with steady state in adults [224]. Miabegron has been FDA approved only for the treatment of neurogenic detrusor overactivity in children aged 3 years and older

Conclusion: Mirabegron is effective in the treatment of children with overactive bladder (LoE:3)

Recommendation: Mirabegron is recommended for the treatment of overactive bladder in children. The use is off-label in non-neurogenic children (GR:C)

7.3. Botulinum Toxin
Botulinum toxin is used in children, mainly with neurogenic detrusor overactivity. Botulinum toxin has recently been approved by the FDA (February 2021) for the treatment of neurogenic detrusor overactivity (NDO) in paediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication. The safety and efficacy of OnabotulinumtoxinA was evaluated in a 48-week prospective, multicenter, randomised, double-blind study in children (aged 5-17 years) with NDO and urinary incontinence [225]. This phase 3 study of more than 100 pediatric patients demonstrated that the intradetrusor administration of OnabotulinumtoxinA of 200 Units (not to exceed 6U/kg) was well tolerated and effective for the treatment of NDO in children. The reduction in daytime urinary incontinence along with a lowered maximum bladder pressure and increased bladder capacity at week 6 (primary timepoint) were the main significant clinical benefits.

In children, botulinum toxin is injected in 20 spots along the detrusor wall. Although the dosage in children varies in different published studies, the FDA labelling is approved for dosing of up to a maximum of 200 U and not to exceed 6U/kg [225]. The results last about 6-9 months.

There is no approved study by the FDA or EMA for the usage of botulinum toxin in non-neurogenic detrusor overactivity in children. One prospective uncontrolled study by Hoebeke et al. in 21 children showed beneficial effects of botulinum toxin in 70% of children with therapy resistant detrusor overactivity [226].

Urodynamic assessment demonstrated improvement after botulinum toxin A in detrusor contractions and bladder capacity in a prospective study with 13 children [227]. Leon et al. published an even smaller prospective uncontrolled series in 2014 on 8 children with favourable results [228]. Other published studies are all retrospective: A retrospective study in 30 patients by Blackburn et

al. published in 2013 and a retrospective study in 57 patients by McDowell published in 2012 demonstrated a good response [229, 230]. Injection of botulinum toxin into the external sphincter is also possible, but the results are more variable and last only 3-4 months [231]. Radojici et al. describe excellent results in the treatment of dysfunctional voiding. In 20 children, good results were described for 17 patients [232]. In a retrospective study by Franco et al. similar results were described in 16 children, however using a higher dosage [233].

These results are confirmed by 't Hoen et al., and by Vricella et al., but the effect in their series was longer: they report safe and persistent satisfactory results during an average of 13 months in 18 of 20 patients and 15 months in 8 of 12 patients respectively with therapy-refractory dysfunctional voiding [234,235].

Less invasively, botulinum toxin can be administered electromotively: a small study in 15 children showed that this type of administration is feasible, safe, and results in considerable improvement on urinary incontinence [236].

Conclusion: Botulinum toxin is an effective therapy for detrusor overactivity in children (LoE:3)

Recommendation: Botulinum toxin is recommended as treatment for detrusor overactivity in children.The use is off-label in non-neurogenic children (GR:C)

7.4. Alpha-adrenergic blockers

Treatment of the overactive pelvic floor and sphincter is much more difficult. Treatment with alpha-adrenergic blockade seems promising, but from the presented studies it is difficult to draw firm conclusions, as most series are small, not randomised and describe a mixed patient population [237-239].

In a more recent uncontrolled study by Donohoe et al. a total of 26 patients with primary bladder neck dysfunction (20 males, 6 females, mean age 12.8 years) were treated with alpha-blockers. Mean average and maximum uroflow rates improved from 5.5 to 12.6 cc per second and from 10.3 to 19.7 cc per second, respectively, while mean EMG lag time decreased from 24.4 to 5.7 seconds and post-void residual urine volume from 98.9 to 8.9 cc (all p <0.001). Mean follow-up was 31 months and no major adverse side effects were observed [240]. Further randomised controlled studies are needed to define the place of alpha-blockers.

Conclusion: alpha-adrenergic blockers are effective in the treatment of primary bladder neck dysfunction in children (LoE:3)

Recommendation: alpha-adrenergic blockers are recommended for treatment of primary bladder neck dysfunction in children (GR:3)

Because there is much variability in presenting symptoms as well as the underlying pathology an individual approach is advisable: a step by step algorithm has been developed by Marschall-Kehrel, which seems to deal with many of these variables [241].

Conclusion: a step by step algorithm is an effective tool for an individual approach of children suffering urinary incontinence (LoE:3)

Recommendation:the use of recommended for the treat a step by step algorithm is recommended for the treatment of urinary incontince (GR: B/C)

The limited number of identified randomised controlled trials does not allow a reliable assessment of the benefits and harms of different methods of management in children. Further work is required in this difficult clinical area. The establishment of outcome measures is needed, to facilitate randomised controlled trials of routine therapy. Interventions that would benefit from further investigations include: bladder and voiding education, bladder retention training, bowel management, hypnotherapy and alternative therapies, psychology, prophylactic antibiotic medication, neuromodulation, biofeedback therapy and pelvic floor muscle awareness and specific relaxation. Only then can the efficacy of new interventions be measured in children with detrusor overactivity or dysfunctional voiding.

Development of less invasive methods of diagnosis and treatment should therefore be encouraged.

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V. NEUROGENIC DETRUSOR-SPHINCTER DYSFUNCTION

1. INTRODUCTION

Neurogenic detrusor-sphincter dysfunction (NDSD) develops in response to a congenital or acquired lesion in the spinal axis at any level below the pons. These lesions result in various lower urinary tract dysfunctions which may be manifested as urinary incontinence, urinary tract infections (UTIs), vesicoureteral reflux (VUR), and renal damage, either on the basis of scarring from infection or as a result of high resting storage pressures. While we commonly place a greater emphasis on the management of incontinence in these patients because it affects their quality of life in the present, **the primary goal of their management must be to preserve a safe low pressure lower urinary tract**. Failure to do so can result in an obstructive uropathy that over the long term leads to renal failure, dialysis, and transplantation. The statistics are sobering; approximately 25% of young adults with spina bifida shows signs of renal insufficiency, and up to 5% have required transplantation [1, 2]. What makes this a particularly difficult problem to manage is that the resulting renal failure develops insidiously with the average age of transplant being 27 years of age (Figure 1).

The problem is further compounded by the lack of an accurate measure of the GFR in these patients [3-5]. This is because the equations to estimate GFR from a creatinine value are based on healthy individuals; they do not take into account the diminished muscle mass seen in these patients and the challenge of measuring an accurate height in patients who may be wheelchair dependent or have severe scoliosis. By the time the creatinine begins to rise, a substantial loss of GFR has occurred. The majority of these patients who present in renal failure do so long after they have left pediatric care; this can diminish the sense of urgency we must have to optimise lower urinary tract function early in life by teaching

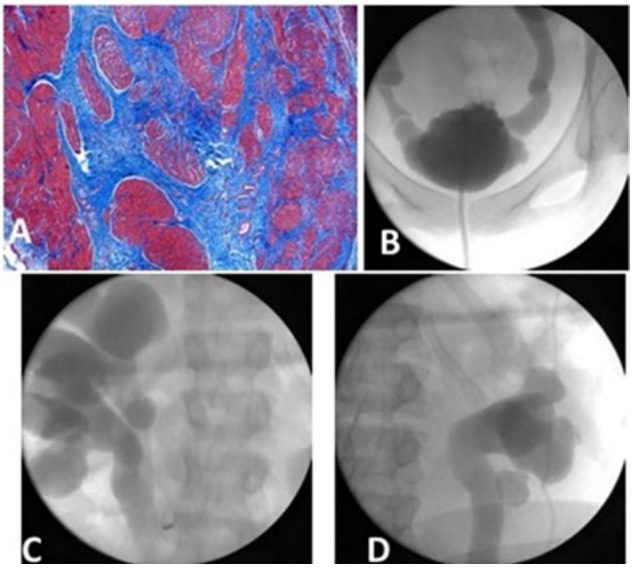

Figure 1 – This patient developed end stage renal disease in her 20s as a result of her neuropathic hostile bladder. Bundles of collagen (blue) are seen among sparse smooth muscle (red) (A). The bladder is small and non compliant (B) and there is massive reflux into the upper urinary tract (C&D)

families and children the importance of learning and adhering to a regimen of clean intermittent catherisation (CIC) [6, 7]. In the ideal setting, patient management should be driven by the scientific principles that describe the physiology of the lower urinary tract and well done clinical trials; but the reality is that managing the social aspects of this condition are as important if not more important than the science alone. **The old adage that is better to be a safe wet, than a dangerous dry remains true**.

Sixty years ago these children rarely survived past infancy. The first major advance for the care of children with spina bifida was the introduction of shunting to manage hydrocephalus [8]. As these children survived beyond infancy, it became apparent that the urinary tract would prove to be a source of major morbidity unless it could be successfully managed [9]. Reflux and recurrent urinary tract infections were noted by the early practitioners of paediatric urology, but urodynamics for children were not available at that time. This resulted in the adoption of urinary diversion with ileal conduits or ureterostomies. The vesicostomy was adopted as a means to drain the lower urinary tract and preserve the upper tracts, and continues to be used today [10, 11]. Such an approach would have preserved the renal function of the patient shown in figure 1 who now suffers the double burden of incontinence and renal failure. A major advance in the management of these children was the introduction of CIC [3, 4]. In reintroducing CIC to modern medicine, Lapides created the possibility for bladder preservation or continent reconstruction. Clearly preservation of the native bladder is the optimal outcome, although it is important to note that even in these cases, malignancies in later life have been described in the absence of augmentation [12]. Numerous approaches to the surgical reconstruction of the lower urinary tract have been described over the past half century. In recent years, the application of robotic assisted reconstruction has begun to take hold. But no matter which of the many reconstructive techniques is selected, **the approach to continence for these children must begin with an assessement of the child's motivation and the total commitment of a motivated and well informed family**. Given the potential for complica-

tions with such surgery and the need for fastidious adherence to CIC and followup visits, a failure to properly select and educate the patient and family can set up the potential for decisional regret [13]. But when patients and families are properly selected, the surgical creation of continence (by whichever method is used) offers the patient an enhanced quality of life [14].

It is worth distinguishing between a neurogenic and a neuropathic bladder. A neurogenic bladder arises from an anatomically defined neurologic deficit such as spina bifida, spinal cord injury (from trauma or compression by tumors), sacral agenesis, or following surgical excision of a sacrococcygeal teratoma. In contrast a neuropathic bladder may arise from posterior urethral valves, connective tissue disorders (such as Ehlers Danlos syndrome), mutations in smooth muscle actin (which results in hollow visceral myopathy) [15], recurrent infections, or behavioural issues. Some cases resist such a categorisation, of which Hinman's Syndrome is one such example [16]. While the Hinman Syndrome was originally felt to fall into the "behavioural" category, Ochoa described several familial cohorts of patients with classic detrusor sphincter dyssynergia some of whom went on to develop renal failure [17, 18]. These patients had no obvious neurologic finding to explain this. This cohort was studied extensively and led to the discovery of mutations in the heparanase 2 gene as the genetic etiology [19]. Deletion of heparanase 2 in mice produces a voiding phenotype of retention, with a higher leak point pressure [20]. Taken together, these findings suggest that even a normal spinal MRI does not rule out a neurologic etiology for detrusor sphincter dysynergia. Another example would be mitochondrial disorders which might cast an effect on the nervous system as well as the smooth muscle of the bladder and bowel [21].

The most common cause of NDSD in children is neurospinal dysraphism which presents across a spectrum ranging from myeloschisis to myelomeningocele. In the neonatal phase many of these infants appear to void and bladder scanning may show that they do empty. However over time, a different picture emerges and the bladder begins to show the strain of being subjected to high pressure voiding and worse yet, high pressure storage. This transition which can occur silently will be detected only through videourodynamics which play a role in the identification of the hostile bladder. Typically the neonate with spina bifida will undergo a videourodynamic study around 3-4 months of age and about 20% of these studies will show fairly normal findings. But with time the urodynamic findings are likely to change as a result of high pressure voiding due to NDSD which can result in bladder wall fibrosis and a loss of bladder compliance which is often accompanied by the onset of reflux. This change in urodynamics serves to point out the need for fastidious follow up of these patients. A carefully done video urodynamic evaluation with a systematic analysis of the individual components of the study can be used in conjunction with a scoring system to predict which patients are at risk of upper tract damage [22]. A classic paper suggested that upper tract changes are more likely to occur once a passive leak point pressure of 40 cm H2O is recorded [23], although today there is a growing awareness that this number is likely to be much lower especially when patients are followed over many years. This pathophysiology makes sense given the established relationship between bladder pressures, and those recorded in the upper urinary tract in clinical [24, 25] as well as investigative [26] settings.

The past half century has seen a remarkable improvement in the management of patients with spina bifida, which in part is the result of better management of the lower urinary tract. However sophisticated our current urodynamics systems look, evocative cystometry has some significant limitations. This is in part due to the higher than normal fill rates used, and a common failure to measure and account for natural urine production during the study. In addition, the study is usually done with a patient supine as opposed to standing or sitting. Microelectronics and nanotechnology offer the promise of prolonged (and perhaps even permanent) ambulatory monitoring that will give more accurate measurements of the physiology of the lower urinary tract in real time [27, 28]. Application of these new technologies in this patient population will represent a significant advance and allow for better stratification of patients to identify those at risk of upper tract decompensation. Another area of need is in the interpretation of VUDS or UDS. There is significant interobserver variability in the interpretation of VUDS or UDS [29, 30]; we can anticipate the application of machine learning and artificial intelligence to help improve the accuracy of these studies which will offer a clinical benefit to the patient, and to research groups trying to assess outcomes [31]. No matter which new tools and technologies are introduced, the goals remain the same; to preserve renal function, and to achieve continence at an appropriate age.

2. PRESENTATION OF NEUROGENIC DETRUSOR-SPHINCTER DYSFUNCTION IN CHILDREN

The most common reason for NDSD in children is spinal dysraphism which arises due to incomplete closure of the vertebral column and malformation of the embryonic neural tube. The closure of spinal canal in utero takes place in a cranial to caudal direction and is complete by 35 days of gestation. The failure of mesodermal in-growth over the developing spinal canal results in an open lesion most commonly seen in the lumbosacral area. The degree of this closure deficiency contributes to a variable presentation of neural injury with varying degrees of LUTD and lower extremity problems. **The type and degree of detrusor sphincter dysfunction is poorly correlated with the type and spinal level of the neurologic lesion**. The process of spinal closure is in part folic acid dependent. Maternal dietary supplementation with folate in advance of conception has been shown to reduce the incidence of spina bifida [32, 33]. In the US alone, dietary folate supplementation has been estimated to prevent some 670 births with spina bifida resulting in a 603 million dollar lifetime health care savings for each birth year cohort [34]. There is a poorly understood genetic component, as the incidence of SB is increased if there is a family history. A patient with spina bifida has about a 4% chance of having a child with spina bifida [35]. Application of copy number variant analysis and or whole exome sequencing in these patients should allow for identification of the genes or gene networks that contribute to this closure and hopefully allow for new approaches to prevention [36].

Myelodysplasia, also commonly known as **spina bifida** (SB), is a general term that describes incomplete closure of the vertebral column and malformation of the embryonic neural tube. A wide spectrum of lesions are seen ranging from a failure of fusion of the vertebral bodies with a herniation of the dura with or without neural elements within the sac (meningocele), or a lipomeningocele in which fat is also contained within the meningocele. The most common and most dangerous form is myelomeningocele in which there is a herniation of the spinal cord out onto the back and there is no dura or skin covering the neural placode. In addition to the danger of sepsis posed by exposed neural elements, these lesions are often associated with hydrocephalus which necessitates placement

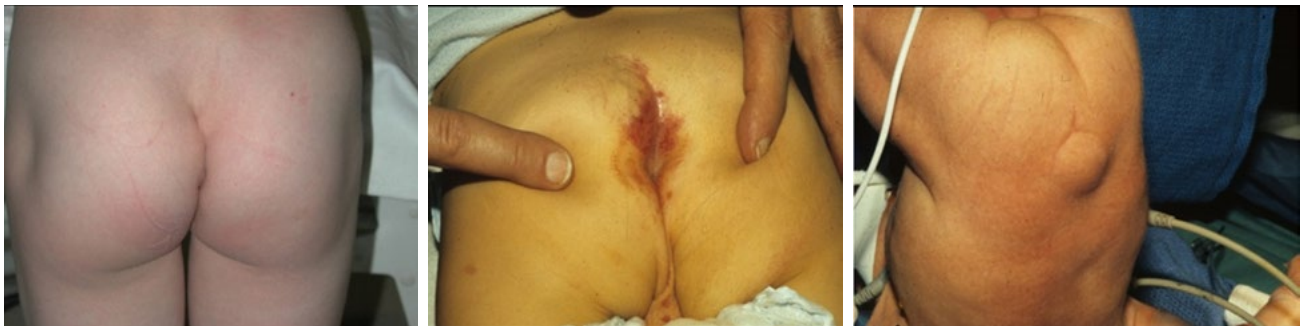

Figure 2 – Examples of the kind of sacral spinal findings on physical exam that should trigger suspicion for a tethered cord and lead to an MRI of the spine. However tethering can be seen even in the presence of a normal physical examination.

of a shunt to prevent herniation. These diagnoses are most likely to be made in utero, or in the newborn nursery. The neurologic lesions are variable and will be effected by the degree to which the neural elements are extruded. Although we can assess the vertebral level of the lesion, this does not correlate well with the neuro-urologic outcomes. In general however the lower the level of the lesion, the less the need for shunting, and the better the neurodevelopmental outcome. Even after a foetal or neonatal closure, the spinal cord can retether producing changes in gait or the urodynamics [37].

In occult myelodysplasia, the lesions are not overt and often with no obvious signs of neurological lesion which explains why these lesions are not diagnosed in the neonatal period. A tethered spinal cord with or without an associated lipoma is the most likely finding in this scenario, and with spinal MRI this diagnosis can now be made with accuracy. While it is true that a cutaneous lesion over the sacral area may be seen in a substantial percentage of these cases (Figure 2), there are many cases that have absolutely normal sacral anatomy . Lesions that arouse suspicion may include a dimple, skin tag, hair tuft, vascular malformation, or lipoma; a study in 70 such infants found a low lying conus in 20% [38]. Many older children present with a normal spinal exam, but worsening gait and new onset bowel/bladder symptoms. They may also present with back pain, a loss of perineal sensation, or a complaint of sexual dysfunction. In a child with recalcitrant bowel bladder dysfunction and a normal sacral examination, it is reasonable to consider an MRI to rule out a cord tether, but it must be recognized that the yield is low [39].

Sacral agenesis is a rare congenital anomaly that involves absence of part or all of one or more sacral vertebrae. Perineal sensation is usually intact and lower extremity function is usually normal and the diagnosis is made when a flattened buttock and a short gluteal cleft is seen on physical examination [40]. Most of these patients will require CIC for continence.

Cerebral palsy patients may also present with varying degrees of LUTD usually in the form of overactive detrusor and wetting. Many of these patients can achieve continence with the use of anticholinergics and timed voiding. Their voiding phenotype does not seem as severe as that seen in patients with spina bifida. This likely is a reflection of the prolonged exposure of the spinal cord elements to amniotic fluid throughout gestation. In contrast, patients with cerebral palsy have normal foetal development until later in the pregnancy when the asphyxia occurs.

Imperforate anus is a rare anomaly and presents with a closed rectum that does not open onto anal skin verge. Traditional thinking was that the incidence of tethered cord was associated with the level of the imperforate anus with a higher incidence of tethering noted if the fistula developed above the levators. However in one series, tethered cords were observed in 35% of patients who were imaged routinely with MRI and the level of the fistula did not matter [41]. These children should all be imaged with a spinal sonogram in the newborn nursery prior to the calcification of the vertebrae. Some series suggest that the tethering does not impact bowel continence and advocate observation [42], while others suggest prophylactic detethering [43]. In another large series, 36% of all patients were shown to have a tethered cord, and if the fistula ended at the bladder neck, this defined a subset at high risk for bowel bladder control [44, 45]. Early detection of this problem in imperforate anus patients is important to improve the child's chance of maintaining healthy kidneys and allows for proper counselling of the family. In the absence of this knowledge they will be more likely to embark upon toilet training and encounter frustration. The sooner a family understands their child has a neurogenic bladder and/or bowel, the better the outcome.

Sacrococcygeal Teratoma presents as a mass arising from the sacrum that is a benign tumor which responds well to excision. In highly selected cases they are amenable to treatment in utero. The lesions can achieve enormous size, and the resection can be accompanied by significant bleeding. Surprisingly many of these children void with low residuals, but a significant cohort are left with a flaccid or underactive bladder [46]. Some of these children valsalva void on their own with a low enough residual that they can stay continent and infection free. For others, CIC will be required.

Inflammatory Diseases such as transverse myelitis and multiple sclerosis are seen in childhood, although they are a rare etiology of NDSD.

Spinal cord injury, tumors, and spinal infarcts are also rare causes of NDSD in childhood. The higher up along the spinal cord that these lesions are found, the greater the likelihood of autonomic dysreflexia.

3. CLASSIFICATION: PATTERN RECOGNITION

Over the past century, multiple classification systems were proposed for categorisation of the neurogenic bladder. They have typically been based on the localisation of the lesion and the findings of the neurourologic examination. In children, the spinal level

and extent of congenital lesion is poorly correlated with the clinical outcome. Urodynamic and functional classifications have been more practical for defining the extent of the pathology and planning treatment in children.

A more simplified classification system is built around the two great dividing points in lower urinary tract function; a failure to store or a failure to empty. The benefit of this approach is that using the tool of video urodynamics, one can readily categorise the majority of these patients into functional physiologic categories. Under normal conditions, the detrusor and sphincter are two units working in a coordinated manner to allow for bladder filling without any rise in pressure, and bladder emptying with low voiding pressures. A successfully executed urodynamic study should be to evaluate the passive filling properties of the bladder and delineate the relationship of sphincteric function during a bladder contraction. The individual performing paediatric video urodynamics must be patient and willing to allow for time for slow filling (which should not exceed 4% of expected bladder capacity/min). Ideally, the surgeon who is considering a patient for a continence procedure will perform the study personally. The goal is to allow the patient an opportunity to recreate their symptoms (incontinence) in the laboratory setting. This might even call for the patient to "stand" by tilting the urodynamics exam table so as to understand how the effect of gravity impacts on the function of the outlet. The physician might also ask the patient to cough or strain in an effort to measure the gradient across the bladder neck and external sphincters. Equally important during the study is the patient's response to filling and their reporting of any sensation or discomfort. All of this data is important to document in the record while the study is underway. **Attempts to interpret a "cold study" hours or days later result in a loss of valuable data**. We have found that recording our interpretations into an electronic flow sheet during the actual study is incredibly helpful because this serves as a checklist to help standardise the study but also because it can allow for retrieval of physiological parameters that were stored in a consistent manner [47]. Such a system might also be applied for multi institutional studies that rely upon urodynamics as an outcome. Urodynamic evaluation (preferably in combination with fluoroscopy) makes pattern recognition possible.

Four major types are usually used to describe the detrusor-sphincter dysfunction:

1. Detrusor overactivity with overactivity of the sphincter (mostly dyssynergia),
2. Detrusor overactivity with normal or underactivity of the sphincter,
3. Detrusor underactivity with sphincter overactivity
4. Detrusor underactivity with sphincter underactivity.

Besides these 4 patterns, one can use the ICS classification: overactive detrusor, underactive detrusor, overactive sphincter and underactive sphincter. Sometimes this is more helpful, as the detrusor may be overactive during filling, but underactive during 'voiding'.

The urodynamic investigation is considered normal when there is suitable age appropriate capacity, a normally compliant bladder with no overactivity and normal innervation of the sphincter with normal sacral reflexes and an increase in pelvic floor activity during filling and no activity during voiding. Presence of detrusor overactivity during filling with or without decreased capacity and compliance, is usually seen when there is an upper motor neuron lesion and this is usually accompanied by overactivity of the sphincter and failure to relax during voiding. A lower motor neuron lesion is considered when the voiding detrusor contractions are weak or lost and the sphincter is underactive. **Urodynamic investigations make it possible to establish a personalised management plan for each individual patient**. Current urodynamic technique has some definite limitations, but managing these patients on clinical symptoms alone is akin to flying an airplane without instruments. A metanalysis of 49 studies suggests the value of urodynamics in predicting upper urinary tract damage in patients with neurogenic lower urinary tract dysfunction [48]. Only 1 of these 49 studies was a randomised controlled trial, 9 were prospective, and the overwhelming majority were retrospective in nature. The number of patients in the series reviewed ranged from 9 to 249 with followup ranges from 3 to 10 years (the majority of studies did not include the mean followup time). Not surprisingly the level of evidence was overwhelmingly at a 3, but as Musco et al. pointed out the evidence strongly favours the use of urodynamics in the management of the child with a neurogenic bladder. They also offer suggestions as to how to better record data to allow for better meta analyses of combined series in the future [48].

Conclusion: Urodynamic investigation is essential in the diagnostic workout and the follow-up of a neurogenic bladder (LoE:3)

Recommendation: urodynamic investigation is recommended in the diagnostic workout and the follow-up of a neurogenic bladder (GR:B)

The combination of an overactive detrusor and sphincter is potentially dangerous because of the high intravesical filling pressures, which will put the upper tract at risk (vesicoureteral reflux and hydronephrosis as seen in Figure 1) [22]. In contrast, the combination of an underactive detrusor and a paralysed sphincter is relatively safe, providing a low-pressure reservoir [23, 49, 50].

Conclusion: the urodynamic result of the combination of an overactive detrusor with an overactive sphincter is potentially dangerous. The combination of an underactive detrusor and paralysed sphincter is relatively safe for the upper tract (LoE:2)

Recommendation: it is recommended to evaluate for the possibility of the urodynamic finding of the combination of an overactive detrusor with an overactive sphincter as it is potentially dangerous for the upper urinary tract (GR:B)

4. PRENATAL DIAGNOSIS AND FOETAL SURGERY

In utero intervention holds the promise of reversing some of the sequelae and improving outcome in SB patients. To prospectively evaluate the value of intrauterine surgery, a randomised controlled trial was established in 3 centres. The endpoints of this Management of Myelomeningocele Study (MOMS) included foetal and infant mortality, the need for a ventriculoperitoneal shunt at 1 year of age, and the evaluation of mental and motor development at 30 months of age. Prenatal surgery for myelomeningocele decreased the incidence of ventriculoperitoneal shunting and improved neuromotor functioning, but was associated with maternal and foetal risk [51]. MOMS's experience permitted to define technical differences between prenatal and postnatal defect closure, identifying some potential pitfalls useful in order to reduce complications [52]. Different surgical approaches have been utilised, both open and endoscopic, in order to improve results [53]. After the MOMS study, foetal myelomeningocele repair became a care option for prenatally diagnosed spina bifida [54]. Foetal repair unchanged CIC re-

quirements at 30-month follow-up but showed improved outcomes (less trabeculation and open bladder neck) compared with postnatal repair [55]). Long-term follow-up of bladder function is unknown [56] despite some encouraging reports [57]. Careful counselling is required for the high risk of persistence of neurogenic bladder dysfunction, requiring CIC in 50% of cases. Although most children use diapers or CIC, children who underwent prenatal closure may be more likely to void volitionally [58], but long-term follow-up is required [59,60], including repeated urodynamic studies. In conclusion although the risk for maternal deaths or complications (uterus rupture mainly) are low as rates of adverse neonatal outcomes, the evidence to suggest prenatal surgery is still really low and it should only be done in high volume designated centres.

Conclusion: prenatal surgery in myelomeningoceles performed in high volume designated centers has a positive effect on bladder function (LoE:3)

Recommendation: prenatal surgery in myelomeningocele is recommended to preserve bladder function when performed in high volume designated centers (GR:C)

5. MANAGEMENT

The main aim in management of NDSD in children is to ensure and maintain a reservoir with normal age-matched capacity and good compliance that can be emptied completely at low pressures and at regular intervals. How to perform the management of a potential NDSD is still debated: some are advocating a proactive management versus others suggesting an expectant one [61]. Nevertheless, it is generally agreed that urological care should be initiated soon after a child with SB is born and is to be maintained throughout childhood. In the first years of life, the kidneys are highly susceptible to back pressure and infection. Bladder drainage is essential during and after the closure of the spinal defect in early life. Following the closure, within a few weeks emphasis will be on documenting the pattern of neurogenic detrusor- sphincter dysfunction and assessing the potential for functional obstruction and whether there is vesicoureteral reflux [49]. Ultrasound studies and a VCUG or video-urodynamics to exclude reflux must be performed soon after birth. Measurement of residual urine during both ultrasound and cystography should also be done. These studies provide a baseline for the appearance of the upper and lower urinary tracts, can facilitate the diagnosis of hydronephrosis or vesicoureteral reflux and can help identify children at risk for upper urinary tract deterioration and impairment of renal function. Regarding the time for first urodynamic evaluation, urodynamics should be performed after the so called phase of spinal shock, approximately 3 months after postnatal closure of spinal defect. In children treated prenatally, urodynamics could be performed earlier, such as in the first month of life, because the spinal shock, related to the spinal procedure, occurred early in foetal life [62].

With respect to evaluating the bladder function, 2 general scenarios are common. One group of patients will have an overactive sphincter and develop high detrusor leak point pressures greater than 40 cm H2O and are therefore at risk for upper tract damage. The other group will have underactive sphincter resulting in free urine flow at low pressures into the diaper with little risk to the upper tract. In newborn and infants urodynamics may be difficult to perform, due to a high risk of artifacts, as well as difficulties in interpretation, with poorly defined normative values. The standards of International Children Continence Society should be applied and reported [63]. Urodynamics should be repeated at regular intervals, in combination with evaluation of the upper tracts [64]: such studies should be obtained after 6 months if at risk based on the initial UDS study and clinical parameters, or can be delayed until 1 year of age if the child is low risk. When urodynamic findings are inconsistent with observed deleterious findings of the upper urinary tract (increased dilatation at ultrasound) natural filling cystometry or repeated conventional urodynamics or videourodynamics, could be useful [61].

Conclusion: a strict urodynamic evaluation is essential in the workup and follow-up of a child with a neurogenic bladder. (LoE:2)

Recommendation: it is recommended to perform the initial urodynamic investigation 3 months after postnatal closure, and repeat these studies after 6 months if at risk on the initial UDS or at the age of 1 year in the low risk case (GR:B)

Overwhelming experience gained over the years with early management of the neurogenic bladder in infants has led to a consensus that such children do not develop upper tract deterioration when managed early with CIC and antimuscarinic medication [65-67]. Therefore, initial treatment should consist of oral or intravesical antimuscarinic drugs in combination with clean intermittent catheterisation, to start soon after birth in all babies and especially in those with signs of possible outlet obstruction [68-71]. The volume of urine collected with CIC and severity of urine leakage in between CIC will provide more information about the characteristics of bladder storage and drainage.

Conclusion: early start of anticholinergics and CIC in children with neurogenic bladder is effective to prevent deterioration of the upper tract (LoE:2)

Recommendation: early start of anticholinergics and CIC is recommended in the treatment of neurogenic bladder (GR:B)

The early initiation of intermittent catheterisation in the newborn period, makes it easier for parents to master it and for children to accept it as they grow older [72,73]. With early management, not only are upper tract changes fewer, but also bladders are better protected and incontinence rates are much lower.

It has been suggested that increased bladder pressures due to detrusor-sphincter dyssynergia cause secondary changes to the bladder wall. These fibro-proliferative changes may cause loss of elasticity resulting in a small non-compliant bladder with progressively elevated pressures. It is believed that early institution of intermittent catheterisation and anticholinergic drugs may prevent this in some patients [65,72,74] (Level of evidence 3)

Retrospective evaluation of patients has also shown that significantly fewer bladder augmentations were required in patients with early start of CIC [71,72]. (Level of evidence 3)

The main disadvantage of CIC is bacteriuria which is found in 60% of the patients, but symptomatic UTIs are less common (20%) with CIC when compared to the group without CIC (40%). Symptomatic urinary tract infections defined as foul smelling urine, suprapubic pain with or without an accompanying fever. Patients on CIC are less likely to develop symptomatic UTIs than those who are off a CIC regimen. There is no evidence that maintaining these adult patients on antibiotic prophylaxis confers a benefit and this increases the likelihood of resistant strains of bacteria [75]. The use of nightly bladder irrigations has been shown to lower the incidence of blad-

der stones and UTIs [76] Since the risk of reflux is similarly low with CIC, the renal scar rates are lower.

CIC alone, when begun in infancy can achieve continence at a rate of 60 %. When combined with newer and more potent antimuscarinic drugs continence rates approach 75-80%. [77-80]

Due to high risk of latex sensitivity in the NDSD population, non-latex catheters are recommended. Hydrophilic-coated catheters have become more popular as they are more practical to use and are associated with less pain during use. In a randomised trial comparing hydrophilic-coated catheters to uncoated catheters, there was a reduction in microscopic haematuria and better overall satisfaction with the hydrophilic-coated catheters [81].

A Cochrane review examined sterile versus clean catheterisation technique, coated (pre-lubricated) versus uncoated (separate lubricant) catheters, single (sterile) or multiple use (clean) catheters, self-catheterisation versus catheterisation by others, and any other strategies designed to reduce UTIs with respect to incidence of symptomatic UTI, haematuria, other infections, and user preference, in adults and children using CIC [82]. This review found a lack of evidence to state that the incidence of UTI is affected by any of these parameters. Another review failed to show that single use hydrophilic-coated catheters decrease the incidence of symptomatic urinary tract infection, when compared to clean multiple use polyvinylchloride catheters [83]. Current data does not show a real difference [84], so the evidence to suggest one specific catheter type, technique, or strategy is weak and choice of catheters and regimens should be made on an individual basis. (Level of evidence 3)

Overnight catheter drainage was introduced by Koff [85] to manage valve bladder syndrome, and serves to take pressure off the upper and lower urinary tract in children with NDSD [86 -88] This will allow for bladder wall reperfusion, as well as for the release of volume as all resistance is eliminated. Institution of overnight catheter drainage may make it possible to avoid augmentation with bowel in a bladder with borderline capacity. This method has been applied to patients with native bladders as well as those with augmented bladders. Anecdotal evidence suggests that overnight drainage has led to fewer perforations of augmented bladders. (Level of evidence 4)

Because it is well known that detrusor overactivity in NDSD is dangerous for the bladder wall as well as the upper urinary tract and that anticholinergic/antimuscarinic medication can reduce high intravesical pressure, when an overactive bladder is demonstrated, anticholinergics are commonly recommended even during the first months of life [67,71,72]. At present oxybutynin, tolterodine, trospium, propiverine and solifenacin are the most frequently used anticholinergic drugs to treat detrusor overactivity in children.

The clinical efficacy and side effects from anticholinergics are related to the receptor subtype present in the target organ. There are several muscarinic receptor subtypes throughout the body: M1, M2, M3, M4, and M5. The predominant muscarinic subtype in the bladder is the M2 receptor (66%); however, it is the M3 receptor subtype (33%) that is more important for detrusor activity [89].

Some clinical studies are available, but not many randomised placebo-controlled studies have been performed in children [65,90-92].

Oxybutynin was the first anticholinergic agent to undergo broad investigation in children with NDSD. It is the first FDA approved anticholinergic for paediatric use in NDSD, and it is still the most frequently used in paediatrics, with a success rate close to 90% [93]. The dosing of oral and intravesical oxybutynin is 0.2 mg/kg/dose every 8 hr. Despite its high efficacy, oxybutynin has major side effects, which include dry mouth, constipation, blurred vision, headache, somnolence, learning disability, flushing, constipation and dry itchy skin.

If children are unable to tolerate oral oxybutynin, other modes of delivery can help reduce side effects. The intravesical route does not rely on gastrointestinal absorption and therefore largely avoids the hepatic metabolite, N-desethyloxybutynin. This compound is an active metabolite with similar pharmacological properties to oxybutynin, increasing the potential for adverse effects [94]. Intravesical oxybutynin use has been recommended in children suffering oral side-effects [95]. A meta-analysis involving intravesical oxybutynin in children with NBD supports its efficacy in lowering the mean maximum detrusor pressure while increasing bladder capacity, but side effects are nevertheless present, although fewer than with oral oxybutynin. Incontinence has been shown to be improved significantly in most studies, with “dry and improved” rates ranging from 61% to 83% [96,97]. The transdermal route is an alternative route with similar benefits as intravesical treatment as it circumvents the production of N-desethyloxybutynin [98]. The main limitations with transdermal delivery are local skin site irritation and the necessity for continual skin adherence. Oxybutynin side effects on the central nervous system are debated [99]. In contrast to what was expected the study of Giramonti et al. showed that long-acting oxybutynin and tolterodine did not have a deleterious effect on children’s attention and memory. They mentioned that other cognitive functions can be affected.[100]

A prospective controlled trial evaluating trospium in children reported that trospium is effective and safe in correcting detrusor overactivity in children but this study did not include patients with a neurogenic bladder [101]. Tolterodine has also been evaluated in patients with neurogenic bladder and found to increase functional capacity in a one-year trial [102] In this particular trial oral and extended-release formulations were tested and found to be effective. Interestingly the functional volume measured at urodynamics increased in the younger patients and did not change in the adolescents. Despite this, both groups reported improved dry intervals and the mean catheterised volumes increased in all subjects. Adverse effects were noted in 7/42 patients who enrolled in the study and were mild including dry mouth and exacerbation of constipation. Two patients withdrew consent and 10 no longer met enrolment criteria leaving 30 patients for the final analysis. These authors had also carried out exploratory studies to assess the optimal dosing strategy [103]. These details serve to point out just how difficult it is to perform a carefully monitored drug trial in this patient population. Similar findings were reported in an earlier trial in patients with overactivity and a neurogenic bladder though this study looked at efficacy defined by urodynamics and the endpoint was assessed at 3 months [104]. Tolterodine has similar efficacy and tolerability to oxybutynin in children with NDSD and the extended-release formulation of tolterodine was as efficient as the immediate release form with the advantages of being a single dose and less expensive [105].

Two open label baseline controlled trials showed that once-daily solifenacin oral suspension in children with neurogenic overactive bladder produced increases in mean cystometric capacity and gains in bladder compliance [106]. Side effects in these studies were few, and lower than those observed with oxybutynin. In a randomised trial solifenacin was superior to placebo for mean voided volume (primary efficacy endpoint) and was well tolerated in

children with detrusor overactivity [107]. Propiverine seems to be effective too [108].

Mirabegron is a beta3 agonist which induces relaxation of the detrusor smooth muscle, and has been studied in refractory cases. In one report 37 patients under age 18 whose neurogenic overactivity was refractory to oxybutynin were started on mirabegron and urodynamic end points were measured showing significant increases in bladder capacity and a decline in end filling pressure [109]. Another report with 66 patients reports similar urodynamic outcomes with dual therapy [110] . Mirabegron added to solifenacin was also shown to be a safe alternative for children with refractory overactive bladder. Dual therapy is well tolerated and the adjusted dose regimen appears safe in this first paediatric study [111]. These encouraging results with mirabegron have led to a pharmacokinetics trial seeking to better define dose adjustments for the paediatric population [112]). This had led to the FDA issuing an approval for mirabegron for paediatric use in case of NBD in March of 2021.

Based on the data available in children with neurogenic bladder overactivity, use of anticholinergic drugs is the mainstay of medical treatment.

Conclusion: anticholinergics are effective to reduce the storage pressure and increase the voided volume in children with NDSD (LoE:2)

Recommendation: anticholinergics are recommended to reduce the storage pressure and increase the voided volume in children with NDSD (GR:B)

Cognitive changes with anticholinergic usage have been described in recent years and are a source of concern for providers and patients. There is a growing literature to suggest that anticholinergic medication must be carefully monitored in geriatric patients some of whom may experience cognitive decline [113,114]. Furthermore this may be related to oxybutynin which has a lower molecular weight and a greater propensity to cross the blood brain barrier [115]. In contrast anticholinergics with a higher molecular weight are less likely to cross the blood brain barrier and are associated with fewer such effects. The challenge in the interpretation of these findings is the co-morbidities that are present, or may be evolving in these patient populations. A new study reported that the dementia risk was higher in older patients prescribed anticholinergics when compared to a β-3 agonist [116]. However fewer studies have been done to evaluate anticholinergic effects on cognition in children. The effect of oxybutynin was studied in children, and at 16 weeks was not found to have any effects on cognitive performance [117]. In a more recent open label study looking at a 42 week trial of solifenacin in patients with spina bifida ranging from 6 months to 18 years, there were gains in cognitive performance that were age appropriate [106]. Oxybutynin has traditionally been used in infants with spina bifida whose urodynamics show low bladder capacity, overactivity, or poor compliance. In a small series of patients 3 to 4 months old who started early treatment (capacity <50% of estimated bladder capacity, overactivity, or poor compliance), 20% stopped the medication due to retention or allergic reaction but 5% of patients stopped the medication due to parental reports of changes in their child's affect [118]. This cognitive outcomes data has led to a call for caution in the use of anticholinergics in children, for the lifetime consequences of chronic use are not defined [119]. These concerns should also point out the future need for developmental testing to assess the effects of these medications in children as most outcomes analysis have focused only on the urodynamics parameters.

The use of medication in children with neurogenic bladder to facilitate emptying has not been studied well in the literature. Few studies investigating the use of alpha-adrenergic blockade in children with neurogenic bladder report good response rates but they are non-controlled studies and long-term follow-up is lacking [120-121]. Studies with selective α1-blockers (doxazosin) in children with NDSD and increased leak point pressure (LPP) did not show any evident efficacy [122-123].

In neurogenic bladders that are refractory to antimuscarinics and remain in a low capacity and high-pressure state, or when antimuscarinics side effects are relevant, injection of onabotulinumtoxin-A (BTX-A) into the detrusor has been proven to be effective and safe [124-125]. Initial promising results in adults have initiated its use in children [143]. In a recent systematic review examining 12 series (all non-randomised and only 2 with a control group) injection of BTX A in therapy resistant bladders caused a significant improvement in terms of continence, maximum detrusor pressure, maximum cystometric capacity, and bladder compliance [126]. This treatment seems to be more effective in bladders with evidence of detrusor overactivity, while non-compliant bladders without obvious detrusor contractions are unlikely to respond to this treatment [126,127]. Other series have also noted that BTX is less effective for fibrotic bladders with no overactivity noted on the urodynamics [128]) . Repeated bladder injections of BTX-A during time have been demonstrated to be effective and safe [129-132].

Conclusion: onabotulinumtoxin-A is an effective treatment of overactive neurogenic bladder (LoE:2)

Recommendation: onabotulinumtoxin-A is recommended to treat neurogenic detrusor overactivity.in children. (GR:B)

Dosage of BTX-A in children should be determined by body weight, and timing adjusted with caution regarding total dose if also being used for treatment of spasticity, and minimum age [133] In most published studies, the dose of BTX-A is 10 U/kg up to a maximal dose of 300 U involving 30 trigone sparing injections of 10 U/kg/ml in the detrusor. BTX-A seems to reach efficacy levels at 2 weeks and maximum effects within a month. Duration of the BTX-A effect ranges from 3 to 8 months depending on short-term versus long-term repeated injections [134]. Recently on the basis of results of a multicentre international phase III study, a recommended dosage of 200 U, not exceeding 6U/kg has been suggested [135]. Few adverse events have been reported in children, but the need for CIC after injection is an important consideration and is higher with higher dosage [136].

BTX-A injection into the urethral sphincter has been shown to be effective in decreasing urethral resistance and to improve voiding [137]. A meta-analysis of BTX-A injection into the sphincter in adults with spinal cord injury has shown its effectiveness in reducing post-void residual urine and demonstrating a statistically significant reduction in detrusor pressure and urethral pressure 1 month post injection [138]. Current evidence is insufficient to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases [139]. The transient sphincteric pharmacological denervation then could be useful in selected cases, when CIC is not well accepted by patients or families [140]

Conclusion: BTX-A injection in the urethral sphincter is effective to treat the overactive neurogenic sphincter (LoE:3)

Recommendation: BTX-A injection in the urethral sphincter is recommended to treat the overactive neurogenic sphincter (GR:B)

Intravesical electrical stimulation of the bladder was introduced more than four decades ago and it has been tested in some open clinical trials in children since 1984 [141]. Its practice is limited to a few centres who have reported varying results. The only randomised controlled trial looking at this mode of therapy has failed to show efficacy [142]. Furthermore, this type of treatment is time consuming, requiring very dedicated personnel, rendering it unattractive for most treatment centres as well as for patients.

Nerve stimulation via the percutaneous, sacral or transcutaneous route has been also studied in the treatment of patients with a non-neuropathic bladder [143]. Although transcutaneous nerve stimulation has been found to be effective in treating overactive bladder disorders in chronic pelvic pain/painful bladder syndrome and in children with non-neurogenic lower urinary tract disorders; its effectiveness has not been established for children with NDSD [144-146]. In a report of a prospective study, in which sacral nerve modulation was conducted in children with NDSD, comparison of urodynamic variables revealed no statistically significant difference except that functional bladder capacity was better in the oxybutynin group and leak point pressure was better in the sacral neuromodulation group [147]. Better results have been reported in children with acquired neurologic dysfunction, as in myelitis, and partial spinal cord injury [148].Although nerve stimulation has good evidence for its efficacy in non-neurogenic bladder overactivity, both in children and adults, there is no clear evidence for its effectiveness in neurogenic overactivity in the paediatric population. Its use remains investigational and must be limited to well selected cases and centers [149-150].

Most children with a neurogenic bladder also have constipation and this is managed most commonly with laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. Faecal incontinence in these children is frequently unpredictable; it is related to the loss of lower bowel sensation and function, altered reflex activity of the external sphincter and the consequent failure to fully empty the rectum [151].

A regular and efficient bowel emptying regimen is often necessary to maintain faecal continence and this may have to be started even at a very young age. With antegrade or retrograde enemas, most of these children's constipation can be managed and they may attain some degree of faecal continence [152-153].

With availability of retrograde devices with a balloon on the rectal catheter to prevent leakage of solution, retrograde enemas have become more efficient and more popular in comparison to antegrade enemas [154,156-158]. Bowel management must be defined individually for each patient and careful follow-up is required in order to improve efficacy. Today conservative management is commonly offered before surgery (ACE stoma, Cecostomy button)[155].

Conclusion: bowel management is essential in the treatment of children with a neurogenic bladder (LoE:2)

Recommendation: bowel management is recommended in children with neurogenic bladder (GR:B)

Biofeedback training programmes to strengthen the external anal sphincter have not been shown to be more effective than a conventional bowel management programme in achieving faecal continence [159]. Electrostimulation of the bowel may also offer a variable improvement in some patients [160].

Conclusion: electrostimulation is an effective method of bowel management in children with neurogenic bladder (LoE:3)

Recommendation: electrostimulation is recommended for bowel management in children with neurogenic bladder (GR:D)

Urinary tract infections are common in children with neurogenic bladders. In the absence of reflux, patients with urinary tract infections should be treated if symptomatic. There is strong evidence not to prescribe antibiotics to patients with asymptomatic bacteriuria [161-163]. Bacteriuria is seen in more than half of the children using clean intermittent catheterisation (CIC), but this is not an indication for treatment. While there is not consensus for prevention, diagnosis and treatment [164], there is a common view to avoid continuous antibiotic prophylaxis, in order to reduce risk of bacterial resistance [165]

Conclusion: continuous antibiotic prophylaxis is to be avoided in children with neurogenic bladder (LoE:3)

Recommendation: continuous antibiotic prophylaxis is not recommended in children with neurogenic bladder (GR:B)

Patients with vesicoureteral reflux and frequent urinary tract infection require prophylactic antibiotics to reduce the incidence of pyelonephritis, which can potentially lead to renal damage [166]. Since vesico-ureteral reflux in NDSD is often secondary, reflux management must always be associated with NDSD treatment. Videourodynamics is the gold standard for a correct diagnosis, defining the presence of high or low bladder pressure in case of high-grade reflux. Endoscopic treatment alone has a high failure rate [167] and a combined endoscopic treatment with BTX-A [168] or button cystostomy [169] has been suggested. The role of reimplantation with or without augmentation or augmentation alone is debated [170-171]

Sexuality is not an issue in early childhood, but becomes progressively more important as the patient ages [172]. This issue has historically been overlooked [173]. Patients with myelodysplasia have sexual encounters, and studies indicate that at least 15-20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. Therefore, counselling patients regarding sexual development is important in early adolescence, and fertility must be preserved [174-176].

Summary:

Children with a good response to antimuscarinic treatment and an overactive sphincter may be continent between catheterisations. Bladder pressure and (normal) development of the upper tracts will determine whether additional treatment is necessary. Children with therapy resistant overactivity of the detrusor, or small bladder capacity and poor compliance will usually need additional surgical treatment such as bladder augmentation [177-179].

Children with detrusor overactivity but with underactive sphincters will be in a better shape in terms of protecting their upper tracts, but they may be severely handicapped because of their incontinence. Initial treatment will be intermittent catheterisation (as it may reduce the degree of incontinence and offers a much better control over urinary infections) in combination with antimuscarinic drugs. Urodynamics or videourodynamics will be

helpful in order to better understand how to correct incontinence. At a later age the outlet resistance may be increased to render them continent [180]. There is no medical treatment of proven efficacy that increases bladder outlet resistance. Alpha-receptor stimulation of the bladder neck has not been very effective. Thus, surgical procedures need to be considered for maintaining continence [181-185]. To avoid negative influence on the upper urinary tract, bladder neck surgery should only be considered in cases with an adequate bladder capacity and compliance. Bladder neck closure is the last option and has to be considered when all other procedures failed and in very selected cases [186-187]

It is important to establish adequate bowel emptying before attempting to correct bladder dysfunction surgically or medically.

Patients with a neurogenic bladder require lifelong supervision; monitoring of renal function is extremely important. Periodic investigation for upper tract changes, renal function and bladder status is mandatory [188]. Therefore, repeat urodynamic studies are needed more frequently at younger ages and less frequently as time progresses. A repeat urodynamic study is warranted when the patient has a change in symptoms or undergoes any neurosurgical procedure. In case of any apparent changes both in the upper and lower urinary tracts or any changes of neurological symptoms, a more detailed examination including urodynamics and MRI of the spine is indicated. Renal failure usually progresses slowly but may occur with startling rapidity.

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VI. SURGICAL MANAGEMENT OF URINARY INCONTINENCE IN CHILDREN

1. INTRODUCTION

The principles for managing incontinence in childhood are much the same as those for adults – although the application and interpretation may differ. The basic principles can be outlined as follows:

1. Achieve and maintain continence
2. Preserve the upper tracts
3. Achieve maximum effect with the least invasive treatment
4. Consider the long-term effects

Many patients do not require surgical intervention and the first 2 criteria can be achieved with a combination of medication and inter-

mittent catheterisation. However, if these measures fail then surgical intervention becomes important.

The choice of surgical procedure needs to be based on the age and wishes of the child and/or parents, their medical history, relevant investigations (eg. Urodynamics) and other comorbidities or physical limitations. A multidisciplinary approach is often important to ensure optimal decision making.

Surgery may be indicated in patients with conditions (congenital or acquired) affecting bladder storage, the sphincter mechanism or the ability to void urine. There are a range of different procedures to improve all of these. It is important that where possible parents and their child understand the potential outcomes. It can be difficult to convey the important 'trade-offs' that may follow – for instance that 'dryness' may not be the same as continence and that the creation of a safe bladder may be at the cost of spontaneous emptying. Many procedures require adjuncts such as catheterisation or medication, along with life-long follow-up.

Therefore, an operation forms part of a contract between the surgeon, initially the parents and subsequently the patient to remain engaged with this in order to achieve the best outcome. It is absolutely key for everyone to understand that this operation often represents the beginning of a pathway of care and not the end. Many families will have only previously seen surgery where it is used as a 'cure' (eg for cancer, a hernia or broken bone) where there is often a finite conclusion to treatment that is facilitated by surgery. For our patients surgery forms a major part of treatment and the aim is a significant improvement in function, but they will often remain under the care of a surgeon for life and may well need further treatment and/or surgery.

In order to operate on patients with an incompetent bladder neck there are some fundamental principles. The majority of procedures employed to reconstruct a bladder neck require the creation of a fixed resistance, creating enough of an outlet obstruction to render a patient dry. For the majority of patients, dryness under these circumstances may well come with the sacrifice of spontaneous voiding at low pressure – for the majority self-catheterising may be the better option.

The management of complex congenital anomalies generally happens in a field with a dearth of high-grade evidence – the conditions are rare; patients require an individual treatment and expertise and treatment approaches vary. The concentration of treatment in specialist centres may improve the variability, but we are still considerably short of high evidence levels to direct surgical treatment. Therefore, graded recommendations for specific procedures cannot be provided.

There are no randomised controlled trials (level 1 and 2 evidence). Based on the available literature most studies have a level of evidence 3-4 and grade of recommendation C or D.

1.1. Abnormalities of storage

Bladder Exstrophy: The incidence of bladder exstrophy is 1 per 30,000 live births. (male to female ratio 3:1). Closure of the bladder is generally performed within the first days of life; many centres use pelvic osteotomies to facilitate reconstruction of the abdominal wall and aim to improve ultimate continence (1-3) Some children will develop more or less normal capacities. Even after successful closure there will be some children who end up with poorly compliant small bladders, requiring subsequent bladder augmentation or urinary diversion (eg. Mitrofanoff, ileal conduit or ureterosigmoidostomy) (4-7). Patients with a good bladder plate who develop sufficient bladder capacity after successful primary closure and epispadias repair may achieve acceptable continence without the need for bladder augmentation and intermittent catheterisation (8-10).

Bladder neck reconstruction may be undertaken at the time of bladder closure or at a later stage. Some data suggest that early reconstruction may facilitate normal bladder function, but should be attempted only at centres experienced with such surgery (11-12). Published data for continence show a considerable range 43 to 87% (13,14) – the reasons behind such variability are not clear.

Cloacal Exstrophy: The incidence of cloacal exstrophy is 1 per 200,000 live births. This is a much more complex deformity that requires an individual approach. Most of these children have additional anomalies including neurological, the upper urinary and gastrointestinal tracts - all may add to the challenges of urinary tract reconstruction. Before reconstructive procedures are considered, a careful, multidisciplinary evaluation is needed.

Bladder Agenesis or Duplication are both extremely rare. Agenesis is rarely compatible with life. In patients affected by bladder duplication, other associated congenital anomalies are common, including duplication of external genitalia or colon.

Abnormal bladder function, in combination with other anomalies are usually the result of a neurological deficit, there may also be bladder outlet obstruction. Sacral anomalies are frequently seen with cloacal malformations and imperforate anus (15-18).

Posterior urethral valves may lead to a small, poorly compliant bladder, the obstruction results in detrusor hypertrophy and surrounding fibrosis (19,20). Even following valve ablation (and thus removal of the obstruction), there is no guarantee that these bladders will return to normal function (21,21).

1.2. Abnormalities of sphincteric function

Primary Epispadias (without exstrophy): has an of incidence 1 in 60,000 live births, male to female ratio: 3-5:1. All patients with bladder exstrophy also have complete epispadias.

In male patients with complete epispadias and in all affected females, the sphincteric mechanism is deficient resulting in complete incontinence. Reconstruction of the bladder neck is performed, either, at the time of epispadias repair or at a later stage. The bladder function may or may not be normal in these patients (23,24).

Urogenital Sinus Anomaly occurs exclusively in phenotypic females. The incidence is 1 in 50,000 live births. In patients with classical urogenital sinus or cloaca, the sphincteric mechanism is insufficient and due to associated neurological abnormalities the bladder function may be abnormal.

Ectopic ureteroceles protruding into the urethra may be responsible for a partial defect of the bladder neck. In these rare cases, sphincteric incontinence may be the result.

Secondary Abnormalities in Sphincter Function associated with spina bifida and other neurological disorders are important. The sphincter may be overactive (like in detrusor-sphincter dyssynergia) or underactive. An overactive sphincter leads to secondary bladder wall changes (increased collagen type III with decreased compliance) and, most worryingly, obstructive nephropathy. Continence can be achieved with antimuscarinic drug treatment or bladder augmentation (using the overactivity of the sphincter for continence).

In cases of sphincter incompetence, there are a variety of surgical interventions to enhance continence. In general, all patients with a neurogenic bladder need clean Intermittent catheterisation (CIC). In patients reliant upon wheelchair mobility a suprapubic channel can be created (Mitrofanoff) to facilitate CIC.

Bypass of the sphincter mechanism

Ectopic Ureter - Instead of the ureter draining into the bladder, it opens into the urethra (below the sphincter), vaginal vestibule or uterus. Ectopic ureters occur more frequently in girls and most commonly drain the upper moiety of a duplex system (25). When the upper pole ureter drains into the mid or distal female urethra or outside the urinary tract (i.e. vulva or vagina), an upper pole nephrectomy or ipsilateral uretero-ureterostomy will cure the incontinence.

If an ectopic ureter is associated with a simplex system, the ipsilateral trigone is usually asymmetrical and poorly developed. This can lead to continuous incontinence (with a deficient sphincter).

In patients who have bilateral ectopic ureters and simplex systems, the trigone and bladder neck are functionally abnormal and treatment includes surgical reconstruction of the bladder neck. The bladder is typically hypoplastic, and achieving a functional bladder capacity may require additional procedures (eg augmentation) combined with ureteric reimplantation (26-28).

Urethral duplication. Most patients with urethral duplication will leak urine from the abnormal meatus during voiding. In rare cases, when the accessory urethra is attached above the sphincter ie it is a conduit without any continence mechanism, continuous leakage may be present (29).

Vesicovaginal fistulae. Acquired fistulae may be traumatic or iatrogenic, following procedures on the bladder neck.

2. EVALUATION AND DIAGNOSIS

A detailed history and physical examination (this is so often missed and can provide very clear information) in combination with imaging studies and urodynamic evaluation are the cornerstones for successful management. Imaging studies will define anatomical abnormalities responsible for and associated with incontinence. Ultrasonography of bladder and kidneys as well as a voiding cystourethrogram are the basic studies. In infants and small children sacral ultrasonography can demonstrate normal position and mobility of the spinal cord. The scout film of the contrast voiding cystourethrogram (VCUG) assesses the lower spine and sacrum, intersymphyseal distance, and constipation. The contrast films will show bladder configuration, presence of vesicoureteral reflux, incomplete voiding, bladder neck competence, urethral anatomy and vaginal reflux. MRI and CT scans/urograms can be helpful in defining spinal abnormalities as well as congenital abnormalities in the urinary tract.

In addition to anatomical imaging studies, functional studies eg. urinary flow studies, urodynamics (cystometrography and when needed, sphincter electromyography) are useful for all patients with neurogenic incontinence. These studies are also valuable following surgery in some cases of bladder exstrophy and after posterior urethral valve resection to define the mechanism of any continued incontinence. However, in many patients much useful information on the function of the lower urinary tract can be obtained with very basic studies including ultrasound and cystometry.

3. INDICATIONS FOR SURGICAL PROCEDURES TO CORRECT URINARY INCONTINENCE

3.1. Storage function

Augmentation cystoplasty is indicated, once appropriate conservative treatment has failed, when reduced capacity, raised end-fill cystometric bladder pressures, reduced compliance and intractable detrusor overactivity (most commonly neurogenic) are present. Each of these scenarios may be congenital, (as part of a condition) eg. myelomeningocele, bladder exstrophy or posterior urethral valves or acquired, eg. scarring following previous surgery, reduced capacity following bladder neck reconstruction or following an infective condition eg bilharzia (where it is either endemic or may be imported with migrant populations).

Published data support aggressive early intervention with CIC and anticholinergic therapy to improve bladder compliance and avoid the need for augmentation cystoplasty (30,31).

A recent survey reported that there has been no change in augmentation rates over a 5-year period: but there was significant inter-institutional variability (32).

3.2. Sphincter function during storage

Many of the conditions described are complex and will affect both bladder and sphincter function – both need assessing and both may require intervention. Conservative measures to improve sphincter function have limited value and surgery is often the only available treatment. The surgical options for the bladder outlet can be categorised into the following:

- Bladder neck reconstruction with urethral lengthening procedures
- The use of native tissue to support the urethra – autologous fascial sling, colposuspension
- Insertion of an artificial urethral sphincter
- Bladder neck closure and creation of a continent catherisable channel (other forms of urinary diversion are also discussed)

The last option clearly involves the need for clean intermittent catherisation (CIC) - patients undergoing any of the other options also need to be prepared for the fact that CIC may be necessary.

3.3. Urinary diversion

If bladder outlet surgery fails or urethral catheterisation is not possible – urinary diversion becomes necessary. Some patients prefer catheterising through a continent stoma rather than through the sensate urethra. The continent stoma (Mitrofanoff principle) may be combined with bladder augmentation and/or bladder neck reconstruction or closure. Further options in this group include a ureterosigmoidostomy (Mainz II) with the anal sphincter becoming the continence mechanism and colon acting as the storage reservoir. Historically, an ileal conduit has been used; this is rarely used as part of modern paediatric urology.

4. BLADDER RESERVOIR CONSTRUCTION

4.1. Ureterosigmoidostomy

This type of continent urinary diversion may be utilised in reconstruction for bladder exstrophy, an incontinent urogenital sinus or

the traumatic loss of the urethral sphincter. As this reconstruction is totally dependent on the normal function of the anal sphincter, contraindications include incompetence of the anal sphincter (therefore it is not suitable for neuropaths), anal prolapse, previous anal surgery and irradiation. These reservoirs have a strong association with metabolic anomalies (hyperchloraemic metabolic acidosis and (rarely) hyperammonaemia) (33), renal insufficiency is also a relative contraindication.

The creation of a low-pressure rectal reservoir is superior to simple ureterosigmoidostomy because the augmented or reconfigured rectal bladder achieves lower pressure storage and accordingly, enhances continence.

The most commonly employed is the recto-sigmoid pouch (Mainz II) in which there is an antimesenteric opening of the recto-sigmoid (which is configured in a 'u'-shape) and a side to side detubularisation anastomosis. Normal calibre ureters are reimplanted with a standard submucosal tunnel (Goodwin, Leadbetter). If the ureter is dilated, a serosa lined extramural tunnel may be more appropriate (34,35).

Data from D'elia et al., showed the outcome of low-pressure rectal reservoirs to be excellent; with day and night continence better than 95% and complications related to the surgical procedure range from 0 -10% with the Mainz II, other techniques have been described but complications appear higher (up to 34%) (36). Late complications for the Mainz II pouch range from 6-12.5%. Early complications include pouch leakage while late complications are mainly related to the ureteric implantation; including stenosis or pyelonephritis secondary to reflux. Metabolic acidosis also occurs, 69% of the patients had a capillary base excess of –2.5 mmol/L and used oral alkalinizing drugs to prevent hyperchloraemic acidosis.

Regular life-long follow-up is important to survey the upper tracts and monitor for/treat metabolic acidosis. There is a documented risk of malignancy at the ureterointestinal anastomosis, so flexible sigmoidostomy should be performed annually beginning at postoperative year 10 (30,37-40). It is valuable to consider this reconstruction in a resource-limited environment where stoma bags and/or catheters are difficult to obtain or expensive. The risks described are important but on balance may be more acceptable than the pre-existing condition or the need for expensive (or unavailable) bags/catheters.

Conclusion: ureterosigmoidostomy is an effective technique for continent urinary diversion (LoE:3)

Recommendation: ureterosigmoidostomy is a recommended type of continent urinary diversion in selected patients (GR:B)

4.2. Bladder augmentation, bladder replacement and continent urinary diversion using intestine

Indications for augmentation or substitution cystoplasty, with or without the creation of a continent urinary diversion, are the anatomical or functional loss of normal bladder function. The main goal of this surgery is to relieve high pressure and improve a low-capacity bladder; creating a continent reservoir with low storage pressures that can be emptied regularly. It is particularly important that the patients understand that spontaneous voiding will not be possible after such surgery and lifelong intermittent catheterisation will be required.

Before deciding on what type of procedure can be performed some significant factors must be considered. These include:

1. The motivation, physical and mental capacity of the patient to undertake intermittent catheterisation.
2. Previous surgery (on urinary tract and bowel – particularly availability of sufficient, healthy bowel).
3. Renal function
4. The presence of reflux
5. Continence vs outlet resistance
6. Preferred method of drainage eg. urethra vs continent catheterisable channel

The different technical approaches to augmentation/substitution cystoplasty may be dependent on a variety of factors – including the clinical presentation of the patient:

- Augmentation cystoplasty may be reasonable if there is a bladder plate, a competent sphincter and/or bladder neck, and a catheterisable urethra,
- Augmentation cystoplasty with additional bladder outlet procedures such as bladder neck reconstruction and/or urethral lengthening are required when both the bladder and outlet are deficient. This is most commonly exemplified in spina bifida or bladder exstrophy.
- Augmentation cystoplasty with surgical closure of the bladder neck may be required primarily, or as a secondary procedure (ideally as an option of last resort). By definition, urinary diversion in the form of a continent stoma will be required. However, most urologists prefer to leave the bladder neck and urethra patent as a safety valve. If the bladder is ever allowed to overfill, urethral leakage should occur (reducing the risk of bladder rupture) and it should also allow urethral catheterisation if catheterisation of the channel fails.
- Augmentation cystoplasty with a continent stoma is utilised primarily following failure of previous bladder outlet surgery or urethral damage – preventing urethral catheterisation. An abdominal wall continent catheterisable channel may be particularly beneficial to the wheelchair bound spina bifida patient who may have considerable difficulty with urethral catheterisation and may be dependent on carers to catheterise. Although the urethra may not be formally closed, it is essential that there is sufficient outlet resistance to prevent urethral leakage.
- Substitution cystoplasty with normal voiding in children is usually an unrealistic expectation (of course there are rare, anecdotal, exceptions). Fortunately, there are very few indications for a total cystectomy in childhood. This type of bladder replacement is much more common in adult urology and is most commonly associated with urological malignancy.

The main contraindications for augmentation or substitution cystoplasty are the inability to perform self-CIC and the anticipation of poor patient compliance. Impaired renal function, generally with a creatinine above 2 mg/dl or a creatinine clearance below 40 ml./min/1.73 m2, constitutes a relative contraindication to enterocystoplasty because of the risk of metabolic complications. However, in a situation where the bladder has caused such renal failure, there is a need for a safe reservoir to avoid further decline in renal function. As a matter of principle the shortest segment of bowel with the least dwell time (ie contact time between urine and bowel) should be the preference – this needs to be carefully balanced against acceptability to the patient and likely compliance with drainage. The stomach with its excretion of acid may be (but is rarely) used with a low creatinine clearance possibly in preparation for transplantation. It is, however, not wise to use stomach in any voiding patient or one with any questions of an incompetent bladder outlet because of

the severe skin irritation that the acid urine may produce (haematuria-dysuria syndrome).

4.3. Which intestinal segment should be utilized?

4.3.1. Stomach

Stomach has limited indications primarily because of the complications related to acid secretion. It may be used in patients with significantly reduced renal function (41- 43).

Additionally, when no other bowel may be available, such as after irradiation or in the presence of a short bowel syndrome, as in cloacal exstrophy, this may be a salvage option.

4.3.2. Ileum / Colon

Clinically, these two intestinal segments appear equally useful. In children, sigmoid colon is widely used. Its use is contraindicated in those who have been treated for imperforate anus. Urological reconstruction using the ileocaecal region may be associated with diarrhoea. Use of this segment should be avoided in patients with a neurogenic bowel (eg. myelomeningocele) or who have had previous pelvic irradiation. The ileum can be satisfactorily used for augmentation cystoplasty: however, because of its smaller diameter a longer segment of ileum is required to create a comparable reservoir to that created from colon. Ileum can be reconfigured into a 'u'-shape to form a double or cup-cystoplasty. Colon has greater flexibility for ureteric implantation and creation of a continent catheterisable channel.

4.3.3. General principles

There are some important principles to consider when using bowel in the urinary tract:

- use the minimal amount of bowel needed and if possible 're-use' segments that have been used previously,
- a low-pressure large capacity reservoir is essential – this is best achieved with detubularisation of any intestinal segment.
- for colonic reservoirs, a sigmoid segment of 20-30 cm is generally satisfactory. A slightly longer segment of ileum is generally used. The length of the segments can be scaled down in smaller children. It is important to ensure that there is at least 200 cm of bowel left in continuity to avoid short-gut syndrome. If necessary, seek specialist imaging and advice prior to operating if there is doubt about the length of bowel available.
- the jejunum is contraindicated for reconstruction of the urinary tract because of its metabolic consequences (hyponatraemia, hypercalcaemia, and acidosis).
- an anti-reflux ureteric anastomosis to the reservoir is important if there is no urethral outlet. If the system has an intact urethra (ie a safety valve) or an incontinent stoma (ileal conduit) then the risk of ureteric stricture outweighs the risk of stricture (44,45).
- a reliable continence mechanism is a priority.
- to reduce the risk of stone formation only resorbable sutures and staples should be used in bladder augmentation and reservoir construction.

4.3.4. Bladder augmentation techniques

1. When performing gastric augmentation, a 10-15 cm wedge-shaped segment of stomach is resected. Most commonly this is based on the right gastroepiploic artery but may be based on the left. The segment is easily brought down to the bladder via the retroperitoneal space, along the great vessels.
2. A large or small bowel segment is opened on the antimesenteric border and detubularised prior to anastomosis to the bladder. The anastomosis of the intestinal segment to the bladder remnant, and to itself, is usually carried out with a running layer of inverting, absorbable sutures.
3. The techniques for urinary diversion with continent stoma (Mainz pouch, Indiana pouch, Kock pouch) are covered in the chapter on urinary diversion in adults (46-48).

Currently, augmentation cystoplasty is the standard treatment for low capacity and/or low compliance bladders secondary to neurogenic, congenital and inflammatory disorders. Whilst other techniques have been discussed and experimental work continues to develop alternatives (eg. through tissue engineering) none have yet become part of routine clinical practice (49-54).

Conclusion: ileal and colonic bladder augmentation are effective in the treatment of neurogenic bladder with therapy resistant overactivity of the detrusor, small capacity, and poor compliance (LoE 2)

Recommendation: bladder augmentation with ileum or colon is recommended in neurogenic bladder with therapy resistant overactivity of the detrusor, small capacity and poor compliance GR: B)

4.3.5. Auto-augmentation

The principle of auto-augmentation of the bladder involves excision of a great portion of the detrusor while leaving the urothelium intact. This creates a large diverticulum for the storage of urine at lower pressures. Urine drainage would normally require intermittent catheterisation. The theoretical advantages of this procedure are the low complication rates of surgery, shorter hospital stay, absence of metabolic anomalies, the absence of mucus production and no increased risk of cancer. Although good results have been reported (55-58), these have not been clinically reproducible (59). Long-term results are disappointing: in a series of 17 patients, with neurogenic bladder, MacNeily et al. reported that 71% were clinical failures and 14 out of 15 were urodynamic failures following auto-augmentation hypocompliance or low bladder volume. All patients had failed to respond to conservative medical and pharmacological treatments. Median patient age at surgery was 10.2 years (range 2.2 to 13.2(60). Similar findings have been reported by others (61,62). The reasons for poor long-term outcomes have been suggested as the regeneration of nerve fibres and ischaemic atrophy of the mucosa – this may result in a reduction in intraluminal pressure but no increase in bladder volume. Thus the procedure has fallen out of favour.

Although there are many potential advantages to this approach to a small poorly compliant bladder the inconsistency of success make it a less favourable option. It is generally felt that pressures can be lowered but that capacity remains unchanged.

More recently there have been attempts to revive the technique with a laparoscopic or robotic approach – to date published data have not demonstrated long-term superiority over historical techniques. Whilst there is little to substantiate the technique of auto-augmentation by any means, there are a number of centres who are developing a range of robotic techniques for urological reconstruction. Data are still early and bigger series will doubtless be forthcoming, but the technology is developing and it appears that with developing experience and technique these technologies may offer comparable results with cystoplasty, ureteric reconstruction and some outlet procedures (63,64).

Conclusion: robotic techniques for urological reconstruction are effective (LoE:4)

Recommendation: robotic techniques for urological reconstruction are recommended for bladder augmentation, ureteric reconstruction and bladder outlet procedures (GR:C)

4.3.6. Seromuscular patch

To overcome enteric mucus formation, techniques have been developed to use intestinal segments free of mucosa. The first attempts resulted in viable seromuscular segments covered with urothelial mucosa (65,66). The intense inflammatory response and shrinkage observed in the intestinal segment prevented its use in humans (67). Further attempts consisted of using the association between demucosalised intestinal segments and auto-augmentation. In a sheep model the procedure was poorly tolerated and resulted in inflamed, haemorrhagic colonic segments at one month following operation. Colonic mucosa regrowth occurred in one third of the animals (68). Later studies using a canine model, suggested shrinkage of the intestinal patch in seromuscular enterocystoplasty was avoided with preservation of both the bladder urothelium and lamina propria, together with the submucosa and muscularis mucosa of the intestinal patch (69,70). This form of bladder augmentation did seem to prevent absorption of toxic substances like ammonium chloride (71). Other authors using the same technique to line de-epithelialised gastric patches in the mini-pig model found it useless due to the fibrotic changes and decreased surface area of the patch (72).

The initial experience in treating humans with colocystoplasty lined with urothelium were reported by Gonzales and Lima who independently developed a slightly different technique (73,74). Bladder capacity increased significantly while bladder pressures decreased. Later biopsies demonstrated urothelium covering the augmented portion of the bladder in the majority of cases. Longer term follow-up is now available and although the results have been encouraging, they seem to be highly operator dependent and the way in which the mucosa is removed seems to be crucial. Lima et al. no longer preserve the bladder urothelium and use a silicone balloon to prevent the augmented segment from contracting (they remove the balloon after 2 weeks: urine is diverted using ureteral stents): in 123 patients, no ruptures were found and only 10% were regarded as failures (75).

Gonzalez et al. reported seromuscular colocystoplasty in combination with an artificial urinary sphincter showing 89% success in their patients; with continence and no upper tract deterioration, they published this as their preferred method of augmentation when adverse bladder changes occur following implantation of an AUS six females(76).

More authors have now reported results of this procedure, it remains a more complex technique for bladder augmentation and has not achieved a place in widespread clinical practice. It is carried out in some designated centres (77-80). Comparison of long-term results with conventional enterocystoplasty has indicated no improvement in outcome.

Conclusion: seromuscular colocystoplasty is an effective bladder augmentation technique overcoming mucus formation (LoE:3)

Recommendation: seromuscular colocystoplasty is recommended as a bladder augmentation technique that overcomes mucus formation (Gr: C)

4.3.7. Ureteric bladder augmentation

Redundant ureteric segments have been used to improve bladder capacity and/or compliance. Megaureters associated with poorly or non-functioning kidneys provide good augmentation material with urothelium and sero-muscular backing, avoiding metabolic disturbance and mucus production (81-82).

In patients with ureteric dilation and good ipsilateral renal function, a combination of transureteroureterostomy with ureterocystoplasty is possible (83) – anecdotally, the long term risk of this is that a problem at the uretero-ureteral anastomosis or distally will risk damage to both kidneys. An additional option in patients with bilateral dilated ureters with preserved renal function is bilateral reimplantation and the use of the distal ends for detubularised bladder augmentation (84).

Bladder augmentation with ureter may be effective for a small group of patients with ureteric dilatation and poor bladder capacity. Overall, long-term results are good and remain so over a longer period (85-90).

Recent evaluation of long-term functional outcomes of ureterocystoplasty showed good functional, urodynamic improvement, however, some patients (4 out of 17 in this series) eventually needed a standard intestinal cystoplasty (91).

This type of augmentation can also be employed in children who require a renal transplant (92-94).

Conclusion: ureter can be used effectively for bladder augmentation (LoE:3)

Recommendation: in cases of a dilated ureter, bladder augmentation with ureter can be recommended (Gr:B)

4.3.8. Experimental Methods

Experimental work to generate a bladder replacement continues – but there has been nothing that merits widespread clinical application. One possible route may be tissue-engineered autologous urothelium and bladder muscle cells. These cells may be grown or seeded on biodegradable scaffolds, both naturally derived and synthetic, for the temporary support of the growing tissue until it is sufficient to become a surgical substrate that can be implanted to augment or replace the bladder. Several synthetic materials and natural matrices have been used in experimental and clinical settings. Techniques of cell harvest, culture, and expansion as well as polymer design continue to develop.

There have been a few ideas that have developed as far as preclinical trials with hope of future clinical application. The mantra that clinical trials may not be far away (95-108) has been stated for many years and continues. Thus, whilst this field of research may become the future of bladder reconstructive surgery, as yet it remains still some way from the front line. We strongly encourage further research in this field.

5. BLADDER OUTLET SURGERY

5.1. Urethral enhancement

In children with sphincteric incompetence as the primary cause of incontinence, procedures to enhance outlet resistance are important. In cases where the bladder has reduced capacity or compliance, bladder outlet surgery may be performed in combination with

other procedures to achieve a continent, low pressure reservoir with sufficient volume.

5.2. Bulking agents

Injection of a peri-urethral or bladder neck bulking agent in children first dates back to at least 1985. Initial concerns about distant migration of the injected substance and risk of granuloma formation prevented widespread acceptance (109,110).

Cross-linked bovine collagen has been trialled, and an initial 20-50% reported improvement was not sustained. The theoretical increase in urethral resistance did not consistently yield the dryness that was aimed for; continued incontinence or short-lived effect meaning this is no longer recommended (111-115).

The following substances remain available and have been tested in children with incontinence: dextranomer / hyaluronic acid copolymer (a nontoxic, nonimmunogenic, non-migrant synthetic substance) and polydimethylsiloxane.

The technique is endoscopic injection at the bladder neck area: more than one procedure may be necessary. On average 2.8 – 3.9 ml is injected. More than 50% of patients need more than one injection. Initial success of 75% has been reported, but after 7 years there is a gradual decrease and only 40% remained dry (113,116,117). Others have reported success rates of 0 - 70% (118-125). Despite limited success bulking agents remain an option for all patients who are poor surgical candidates and those who want to avoid extensive bladder neck reconstruction. An alternative route may be the injection around the urethra using laparoscopy (126).

Conclusion: bulking agents are effective to increase bladder outlet resistance (LoE:3)

Recommendation: bulking agents are recommended to increase bladder outlet resistance (GR:C)

5.3. Artificial urinary sphincter (AUS)

Since the AUS was first introduced in 1973, it has undergone several iterations. Currently, the most frequently used device (for around 30 years) is the AMS 800 (127). It is a 3-part device with an inflatable cuff, a pressure regulating balloon and a control pump. The inflatable cuff needs to be implanted around the bladder neck in females and pre-pubertal males. In post-pubertal males, bulbar urethral placement is possible but not recommended for patients in a wheelchair (128). For those who have had extensive urethral surgery (eg. exstrophy and epispadias) placement may be extremely difficult but possible at the bladder neck (129).

AUS implantation is specialist procedure, as technical difficulties may be encountered in dissection around the bladder neck in obese, post-pubertal males or those with a history of previous bladder neck procedures. In principle, a 61-70 cm H2O pressure balloon is used when the cuff is around the bladder neck and a lower pressure balloon with bulbar cuff placement. The AUS remains the most effective means of increasing urethral resistance, whilst preserving the potential to void spontaneously. The ideal candidate for an AUS implantation has isolated sphincter incompetence with spontaneous voiding, good bladder capacity and compliance. Unfortunately, only a small proportion meet these criteria. The AUS may be used in those dependent on clean intermittent catheterisation. The combination of AUS placement and enterocystoplasty with subsequent intermittent catheterisation is well documented (130-132).

Spontaneous or strain voiding may be possible following AUS implantation. Spontaneous voiding was reported in 25 % of children with AUS, the majority (in this series) having neurogenic incontinence (133). If an AUS is implanted before puberty, the ability to void spontaneously may deteriorate after puberty. 40 to 50% of neurogenic patients require their AUS to be combined with augmentation cystoplasty either simultaneously or subsequently to initial implantation (134-137). Reported rates of continence range between 63 and 97% (138-144). Herndon et al. reported success in 86% (n=134): 22% voided, 11% needed post-void CIC, 48% emptied exclusively with urethral CIC, 16% performed CIC through a continent channel and 3% had urinary diversion 142 patients underwent implantation of an artificial urinary sphincter, of whom 93 males and 41 females with a median age of 10 years (range 3 to 39(145). 28% required a secondary bladder augmentation. Mechanical device problems occurred in 30% with an AMS 800 (versus 64% in the old model). Revisions (16%) were significantly less with the AMS 800. Erosion occurred in both groups (16%). Perforation of the augmented bladder occurred in 10 patients.

In some children (and adults) with an AUS, the device is deactivated or no longer functions but they remain dry: others have reported continence following placing the cuff only (146,147).

Children who have had an AUS require life-long follow up. Data relating to device failure vary widely – some reporting a mean device survival of 4.7 years (148) others report (in an adult population) 10 year device survival of 66 % (149). In all (but especially those with a neuropathic bladder) long-term bladder behaviour may change – decreased compliance and raised end-fill pressure risk obstructive uropathy and nephropathy. Long-term monitoring with renal ultrasound is essential – where changes are seen renal scintigraphy and/or urodynamics are likely to be needed.

Infection or erosion of an AUS is seen in 15-20 % (149). Rates of both are much lower when there has been no previous surgery, when used as a salvage procedure following bladder neck reconstruction, the erosion rate may be higher at 30% 136). Despite the high complication and revision rate, AUS results show that acceptable continence rates can be achieved in the long-term. It is worth considering an AUS as primary treatment in selected cases (146,150).

5.4. Fascial slings.

Fascial slings, harvested from rectus abdominis, were first described to treat incontinence in children, in 1982 (151). The principle is to increase outlet resistance, with elevation and compression of the bladder neck and proximal urethra. In post pubertal females, urethral dissection may be facilitated with a combined vaginal and abdominal approach (152). Although the short-term success rates were encouraging and yet may affect bladder behaviour (153,154), more recent long-term data show 76.7 % of girls were dry with a mean follow-up of 11 years (155). Most authors report a greater success when fascial slings are used in conjunction with bladder augmentation and success seems more likely in females than in males (156). In patients with neurogenic incontinence, postoperative CIC is recommended (155).

In girls a pubovaginal sling, may be placed through the vagina: of 24 girls with spina bifida this was successful in 19, a further 3 became dry with additional injections of a bulking agent around the bladder neck via a suprapubic needle. CIC was possible in all patients. One patient developed a vesicovaginal fistula (157). Complications of sling procedures include difficulties with intermittent transurethral catheterisation and persistent incontinence. The increase in outlet

resistance provided by slings seems less than that provided by the artificial sphincter, however, data show a success rate between 50 and 80% in females. Small series have shown similar outcomes with 'off-the-shelf' alternatives such as small intestinal submucosa. Continence was better in girls than in boys (85 vs 43%) (158-160). There are data looking at tissue engineered solutions in adult women that suggest positive outcome but there is little further in the paediatric population (161,162).

There is no place for midurethral tapes made from mesh or other artificial materials in children.

Published data support the use of an AUS for the most consistent results in boys and for girls, with a history of spontaneous voiding and no previous bladder neck surgery. Bladder neck slings may enhance outlet resistance in neuropathic patients who need augmentation cystoplasty and who are likely to rely on CIC. At present, given the cost and lack of effectiveness of injection procedures, their use does not appear justified in incontinent children. The cost of an AUS may restrict its use in some healthcare environments.

Conclusion: Fascial sling is an effective treatment to treat incontinence in children due to a functional or anatomical deficiency (LoE2)

Recommendation:Fascial sling is recommended to treat incontinence in children due to functional or anatomical defieciency. (Gr:B)

All patients who undergo bladder outlet surgery need long-term follow-up to monitor for complications, changes in bladder and renal function whether they have had bladder augmentation or not (163).

5.5. Bladder neck closure

Bladder neck closure remains an important option however, for most, should be reserved as the option of 'last-resort' and will often follow multiple other procedures. This is a life-long option – long term difficulties include persistent urinary leakage, stomal stenosis, leakage or stone formation (in up to 40%) (164,165). Surgery and provision of good follow-up are vital, and it is also important that patients are compliant with intermittent catheterisation and regular bladder irrigation.

5.6. Bladder outlet reconstruction

Surgical procedures to achieve urinary continence are directed by functional and anatomical deficiencies; with the goal of either continence (with normal voiding) or dryness (dependent on intermittent catheterisation).

Reconstruction of a functional urethra for continence and emptying, usually implies an anatomical defect with no neurogenic component (eg epispadias / exstrophy) and includes bladder neck reconstruction and urethroplasty with urethral lengthening (166-168). Continence rates (for instance in exstrophy/epispadias) vary widely (22-80%)the management of bladder exstrophy (BE(169).

Postoperatively, intermittent catheterisation or post voiding catheterisation may be necessary but bladder emptying by voiding is possible for some.

Urethral reconstruction for dryness will require intermittent catheterisation. The goal in surgery is to stop incontinence and create a urethra suited to catheterisation. The most dependable procedures for dryness utilise a flap valve or tunnel to achieve urethral integrity, additionally urethral slings, wraps and injections have also been used (170-172).

Conclusion: urethral reconstruction is effective to treat urinary incontinence due to functional or anatomical deficiencies (LoE:3)

Recommendation: urethral reconstruction is recommended to treat urinary incontinence due to functional or anatomical deficiencies (GR:C)

Urethral reconstruction for continence is based on the physical principle that reduction of urethral calibre will support the sphincter mechanism at the bladder neck and proximal urethra. Ideally, narrowing should be dynamic, permitting apposition for continence and urethral opening with funnelling during voiding (3,165-174). Young (1922) described a "double sphincter technique" involving excision of a wedge of anterior bladder neck tissue, as well as removal of a wedge of tissue just proximal to the epispadiac meatus (external sphincter). Dees (1949) added the concept of the urethral lengthening to that of narrowing, parallel incisions were made through the region of the bladder neck creating a posterior urethral plate from the bladder trigone. This plate is tubularised to lengthen the proximal urethra. The added length provides increased potential for urethral closure, increases resistance and moves the proximal urethra into the pelvic cavity. Leadbetter (1964) modified the Young-Dees procedure by creating muscular flaps from the area of the bladder neck and proximal urethra which were used to wrap the newly created proximal tube. This procedure was popularised by Jeffs (1983) who applied it to a staged repair in exstrophy. The Hopkins group reported their long-term continence rate with this procedure as greater than 80%, without the need for CIC or augmentation and to help reapproximate the pelvic floor musculature facilitating urinary continence. RESULTS: Primary closure was done within 72 hours of life elsewhere in 41 (60%(175).

Arguably, bladder neck reconstruction represents a gold standard for continent outlet reconstruction, however, modifications of the technique have sought to improve outcomes. Typically, urethral lengthening procedures require ureteric reimplantation and preservation of the posterior urethral plate. The trade-off for use of bladder tissue to lengthen the urethra, is a reduction in bladder capacity – the creation of continence and resultant bladder cycling may mitigate this. A question remains over how the neourethra functions – whether there is genuine apposition and closure or simply a fixed, anatomical resistance. As before, life-long follow up of bladder and upper tract well-being is essential. Long-term outcomes of urethral lengthening procedures show nearly 80% dryness with 4 hour emptying intervals and 90% at 3 hour intervals; however, the need for additional procedures remained high (catheterisable channel: 54%, subsequent augmentation: 47%) (176). Outcomes for all are also dependant on patient compliance with their catheterisation regime.

An alternative technique is the creation of a flap valve, using a full thickness bladder flap to construct a tube, placed in a submucosal tunnel (168,173,174). The disadvantage with an effective flap valve, is that it will not allow leakage with high intravesical pressures; the lack of a 'pop-off' mechanism risks renal damage. Patient compliance is essential for the safety of these procedures – worsening renal function needs investigation and may trigger a discussion about conversion to an alternative reconstruction.

Bladder outlet procedures without augmentation cystoplasty are controversial. Combination with augmentation is generally accepted as the means to avoid nephropathy and/or continued incontinence. In a review of 109 patients who underwent bladder outlet

procedures without augmentation cystoplasty the need for subsequent augmentation cystoplasty was 30% and additional continence procedures 70%. Imaging showed upper tract changes in more than 50% and chronic kidney disease 20% in a cumulative 10-year follow-up (177-179).

In order to achieve the best outcomes, the surgical approach to childhood urinary incontinence needs to be tailored to the individual and multimodal, where necessary.

Recent data support the concept that very early reconstruction in the exstrophy / epispadias group leads to more physiological bladder cycling, which facilitates normal bladder and urethral development. In the long-term this may improve continence without the need for bladder augmentation and bladder neck reconstruction (Level 3) – more data are needed to support these early conclusions.

5.7. Robotic Procedures

It is clear that robotic assisted laparoscopic (RAL) procedures are being developed in reconstructive and paediatric urology. There is a lack of consensus about which is best for continence outcomes but review data suggest continence rates between 60 and 100 %. Data for RAL artificial sphincters in children are very early (180) but adult data for female bladder neck sphincters with just under 18 month follow-up suggest 72.7 % successful implantation rate (181). A series comparing peri-operative and continence outcomes for bladder neck reconstruction between open and RAL procedures suggest comparable safety and continence outcomes operative time, length of stay, complications within 30 days of surgery and future continence procedures (injection of bladder neck/catheterizable channel, additional bladder neck surgery, botulinum toxin A injection(182).

Conclusion: robotic bladder neck reconstruction is effective to treat urinary incontinence due to functional or anatomical deficiencies (LoE: 3)

Recommendation: robotic bladder neck reconstruction is recommended to treat urinary incontinence due to functional or anatomical deficiencies (GR:C)

6. ALTERNATIVE CONTINENCE CHANNELS

There is no doubt that the job of a reconstructive paediatric urologist is to preserve the original bladder, sphincter and urethra, where possible – there is no better alternative. The bladder can be augmented or replaced as previously described. Urethral reconstruction has been discussed, however there are occasions where it is not salvageable for either spontaneous voiding or catheterisation – in these patients continent suprapubic diversion is indicated.

6.1. The Mitrofanoff principle.

The most widely used continent catheterisable channel is eponymously known as the Mitrofanoff. The technique, tunnelling a narrow tube (originally the appendix) into the bladder or reservoir wall, was published by French paediatric surgeon Mitrofanoff, and the distal end is brought to the abdominal wall to form a catheterisable stoma (183). A number of tubes have been described as the Mitrofanoff conduit (184,185). Data show use of the appendix to have the best outcomes, however, it may not be usable in 31% of patients (185,186).

An alternative is formed by tailoring ileum using the Monti-Yang principle (186-188). The appendix has the best outcomes followed, in order, by a single Monti, double Monti and spiral Monti, although a pragmatic approach may be necessary in complex and/or revision cases (189-191). Use of the ureter is described although data are sparse – it appears that use of a ureteric channel is dependant on a pre-existing mega-ureter.

The Mitrofanoff system achieves reliable continence, which is maintained in long-term follow-up, for a high proportion of patients. Long-term data, from the original (Mitrofanoff) series, (n=23) with a mean follow-up of 20 years, showed 22 patients with no metabolic changes, 1 patient had died. The bladder neck had been closed in 21 patients, secondary bladder augmentation had to be performed in 8, while in 4 children conversion to an incontinent diversion was necessary. With time the need for additional surgery decreased and after 20 years 16 patients had a good and stable continent diversion 23 continent cystostomies were performed on 15 boys and 8 girls with neuropathic bladders. Mean patient age at surgery was 8 years and 4 months (range 3 to 16(192). Recent data support this with the outcome for those having a Mitrofanoff in childhood showing a lower revision rate than in other groups (193). The technique works on the basis of a intraluminal pressure (in the channel) that is 2 to 3 times higher than that within the reservoir to achieve continence even if intra-abdominal pressure is raised. Conversely, the pressure in the lumen of Kock nipple is only slightly higher than that in the reservoir, meaning continence is less reliable (192,194). The Mitrofanoff channel may be buried either between the mucosal and muscle layers of the reservoir, or may be completely Imbrlcated with the full-thickness of a reservoir wall. A well supported tunnel of about 2- 4 cm should function well. Continence rates of 90-100% are reported, with the Mitrofanoff principle, this appears to be irrespective of diagnosis, reservoir or conduit type (195-197). Follow-up for at least ten years has shown that the system is resilient (198-200). Retrospective review of short and long-term outcomes of patients with the Mitrofanoff procedure reveal that stoma stenosis and leakage are the most frequent complications (within wide ranges of 10 – 60 % each) and, most commonly, occur early during the first two years after creation. After the initial peak of complications, there is a relatively complication-free period. Late complications are recorded, probably because of wear and tear of the channels and changes in body habitus at adolescence or in adult life (193,201-205).

RAL Augmentation cystoplasty and Mitrofanoff are developing as techniques, with comparable surgical outcomes and data to suggest improved length of stay (206). A multicentre study, focussed on RAL Mitrofanoff procedures, with 29.5 month median follow-up included 88 patients and showed an 85.2% initial continence rate which climbed to 92 % with additional procedures (207).

A modified vesicostomy is described using a gastrostomy button, which could be used as an alternative, short to medium continent urinary stoma in children with incomplete voiding (208). Although perfect continence seems attractive, it may not be in the child's best interests. A 'pop-off' valve may be in the interest of the child if catheterisation is impossible or forgotten.

6.2. The Ileo-caecal valve.

The ileo-caecal valve has been used as a convenient, alternative 'sphincter' mechanism to use if caecum and ascending colon are used to create a reservoir and terminal ileum becomes the con-

duit. Early published continence rates of 94% were not sustained because of high pressures in the tubular reservoir and failure of the valve (209,210). The Indiana system is based on the competence of the ileo-caecal valve but with a detubularised reservoir. The valve itself is reinforced with non-absorbable plicating sutures and the terminal ileum which forms the conduit is tailored. The best reported continence rates are 96% with 2% describing catheterisation difficulties (211).

The Mainz I pouch relies on a similar principle with the addition of ,a length of terminal ileum that is intussuscepted through the ileo-caecal valve as a Kock nipple (212). It is impossible to say whether the nipple or the ileocecal valve (or both) produce the 96 % reported continence. Both systems work well as complete reconstructions and are widely used as bladder replacements in children. The sacrifice of the ileo-caecal valve may result in gastro-intestinal complications.

6.3. Kock pouch

The first workable continent diversion was the Kock pouch (46). The reservoir is made from 40cm ileum reconfigured to reduce the intraluminal pressure. The continence mechanism is formed by intussusception of 12cm of ileum. In a complete form it requires 72cm of ileum which will limit the number of patients for whom this is suitable. The length of bowel needed, subsequent stone formation and stomal leakage saw it fall out of favour (213,214).

6.4. Artificial Sphincter

Authors have described the use of a low pressure AUS cuff around the channel as a last resort, to achieve continence in a reconstructed outlet (210,215). Published data are sparse and appear to show a significant device infection risk, this is reduced from 50% to 9.5 % with a staged procedure (216).

6.5. Siting a cutaneous stoma

The most commonly chosen sites are the umbilicus or the right iliac fossa (ideally below the level of underwear). It is common for a wheelchair-bound spina bifida patient to experience worsening posture with spinal collapse, and a propensity for obesity. As result, the abdomen becomes more pendulous and more difficult to for a patient to access – the umbilicus may be more suitable in this situation. The site should be determined and marked, preoperatively in a sitting position. Fundamentally, the position should be chosen allowing the patient to manage bladder emptying and irrigation for themselves.

Many other patients will chose stomal site on the basis of cosmesis. The umbilicus is discrete, the risk of stenosis is low and it is a readily identifiable landmark. The alternative is a site as low as possible on the abdominal wall ideally hidden by underwear.

The published rate of stomal stenosis is between 10 and 23% (189,193). The siting of the stoma does not appear to influence revision rates (189).

7. COMPLICATIONS OF SURGERY FOR INCONTINENCE IN CHILDREN

7.1. Storage and emptying complications

However well-functioning at first, a reservoir containing bowel, with or without a continent catheterisable channel needs life-long follow-up in a centre capable of surgical revision if needed. Published data in neuropaths showed a median time to revision surgery of ten years (217,218).

The most common issues are difficulties with catheterisation, stomal stenosis and false passages which may occur in up to 34% of patients (196). A retrospective evaluation of 500 augmentations over 25 years with a median follow-up of 13.3 years, showed the cumulative risk of further surgery at the bladder level was 0.04 operations per patient, per year of augmentation and 34% of the patients needed further surgery for complications. Bladder perforation occurred in 43 patients (8.6%) with a total of 53 events and 125 surgeries done for bladder stones in 75 cases (219). It has been suggested that urothelium should be used as preservation of the bladder epithelium may give fewer complications than enterocystoplasty (220) – although data are sparse.

Ureterocystoplasty, appears to offer good outcomes with a low complication rate, even in children with compromised renal function or transplantation (221). All intestinal reservoirs produce mucus. There is no feasible way to measure the volume of mucus, all estimates are subjective. No regime has been shown to dependably reduce mucus production (222). Anecdotally, mucus production will increase with coughs and colds, spicy food and dairy intake. For those who are troubled by mucus it is important to ensure a good oral fluid intake, perhaps a food diary and regular bladder washouts.

7.2. Reservoir rupture

The most morbid and disastrous complication following bladder augmentation is perforation; if unrecognised this will lead to peritonitis, sepsis, and even death. Reported rates of cystoplasty perforation range between 6 and 13% (52,223-225). The incidence of perforation is strongly correlated with non-compliance (relating to catheterisation) and substance abuse (226).

The diagnosis may be delayed (especially if the patient presents to a centre not familiar with their condition or surgery); the history of sudden abdominal pain and diminished or absent urine drainage are important observations. A patient will develop generalised peritonitis and deteriorate quickly (227). A ‘pouchogram’ may not be sensitive enough to demonstrate a leak. Diagnosis is best made by history, physical examination, ultrasonography, CT cystogram and clinical suspicion. If diagnosed early, abdominal drainage, catheterisation and broad spectrum antibiotics may sometimes lead to recovery (228). If a patient does not improve markedly within 12 hours (on a non-operative regime) or if the patient is clinically sick an urgent laparotomy is needed – failure to intervene may be lethal.

Conclusion: adequate detection and treatment of reservoir rupture in patients with cystoplasty is essential to prevent clinical deterioration (LoE:2)

Recommendation: in cases of suspected reservoir rupture early detection and treatments is recommended to prevent serious, and even life threatening clinical deterioration (Gr:A)

A multicentre review from Scandinavia reported an incidence of perforation was found in 1.5% of patients with either augmentation or substitution cystoplasty. The rate was higher in neuropathic patients than any other group (227). A series of 264 children showed 23 perforations in 18 patients, resulting in one death (229). These series demonstrate the importance of a high level of clinical suspicion in any child presenting with abdominal symptoms, if they have had any form of cystoplasty (225). In a review of 500 patients with

bladder augmentation (performed in the preceding 25 years), spontaneous perforation occurred in 43 patients (8.6%), for a total of 54 events. The calculated risk was 0.0066 perforations per augmentation-year (230).

Patients and their families should be warned of this complication and advised to present to hospital immediately with abdominal symptoms, especially if there is any problem with urinary drainage. All young patients with urinary reconstructions, including enterocystoplasty, should carry suitable information to warn attending physicians, in case of emergency.

7.3. Metabolic complications

Bowel retains all its absorptive and secretory properties no matter where and for how long it is in the urinary tract, the resulting consequences may affect children more than adults simply because of the expected lifetime of the cystoplasty (231,232). In short anyone with a cystoplasty needs monitoring for metabolic complications (233). Nurse et al. found that all patients absorbed sodium and potassium from the reservoirs but the extent was variable (234). A third of patients (but 50% of those with an ileocecal reservoir) had hyperchloraemia. All patients had abnormal blood gases, the majority having metabolic acidosis with respiratory compensation. The findings were unrelated to renal function or the time since the reservoir was constructed. In 183 patients of all ages at St Peter's Hospital who had any form of enterocystoplasty, hyperchloraemic acidosis was found in 25 (14%) and borderline hyperchloraemic acidosis in an additional 40 (22%) patients. The incidence was lower in pure ileal reservoirs when compared to those containing any colon (9% v 16%). When arterial blood gases were measured in 29 of these children a consistent pattern was not found (235). In a series of 23 patients, Ditonno et al. found that 52% of patients with a reservoir of right colon had hyperchloraemic acidosis (236). Most studies do not distinguish between patients on the basis of renal function. All of 12 patients in one series with a pre-operative serum creatinine above 2.0mg developed hyperchloraemic acidosis within 6 months of enterocystoplasty (237). Patients need monitoring for metabolic abnormalities, including hyperchloraemic acidosis – whilst this may be subclinical if it is progressive, severe or combined with renal failure it is more likely to need treatment (238).

It is mandatory to monitor for vitamin B12 deficiency in all patients who have had ileal cystoplasty, the consequences are irreversible and failure to monitor and detect would be open to criticism. Ileal resection in children, probably leads to an incomplete defect in absorption. Stores of B12 may last for several years before the serum level becomes abnormal. At a mean follow up of six years, low levels of B12 have been found in 14% of children. There was a corresponding rise in the serum methyl malonic acid which accumulates in B12 deficiency, suggesting that the finding was clinically significant. Similarly, in adults, 18.7% have B12 deficiency at five years, following cystoplasty. In adults, the mean B12 level was significantly lower when the ileo-caecal segment as opposed to ileum alone had been used (413 ng/ml compared to 257 ng/ml) (239,240). To avoid the serious neurological complications, regular monitoring of B12 levels is essential. In a review of 500 augmentations starting at 7 years postoperatively, 6 of 29 patients (21%) had low B12 values, while 12 of 29 (41%) had low-normal values (241). Paediatric patients who have undergone ileal enterocystoplasty are at risk for development of vitamin B12 deficiency. These patients are at the highest risk beginning at 7 years postoperatively, and the risk increases with time. Annual monitoring of serum B12 with replacement where necessary, beginning at 5 years following cystoplasty is recommended.

Conclusion: monitoring of metabolic changes in children who underwent a cystoplasty is essential (LoE:2)

Recommendation: monitoring of metabolic changes is recommended in children with a cystoplasty (GR:B)

The stomach is rarely used as a urinary reservoir. Its non-absorptive role in the gastro-intestinal tract has made it particularly useful in reconstruction of children with inadequate intestine, such as those with cloacal exstrophy. There is little effect on gastrointestinal function. Metabolically, the acid production leading to hyperchloraemic alkalosis may be positively beneficial in children with renal failure. It produces no mucus and the acidic urine is less easily infected and seldom grows stones. However, about a third of children have had serious long-term complications, often multiple. The quite severe dysuria / haematuria and the skin complications from the acid urine, particularly, have limited its use (242,243).

7.4. Effects on the gastrointestinal tract

Little attention has been paid to the effects on gastro intestinal motility of removing segments of ileum or caecum for urinary reconstruction in children. In adults, disturbance of intestinal function has been found to be more frequent and more debilitating than might be expected. Disturbance of bowel habit does not mean diarrhoea alone. It also includes urgency, leakage and nocturnal bowel actions. Quality of life may be seriously impacted by changes in bowel habit(244). It is known that the bowel has a considerable ability to adapt, especially in young animals, when parts are removed. For all the reasons above, reconstruction should be undertaken with the smallest length of bowel possible. Care should be taken in children with neurological abnormality in whom faecal continence may already be poor. Faecal incontinence may occur in a third of patients (245,246), and has been shown to have a significant impact on quality of life (247).

7.5. Renal function

Obstruction and high pressures in the bladder during storage will cause nephropathy and renal deterioration if they are not treated with (for instance) cystoplasty. Postoperatively, urinary diversion may be followed by difficult urinary tract infections and stone formation with the potential to damage renal function. It is important to monitor renal function in anyone who has undergone reconstruction or diversion. The procedures themselves do not appear to have a direct, damaging effect on renal function, unless there is a technical failure or complication. In rats with near complete nephrectomy the rate of progression of renal failure is no worse in those with ileocystoplasty compared to those with normal bladder (248). This suggests, at least experimentally, that storage of urine in small intestine is not, on its own, harmful to renal function.

In the longer term, renal deterioration has been related to obstruction, reflux and stone formation. In one study of patients who have had a Kock pouch, these complications occurred at the same rate as found in patients with ileal conduits: 29% at 5 to 11 years (249). Similarly, in a prospective follow-up to a minimum of 10 years, it was found that the deterioration in glomerular filtration rate (GFR), that was found in 10 of 53 patients, was attributed to a 'surgical' cause in all but one (250).

Although a more complicated procedure, a renal transplant can be anastomosed to an intestinal reservoir with similar long-term results as those using an ileal conduit (251,252).

7.6. Infections and stones

The incidence of bladder reservoir stones varies between 12 and 25%. This is higher in children compared to adults. Palmer et al. reported an incidence of 52.5% during a follow-up of four years (253) with a predicted recurrence rate of up to 50%, greatest in the first two years following removal of the first stone and independent of the method of removal (254). Renal stones are uncommon, occurring in about 1.6% of patients, an incidence which would be expected in a group with congenital urinary tract anomalies.

In a series comparing the Kock pouch with the Indiana pouch (which does not have staples), 43.1% of 72 Kock reservoirs formed stones compared to 12.9% of 54 Indiana reservoirs (255). Furthermore, no patient with an Indiana pouch formed a stone after 4 years, but patients with Kock pouches continued to do so at a steady rate up to eight years.

Apart from the presence of a foreign body, several factors have been blamed for the high stone risk. Almost all reservoir stones are triple phosphate on analysis, though Terai et al. found carbonate apatite, urate and calcium oxalate in up to 50% of stones from patients with an Indiana pouch (256). This suggests that infection rendering the urine alkaline is a key factor. Micro-organisms that produce urease and split urea to form ammonia are the main culprits. The incidence of infection in reservoirs is high, 95% in one series, and yet the majority of patients do not form stones, suggesting that there are predisposing factors other than infection and the anatomical abnormality of the urine reservoirs (257). It has been suggested that the immobility associated with spina bifida may be responsible, but this seems to have been in series with a predominance of such patients and was not confirmed in other studies (214). There has been much speculation about the importance of mucus, as to whether it acts as the initial nidus for stone formation or additive by 'sticking' to a small stone and increasing the size. Recent data suggest that daily bladder washouts may reduce the incidence of stones and infections in reconstructed reservoirs (258). In a comparison looking at stone formers versus non-stone formers, those forming stones were found to have a lower urinary citrate and 24 hour urine volume suggesting a lower fluid intake and possible dietary factors (259). Mathoera et al. found an incidence of 16% during a follow-up of 4.9 years in 90 patients: girls were more frequently affected than boys and concomitant bladder neck reconstruction, recurrent infections and difficulties with CIC were other risk factors identified (260).

Mucins are an important component of the epithelial barrier and protect the epithelium from mechanical and chemical erosion. Mucins are known to act as important adhesion molecules for bacteria. Mucins may also enhance the formation of crystals (261). Mucin expression changes after incorporating the intestinal segment in the bladder. Upregulation of MUC1 and MUC4 expression occurs in transposed ileal segments resembling normal epithelium, whereas ileal segments in enterocystoplasty showed an upregulation of MUC2,3,4 and 5AC expression towards the site of anastomosis with the ileal segment. These changes which may be due to exposure to urine coincide with a change from ileal sialomucins to colonic sulfomucins by a change in glycosylation. The mucins bind calcium and may form a template resembling the crystal structure on which crystals are formed and grow. From these studies, it is concluded that inhibition of bacterial adhesion (by using different irrigation fluids based on sugars) could be of eminent importance in the prevention of certain types of infection stones. An interesting comparison has been made between children with a native bladder alone and those with an augmentation, all of whom were emptying by self-catheterisation. Interestingly, there was no significant difference in the incidence of stones with or without an augmentation (262).

Stones are associated with inadequate drainage in the sense that in CIC through the urethra, the most dependent possible drainage, has the lowest stone rate. Patients with the most 'uphill' drainage, that is with a Mitrofanoff channel entering the upper part of an orthotopic reservoir have a higher incidence of stones (261). Kronner et al. made the observation that the incidence of stones was statistically associated with abdominal wall stomas and a bladder outlet tightening procedure (21.1% compared to 6% in patients with augmentation alone) (257). Once a bladder stone has been diagnosed it has to be removed: several methods are available, but ESWL should be avoided as residual fragments may form the nidus for a new calculus. Because of the recurrent nature of these stones the least invasive method should be recommended (254,263,264). The high incidence of stones following enterocystoplasty suggests several measures should be recommended to the patients and their parents. Regular CIC under hygienic circumstances with adequate fluid intake and irrigation seem to be the most important (265). There is no evidence that prophylactic antibiotics are useful, but a clinical infection should be appropriately treated.

7.7. Growth

This short section is included to establish that there is no long-term effect on childhood growth as a result of having a cystoplasty. An initial report examining 60 children reported in 1992 found that 20% had delayed growth (266). Updated data from the same group has shown that all have caught up and achieved their final predicted height. A further study of 123 children from the same unit have shown no significant delay in linear growth (267). Animal data did show that with enterocystoplasty there was significant reduction in bone mineral density especially in the cortical compartment where there is endosteal resorption. These changes are not associated with metabolic acidosis and are lessened by continuous antibiotic administration , under experimental conditions - it is not clear how this would relate, if at all, to clinical practice (268,269). More recent follow-up data confirms no effect on growth (270-273) .

7.8. Pregnancy

Young girls and women who require urological reconstruction will commonly wish to have a family, in the same way as their peers. Consideration of this needs to be an active part of their follow-up (274). It is important that when young women reach adolescent they are informed about important risks – for instance the need for high dose folic acid for at least three months before and after conception if they have spina bifida (275). Patients also need to know that once they have bowel in the urinary tract a urine pregnancy test has a 57% false positive rate and always needs confirmation with a serum HcG test (276,277).

Surgically, paediatric urologists have described fixing pedicles out of the way to leave room for a gravid uterus in later life. Whist this sounds logical there are no data to say this makes a difference in the long term. Pregnancy (when it happens) may be complicated and requires the joint care of a high-risk obstetrician and an experienced reconstructive urologist (278). Problems can include upper tract obstruction and incontinence as the pregnancy develops. Pregnancy with a cystoplasty appears to have a good outcome, urine infection may be an issue and occasionally an indwelling urethral catheter may be necessary in the third trimester (279). With a catheterisable channel, as the pregnancy develops the channel may become distorted making catheterisation difficult, less commonly the channel may leak more – either way indwelling catheter drainage may be needed for the latter stages (280). When it

comes to delivery the important principle is to avoid an emergency caesarean section without urological support. The decision on mode of delivery is an obstetric one but may involve discussion with their urologist. Major pelvic distortion or reconstruction eg. bladder exstrophy will probably make an elective caesarean section more likely as a choice. This should be planned for around 37 weeks of gestation. The urologist should be present during Caesarean section to ensure protection for the reservoir, the continent channel and its pedicles (278). During any delivery, the bladder reservoir should be empty and an artificial sphincter deactivated.

7.9. Malignancy

The risk of malignancy in enteric augmentations has been reported to be higher than expected, and the risk increases with length of follow-up. Malignancy occurs in 0.6-2.8% of patients during median follow-up of 13-21 years. In a study including 153 patients with a median follow-up time of 28 years, malignancy was found in 4.5% (281). Animal data suggest that faecal and urinary streams must be mixed in bowel for neoplasia to occur – the risk of malignancy does seem predictably higher in patients who have had a ureterosigmoidostomy, and thus they are one of very few groups in whom regular surveillance is recommended. However, if it is chronic mixed bacterial infection, rather than the dual effluent, then all bowel urinary reservoirs are at risk. The malignancy seemed to be associated with coexisting carcinogenic stimuli, immunosuppression or with the inherent risk present with bladder exstrophy. In patients with colonic and ileocystoplasties high levels of nitrosamines have been found in the urine of most of the patients examined (282,283). Clinically significant levels probably only occur in chronically infected reservoirs (284). Biopsies of the ileal and colonic segments showed changes like those that have been found in ileal and colonic conduits and in ureterosigmoidostomies. More severe histological changes and higher levels of nitrosamines correlated with heavy mixed bacterial growth on urine culture (285). In a review by Filmer et al., 14 cases of pouch neoplasm were identified (286). Special features could be found in nearly all the cases. Ten patients had been reconstructed for tuberculosis; four tumours were not adenocarcinomas; one patient had a pre-existing carcinoma; six patients were over 50 years of age. Cancer was found in bowel reservoirs at a mean of 18 years from formation. In a review of 260 patients with a follow-up of more than 10 years, Soergel et al. found 3 malignancies (all transitional cell carcinoma): 2 following ileocecal and 1 after caecal augmentation. Age at augmentation was 8, 20 and 24 years respectively: the tumours were found when they were 29, 37 and 44 years old. All had metastatic disease and died. The incidence of malignancy in this group was 1.2%: considering that the development of tumours usually takes 20-25 years the probable incidence of malignancy following enterocystoplasty may be as high as 3.8% (287). Hussmann et al. studied a group of 153 patients with a mean follow-up of 27 years (10-52 yrs.) after augmentation cystoplasty. In those with a neurogenic bladder (n=97) they found 2 patients with transitional cell carcinoma (both smokers), in 38 patients with bladder exstrophy 3 multifocal adenocarcinomas in the augmented segment were found and in 2 of 18 patients with urethral valves an adenocarcinoma was discovered. The overall risk of cancer was 4.5% after a median period of 32 years. Of the 7 patients, 5 died suggesting that these tumours are very aggressive and metastasised early (281). This level of carcinogenesis was supported by data from Sung (288).

Patients with a gastrocystoplasty are at increased risk of malignancy. In a review of 119 patients who underwent gastrocystoplasty across two institutions, three patients developed gastric adenocarcinoma, another had poorly differentiated transitional cell carcinoma, all occurred more than 10 years after augmentation (289-291). Unreconstructed patients with neurogenic bladder reliant solely on CIC have an increased risk of bladder cancer; this risk may increase following bladder augmentation (292). There is no universally agreed means for follow-up by either imaging or endoscopy (293). Annual endoscopy is never been proven as effective as tumours that occur have done so in screening intervals – it is important to be responsive and investigate patients who develop new symptoms including haematuria, pain or unusual urine infections (294-295).

7.10. Psychological consequences and quality of life

The main justification for performing a bladder reconstruction or continent diversion is to improve urological function and thus Quality of Life (QoL). It would seem logical that continent urinary diversion would be better than a bag. This is not always the case. In adults, the only sure advantage is cosmetic. Validated QoL surveys in children have not been reported, primarily because of the lack of suitable instruments. Our prejudice is that reconstruction does, indeed, improve the lives of children although supporting evidence is very thin and based on experience in adults. The Indiana group have certainly shown that incontinence has a detrimental impact on QoL (296), thus we infer that surgery to improve continence will improve quality of life.

The ileal conduit has been a standard part of urological surgery for over 50 years. It has well known complications but few would seriously suggest that they were more troublesome than those of the complex operations for bladder replacement. In an early investigation into quality of life issues, Boyd et al. investigated 200 patients, half with an ileal conduit and half with a Kock pouch: there was little difference between the groups except that those with a Kock pouch engaged in more physical and sexual contact. The only patients that were consistently 'happier' were those who had had a conduit and subsequently were converted to a Kock pouch (297,298).

In a recent QoL survey in adults, a wide range of complications were considered to be acceptable, although an ordinary urological clinic would be full of patients trying to get rid of such symptoms: mild incontinence (50%), nocturia (37%), bladder stones (12%), urinary infections (9%), hydronephrosis (5%). Nonetheless, their QOL was judged to be good, primarily because 70% had experienced no adverse effect on their normal daily lives (299).

Quality of life does not mean absence of disease or a level of complications acceptable to the reviewing clinician. It is a difficult concept to measure because of a lack of validated instruments, difficulties in translating from one culture or language to another, and the difficulties in selecting control groups and variations in clinical situations. Gerharz et al. constructed their own 102 item instrument and compared 61 patients with a continent diversion and 131 with an ileal conduit. Patients with a continent diversion did better in all stoma related items indicating that containment of urine within the body and voluntary emptying is of major importance. In addition, they had better physical strength, mental capacity, social competence and used their leisure time more actively. There was little difference in satisfaction with professional life, financial circumstances and in all interactions within the family including sexual activity (300).

Consensus statement on surgical treatment of urinary incontinence in children

Urinary incontinence in children requires careful assessment with a thorough history, physical examination and voiding diary obviating the need for further investigation in the majority. A limited group will benefit from surgery. Many patients in this group will have obvious severe congenital/anatomical abnormalities.

The rarity of conditions may dictate an individualised approach to treatment that may be tailored by the expertise and training of the treating physician. Surgical procedures develop gradually and almost never undergo systematic evaluation. The concentration of care in specialist centres removes the need to rely on one surgeon with an unlikely expertise that would allow treatment of all conditions. The combined expertise of an expert team seems to offer a model for improved clinical care.

Such centres may allow the development of improved surgical approaches for severe complex anomalies such as exstrophy, myelodysplasia and urethral valves with the goal of improved future outcomes. Centralisation may also provide the opportunity for randomised studies to determine the most specific and effective treatment.

The committee would encourage vigorous research on the molecular basis of bladder development and support the development of surgical and treatment strategies which utilise the natural ability of the bladder to develop and transform in early life.

Endeavours to promote bladder healing, protect and achieve normal bladder function should be supported. Such studies and research may lead to earlier and improved treatment of many of the complex anomalies now treated by the surgical procedures outlined in this report.

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VII. PSYCHOLOGICAL ASPECTS OF URINARY INCONTINENCE, ENURESIS AND FAECAL INCONTINENCE

List of abbreviations used in this section

ADHD	Attention-Deficit/Hyperactivity Disorder
CBCL	Child Behaviour Checklist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5
DUI	Daytime urinary incontinence
FI	Faecal incontinence
ID	Intellectual Disability
ICD-10	International Classification of Diseases – 10
LUTS	Lower urinary tract symptoms
NE	Nocturnal enuresis
ODD	Oppositional Defiant Disorder

1. INTRODUCTION

During the past years,, an increasing body of reviews has been published on psychological factors of incontinence in children, as well as adults (1-5). A new focus of research and clinical practice is on children with special needs, who have higher rates of incontinence and behavioural problems (6). This chapter includes an update based on the recent literature and especially the ICCS standardisation document on psychological aspects in urinary and faecal incontinence (7), as well as other ICCS documents.

Children with urinary incontinence, enuresis and faecal incontinence carry a higher risk for manifest behavioural disorders, as well as for subclinical emotional and behavioural symptoms. It is important to assess and integrate psychological factors in treatment for two reasons:

1. As can be seen in Table 1, the rate of comorbid behavioural and emotional disorders is much higher than possible organic causes (7). The same care used to exclude organic causes should be applied to the assessment of behavioural aspects. Therefore, paediatricians and urologists should have a basic understanding of psychological principles to treat their young patients adequately.
2. In functional or non-organic incontinence, provision of information, cognitive therapy and behavioural modification are the most effective, first-line approaches to treatment. Medications can be helpful in many cases, but are usually not the mainstay of treatment. Surgery is rarely indicated. As most of the techniques used in “urotherapy” are based on cognitive-behavioural psychotherapy, it is essential to be acquainted with the basic psychological principles.

This chapter provides information on comorbid manifest clinical disorders, as well as symptoms which might be emotionally distressing for children and parents, but do fulfil the criteria for a disorder. Often, these will resolve upon attaining continence, while manifest disorders usually do not. In addition, children with psychological disorders are less compliant, and this explains why the failure rate of children’s incontinence treatment is much higher. It is recommended that both incontinence and any comorbid psychological disorder are treated separately to ensure effective therapy.

The relevance of psychological factors for the different subtypes of incontinence will be considered. The terminology of the ICCS for

Table 1: Organic causes and comorbidity of clinically relevant psychological disorders or symptom scores*

Nocturnal enuresis	
Organic causes	< 1%
Behavioural comorbidity*	20-30%
Urinary incontinence	
Organic causes	<10%
Behavioural comorbidity*	20-40%
Faecal incontinence with constipation	
Organic causes	< 5%
Behavioural comorbidity*	30-50%
Faecal incontinence without constipation	
Organic causes	< 1%
Behavioural comorbidity*	30-50%

**** Comparable population norms: 10%***

enuresis and urinary incontinence as well as of the Rome-IV classification for faecal incontinence will be used (8,9).

2. CLINICAL BEHAVIOURAL DISORDERS

Worldwide, approximately 10 to 20% of children are affected by clinically relevant mental health disorder according to ICD-10 (10) or DSM-5 (11) criteria (12). Even under most conservative estimates, 15% of children and adolescents have psychological disturbances with daily incapacitation. But are these disorders increasing? Bor et al. tackled this question in their very carefully conducted review and found that for toddlers and children, there was no major increase of psychological disorders (13). However, adolescents show an increasing risk for internalising disorders such as anxiety and depression, especially girls. The rate of comorbid behavioural disorders is increased in children with all types of incontinence. Comorbidity denotes the co-occurrence of two or more disorders at the same time (concurrent comorbidity) or in sequence (sequential comorbidity). The focus on comorbidity allows a descriptive approach without referring to possible causal associations. Basically, four combinations are possible:

- A behavioural disorder can be a consequence of the wetting problem,
- A behavioural disorder can precede and induce a relapse when a genetic disposition for enuresis is present, for example in secondary nocturnal enuresis,
- Wetting and a behavioural disorder can both be due to a common neurobiological dysfunction (such as in nocturnal enuresis and ADHD),
- With such common disorders, no causal relationship can be present and the two may co-exist by chance.

A psychological disorder (synonyms: psychiatric, psychic, mental disorder) “is a syndrome characterised by clinically significant disturbance in an individual’s cognition, emotion regulation, or behaviour that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning. Mental disorders are usually associated with significant distress or disability in social, occupational, or other important activities” (DSM-5) (11).

Clinically relevant disorders can be assessed by two basic methods: the categorical and the dimensional approach. The categorical method is based on a detailed diagnostic process (including history, observation, exploration, mental state examination, questionnaires, testing, physical examination and other procedures) and are professional diagnoses according to standardised classification schemes: ICD-10 (10) or DSM-5 (11). Dimensional assessment is based on symptom scores by questionnaires, but do not represent diagnoses. Cut-offs are defined to delineate a clinical (and sub-clinical) range.

One can differentiate three broad categories:

- Externalising or behavioural disorders with outwardly-directed, visible behaviour (examples: conduct disorders and ADHD),
- Internalising, i.e. inwardly-directed, intrapsychic disorders such as emotional disorders (examples: separation anxiety, social anxiety, phobias, sibling rivalry and depressive disorders),
- Other disorders that do not fit into the two categories, such as anorexia nervosa, tic disorders and autism spectrum disorders.

Five of the most important disorders occurring in children and adolescents with NE, DUI and FI are summarised below:

Major depression has a prevalence of 2-5%. The aetiology is multifactorial with a 40-50% contribution of genetic factors. Symptoms include sadness, unhappiness, loss of enjoyment, lack of energy and interest, negative thinking, sleep and appetite problems. Treatment includes counselling, cognitive-behavioural, interpersonal and psychodynamic psychotherapy which can be combined with antidepressant medication. A population-based study of 2079 6-year-old children has shown that depressive and anxiety symptoms are more common in children with NE and DUI, and especially high in FI (14).

Anxiety disorders affect 5% of children. Again, aetiology is multifactorial, including family, temperament and to 40% genetic factors. Four subtypes predominate: separation anxiety disorder, characterised by fears associated with separation; generalised anxiety disorder with the main symptom of worrying; in social phobia avoidance of social situations is typical and in phobia a fear of objects. Treatment consists of counselling, cognitive-behavioural therapy, relaxation, exposure and skills-based techniques, psychodynamic psychotherapy and medication in severe cases (antidepressants). Studies on anxiety in children with incontinence are still rare; exceptions are the study by Equit et al. (14). A new study using DSM-5 definitions showed that 34.6% of young incontinent children had at least one anxiety disorder (15).

Attention-deficit/hyperactivity disorder (ADHD) has a prevalence of 6% and a predominantly genetic aetiology (70-80%). The main symptoms are inattention, hyperactivity and impulsivity. Treatment includes counselling, parent training and cognitive-behavioural therapy. Medication plays a major role (mainly stimulants). In one population-based study of 1391 6-year old children, children with DUI had the highest rates of ADHD (16). Many studies have been conducted on the associations of ADHD and incontinence, which have been summarised in the systematic review of von Gontard and Equit (5).

Oppositional Defiant Disorder (ODD) is characterised by persistent hostile, provocative and noncompliant behaviour and affects 2-5% of children. The aetiology is best explained by a gene-environment interaction, including a genetic disposition and dysfunctional parenting practices. Treatment consists of counselling, parent training, cognitive-behavioural therapy, school-based interventions, but usu-

ally not medication. One population-based study on 718 6-year-old children showed a high rate of ODD, especially in children with DUI (17); and another study of 1676 6-year-old children, especially those with FI were affected by ODD, ADHD or both (18).

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder, defined by persistent deficits in social communication and social interaction and restricted, repetitive patterns of behaviour, interests and activities (DSM-5) (11). These disorders are present from the early developmental period, cause clinically significant impairment and are associated with intellectual and language impairment, and other disorders. The prevalence of ASD is 0.6-1%. The aetiology is mainly genetic, with up to 90% of the variance being due to genetic factors. 15% of ASD are syndromal forms, with the Fragile-X Syndrome, Tuberous Sclerosis being the most important syndromes. The diagnosis is based on a full child psychiatric, paediatric and genetic assessment. Treatment consists of parent training and counselling, autism-specific training programmes and behavioural therapy. Medication includes neuroleptics, stimulants, antidepressants (SSRI), which are not given routinely, but only when indicated. In a recent systematic review, the associations of ASD and incontinence were summarised, as well as the many open research questions (19).

3. CLINICAL BEHAVIOURAL DISORDERS IN CHILDREN WITH NOCTURNAL ENURESIS AND DAYTIME URINARY INCONTINENCE

Children with urinary incontinence show a higher rate of comorbid behavioural and emotional problems (16.5% to 51.9%) than non-wetting children (7.8% to 10.2%), in both epidemiological and in clinical studies. The overall relative risk is 1.4 – 4.5 times higher, based on early population-based studies (7). Epidemiological studies have the advantage of revealing representative associations. They often cannot differentiate well between subgroups. To date, the largest and best population-based studies are those of Joinson et al., based on the British ALSPAC birth cohort (20, 21, 22) (see table 2).

3.1. Nocturnal enuresis

The ICCS differentiates between primary (never dry) and secondary NE (relapse after a dry period of 6 months); and monosymptomatic (no lower urinary tract symptoms - LUTS) and non-monosymptomatic NE (with LUTS). Therefore, four subgroups of nocturnal enuresis can be differentiated:

- Primary monosymptomatic nocturnal enuresis
- Primary non-monosymptomatic nocturnal enuresis
- Secondary monosymptomatic nocturnal enuresis
- Secondary non-monosymptomatic nocturnal enuresis

Epidemiological studies show clearly that, depending on definitions and instruments used, 20-30% of all nocturnal enuretic children show clinically relevant behavioural problems, 2 to 4 times higher than non-wetting children (7).

Table 2: Epidemiological, population-based studies: Percentage of children with clinically relevant behavioural problems in comparison to controls and their relative risk*

Study	Age (yrs)	N	Type of wetting	Incontinent children	Controls	Odd's ratio
Joinson 2007 (19)	7 ½ years	8242	NE	Separation anxiety: 8.0%	6.40%	1.3
				Social anxiety: 7.0%	4.60%	1.5
				Specific phobia: 14.1%	11.50%	1.2
				Generalised anxiety: 10.5%	7.70%	1.4
				Depression: 14.2%	10.90%	1.3
				ODD: 8.8%	4.70%	1.9
				Conduct disorders: 8.5%	5.70%	1.5
				ADHD: 17.6%	11.90%	1.5
Joinson 2006 (20)	7-9	8213	DUI	Separation anxiety: 11.4%	6.80%	1.8
				Attention/activity: 24.8%	13.80%	2.1
				Oppositional behaviour:10.9%	5.80%	2
				Conduct problems: 11.8%	6.20%	2
Joinson 2006 (21)	7-8	8242	FI	Separation anxiety: 4.3%	0.80%	5.4
				Specific phobia: 4.3%	1.00%	4.3
				Generalised anxiety: 3.4%	0.40%	8.5
				ADHD: 9.2%	1.90%	4.8
				ODD: 11.9%	1.90%	6.3

**DUI = Daytime urinary incontinence*
**FI = Faecal incontinence*
**NE = Nocturnal enuresis*

In the British population-based ALSPAC-study of 8242 children at the age of 7 ½ years, children with NE were affected by: separation anxiety (8.0%), social anxiety (70%), specific phobia (14.1%), generalised anxiety (10.5%), depression (14.2%), ODD (8.8%), conduct disorders (8.5%) and ADHD (17.6%) (table 2) (20).

Children with primary nocturnal enuresis were not different from controls in epidemiological studies (23). Secondary nocturnal enuresis was preceded by a higher rate of weighted life-events (24) and was significantly associated with a higher rate of psychiatric disorders, which can persist into adolescence (23). By adolescence, the attainment of dryness after the age of 10 years increased the risk for behavioural problems, independently of the primary or secondary status (25). Newer studies show that 1-2% of adolescents are still affected by nocturnal enuresis, often accompanied by psychological symptoms (26).

The only epidemiological study addressing monosymptomatic nocturnal enuresis included 8242 children aged 7 ½ years (27). Though not adhering to the ICCS criteria, children with monosymptomatic nocturnal enuresis showed fewer behavioural symptoms than those with daytime problems (i.e. the non-monosymptomatic forms), although the differences did not reach significance. In a new series of 1638 children, those with primary non-monosymptomatic enuresis had higer rates of psychiatric disorders than those with primary monosymptomatic enuresis (31.5% vs. 19.5%) (28).

Regarding the types of behavioural and emotional disorders, externalising disorders such as ADHD and ODD predominate (5, 16,17,18, 29).

In a retrospective study of patients with ADHD, 20.9% wet at night and 6.5% during the day. The odds-ratios were 2.7 and 4.5 times higher, respectively, which means that there is a nonspecific association of ADHD and both night and daytime wetting (30). 25% of 140 children with ADHD were affected by nocturnal enuresis compared to 10.8% of 120 controls (31). The highest comorbidity rates of 40% for ADHD and nocturnal enuresis were reported by Baeyens et al. (32), possibly due to selection bias: 15% had a combined, 22.5% an inattentive and only 2.5% a hyperactive type of ADHD. In a community based sample, the prevalence rate was much lower. ADHD continued to be present in 72.5% of children in a two-year follow-up indicating a high stability (32). Children with ADHD continued to wet at follow-up much more often (65%) than controls (37%) (Odds-ratio 3.17). At a 4-year follow-up, 64% still had ADHD: of these, 42% continued to wet at night (compared to 37% of the controls) (33).

In clinical practice, children with ADHD are more difficult to treat. In a retrospective study, 113 children with ADHD and nocturnal enuresis had a worse outcome on alarm treatment than controls (with nocturnal enuresis only): 43% (vs. 69%) were dry at 6 months and 19% (vs. 66%) at 12 months. There was no difference if they were treated with medication, which does not require active cooperation. Non-compliance was reported in 38% of children with ADHD, but only in 22% of the controls (34). This means that children with both enuresis and ADHD require special attention – and both need to be treated separately.

3.2. Daytime urinary incontinence

Daytime wetting has been neglected in epidemiological research. The most important study is based on a cohort of 8213 children aged 7 ½ to 9 years (21). Children with daytime wetting had significantly increased rates of psychological problems, especially separation anxiety (11.4%), attention deficit (24.8%), oppositional behaviour (10.9%) and conduct problems (11.8%). Externalising disorders predominate in daytime wetting children, which, in turn, will interfere with treatment. In the same cohort, 10,000 children aged 4 to 9 years were analysed. Delayed development, difficult temperament and maternal depression / anxiety were associated with daytime wetting and soiling (35). In another population-based study, 36.7% of children with urinary incontinence had ADHD symptoms, in comparison to 3.4% of dry children (16).

ADHD is a common problem among day wetting children, as well. Compared to controls, children with ADHD had more symptoms of incontinence, constipation, infrequent voiding and dysuria (36). With ADHD, treatment outcome is worse. In a retrospective analysis, 68% of day wetting children with ADHD became dry compared to 91% of controls. Non-compliance was much higher for timed voiding (34).

Daytime wetting is a heterogeneous group of disorders. According to the ICCS terminology, following subgroups can be differentiated (8):

- Over-active bladder including urgency incontinence
- Voiding postponement
- Underactive detrusor
- Dysfunctional voiding
- Obstructive voiding
- Stress urinary incontinence
- Vaginal reflux
- Giggle incontinence
- Extraordinary daytime urinary frequency

Only some of these subgroups have been studied regarding comorbid psychological disorders.

Children with urgency incontinence have fewer behavioural problems than those with other types of DUI. 29% of children with urgency incontinence had an ICD-10 diagnosis and 14% had an internalising disorder. 13.5 % had a clinical total problem score in the CBCL, again mainly internalising problems (37, 38). The children are distressed by their wetting and family functioning is intact. In another study, 35% of children with urgency incontinence fulfilled the criteria for an ICD-10 diagnosis (39). Children with urgency incontinence have lower rates of comorbid disorders than those with voiding postponement (36% vs. 59%), but higher than controls (9%). Children with urgency incontinence predominantly have emotional, introversive disorders. In summary, children with urgency incontinence have only a slightly increased rate of comorbid psychiatric disorders. If they are affected, emotional, introversive symptoms predominate.

Children with voiding postponement, on the other hand, fall into two groups: in some it represents an acquired habit, in others, it is associated with externalising psychological disorders, especially oppositional defiant disorder (ODD). In a systematic study of children with voiding postponement in a paediatric and child psychiatric setting, 53.8 % fulfilled the criteria for at least one ICD-10 diagnosis (37). These were mainly externalising disorders in a third of children such as Oppositional Defiant Disorder (ODD). Also, 37.3 % of children had a CBCL total score in the clinical range, again, with externalising symptoms predominating. In addition, family functioning was impaired (37,38). In another sample, 53% of children with voiding postponement had at least one ICD-10 diagnosis (39). In summary, children with voiding postponement have highly increased psychiatric risks. Voiding postponement as one of the most important subgroups of DUI was the topic of a recent review (41).

Studies on comorbid behavioural problems in children with underactive bladder have not been performed. Systematic investigations of psychological aspects of dysfunctional voiding are rare. In some children, it represents an acquired habit, in others severe psychological disturbances are present (42). Dysfunctional voiding following severe sexual abuse and deprivation as well as other familial stressors such as migration has been described in case reports (43). DV can persist into adulthood and can be associated with anxiety and depression, especially in women (44). There have been no systematic investigations of children with giggle incontinence. From clinical experience, they are highly distressed by the symptom and try to avoid situations in which they might be forced to laugh. Social withdrawal, not going to parties and meeting with friends has been observed. It is not known if the rate of behavioural disorders is increased. Regarding the other subtypes of urinary incontinence, anecdotal data have been reported for adolescents (26).

4. CLINICAL BEHAVIOURAL DISORDERS IN CHILDREN WITH FAECAL INCONTINENCE

According to the Rome-IV classification, two subtypes of faecal incontinence can be differentiated (9):
- Functional constipation (with or without incontinence)
- Non-retentive faecal incontinence

4.1. Epidemiological Studies

In the large ALSPAC study of 8242 children aged 7-8 years, children with faecal incontinence had significantly increased rates of separation anxiety, specific phobias, generalised anxiety, ADHD and ODD (see table 2) (22). In other words, soiling children show a completely heterogeneous pattern of both internalising and externalising disorders. Again, these will require assessment in the individual child, as they will interfere with treatment of the incontinence.

In clinical studies, 35% to 50% of all children with faecal incontinence had a total behavioural score in the clinical range in this parental questionnaire. Compared to the normative population (10%), 3.5 to 5 times more children with faecal incontinence have total behaviour scores in the clinical range (7). Children with behavioural maladjustment are less compliant than children without psychological disorders (71% vs. 38% non-compliant) – so if these behavioural problems are not addressed treatment will be less successful (45).

A new study demonstrated, that 27.6% of adolescents with anorexia nervosa had constipation, an over-looked comorbidity in this severe eating disorder (46).

Children with faecal incontinence and constipation have the same rate of behavioural scores in the clinical range as children without constipation (39% vs. 44%, (47) and 37% vs. 39%, (48). This means that the two major types of faecal incontinence cannot be differentiated according to the behavioural comorbidity. More importantly, regarding the aetiology, there is no evidence that one type (i.e. with constipation) has more somatic aetiology, while the other type (i.e. without constipation) has a more psychogenic aetiology. There is no specific psychopathology typical for faecal incontinence: all types of behavioural and emotional disorders can co-exist.

4.2. Subclinical signs and symptoms

Subclinical behavioural signs and symptoms are common, understandable, adequate reactions to-wards the wetting problem and not disorders. Many studies have addressed the impact of wetting on children.

4.2.1. Impact on children

Most children are distressed by enuresis. For example, 35% said that they felt unhappy, 25% even very unhappy about wetting at night (40 children aged 5-15 years) (49). In a Finnish population-based study, 156 day and night wetting children (from 3375 7-year olds) showed significant differences compared to 170 controls regarding following personality traits (50): they were more fitful (vs. peaceful), more fearful (vs. courageous), more impatient (vs. calm), more anxious (vs. does not worry) and had more inferiority feelings (vs. feels equal). In a large population-based British study of 8209 children aged 9 years, 36.7% of children consider bed-wetting to be “really difficult” – ranking 8th behind other stressful life-events (51).

One construct of special importance is that of self-esteem. In one study, lower self-esteem in children with enuresis disappeared upon attaining dryness (52). In another, global self-esteem was significantly lower in children with nocturnal enuresis than in controls (53) and in yet another, the self-esteem total score was higher among enuretics than norms (54). Therefore, it was concluded that there is no clear evidence that bedwetting leads to lower self-esteem (55) – but there can be no doubt that self-esteem can improve upon attaining dryness (54). Self-esteem increases even if treatment of enuresis is not successful (56), showing that care and “good doctoring” for children and parents is of great help – regardless of outcome. Recently, a focus has been on quality of life, which is reduced in children with urinary incontinence (57). Questionnaires to assess quality of life will be presented later.

Children with faecal incontinence tend to feel less in control of positive life events and had a lower sense of self-esteem than children with other chronic conditions (58). In another study, self-esteem did not differ between children with faecal incontinence and controls (59). In a more recent study, adolescents clearly had a lower self-esteen and were highly distressed (60). In yet another study, 95% of 141 children with faecal incontinence seen in a pediatric setting had at least one psychosocial risk factor (61).

Repeatedly, quality of life was shown to be reduced in patients with faecal incontinence and constipation, as summarised in the review by Vrisman et al. (62, 63, 64).

4.2.2. Impact on parents

Enuresis and urinary incontinence may be just as distressing for parents as for children. Generally, parents are very concerned about the welfare of their child. In a population based study, 17% worried a great deal and 46% some or a little (65). In one study, the greatest maternal concerns were: emotional impact, social relationships, smell, extra washing and financial aspects (66). Mothers of children with nocturnal enuresis had a reduced quality of life scores (bodily pain and emotional role) and more depressive symptoms (67).

Parents also believe that their child should be dry at a very early age, which can induce anxiety and stress: the mean anticipated age of dryness was 3.18 years in one study (68) and 2.75 years in another (69). Also, many parents think that emotional factors are the cause of nocturnal enuresis and forget that they might be the effect of the wetting problem instead (68,69).

A minority of parents show an attitude that was described as “maternal intolerance” by Butler et al (70). Convinced that their child is

wetting on purpose, the risk for punishment is increased. In some cultures, punishment is very more common: 42% of Turkish children were spanked and 13% beaten (71). Chinese parents show a high level of parenting stress associated with externalising behavioural problems or their child (72). These parental attributions and experiences must be considered in all treatment plans for enuresis, as they can decisively influence the outcome.

Parents of children with faecal incontinence are also stressed and worried about the problem (73). In one study, children with faecal incontinence had family environments with less expressiveness and poorer organisation than controls (59). In another study of 104 families, nearly half (51%) had no unusual family problems; 23 had severe and widespread difficulties including sexual abuse; 11 families described moderate difficulties and 18 a single traumatic event (74). In other words, the atmosphere was warm and supportive without major difficulties in at least half of the families.

In recent studies, parents of children with constipation were stressed and had increased psychological symptoms and had more child-rearing difficulties (75, 76).

5. CHILDREN WITH SPECIAL NEEDS

Special needs is an umbrella term referring to individuals who require additional medical, psychiatric, psychological and educational assistance (6). Those with special needs comprise heterogeneous groups of physical and intellectual disability, as well as a wide variety of neurodevelopmental disorders. These disorders and disabilities continue to affect adults, i.e. they are life-long conditions. Incontinence is major, but often neglected disorder in people with special needs.

Studies have shown repeatedly that all types of incontinence are more common in children with special needs than in normally developing children, i.e. nocturnal enuresis (NE), daytime urinary incontinence (DUI) and faecal incontinence (FI). Also, incontinence has a higher likelihood of persisting into adolescence and adulthood, i.e. becoming a chronic condition. Incontinence can have an additive negative effect on the emotional state, self-esteem and quality of life of the child with special needs – and can affect his/her own daily school and family functioning.

Due to this focus on incontinence in children with special needs, the ICCS has issued an position paper specifically on neurodevelopmental disorders. These begin early in life, are mainly genetically determined and are associated with higher rates of all types of incontinence. The three most important neurodevelopmental disorders are ADHD, autism-spectrum-disorders and intellectual disability (77).

Many children with intellectual disability have special needs. Intellectual disability (ID) is defined by an IQ < 70. Mild ID (IQ 50-69) and severe ID (IQ < 50) are the two broad categories. Many different syndromes and disorders are associated with ID, most with prenatal, genetic causes. Overall, incontinence is more common in children, adolescent and young adults with ID (78). Also, there is an inverse relationship between IQ and incontinence, i.e. the lower the IQ is, the more often incontinence occurs.

Incontinence has been studied only in some of the specific syndromes of ID, such as Fragile-X, Williams, Down and Angelman syndromes (79-82). Incontinence rates of many other syndromes are summarised in von Gontard et al. (77). In addition to the IQ-level, syndrome-specific risk factors for incontinence have been identified, such as .epilepsy in Angelman syndrome and behavioural factors in other syndromes.

As many children with special needs do not receive standard assessment and adequate treatment, professionals working with children with special needs should realise that incontinence is a major and common problem in their patients and should actively offer effective treatment of incontinence, the underlying condition and associated, comorbid disorders. Daily distress will be reduced for patients, as well as parents and caregivers.

6. GENERAL PRINCIPLES: ASSESSMENT

6.1. Screening Questionnaires

Due to the high rate of comorbid behavioural disorders, the ICCS recommends screening with a broad-band, validated questionnaire (7,8). An ICCS-document provides an overview of the most important questionnaires (83). Broad-band means that a wide range of psychological symptoms are assessed. Narrow-band questionnaires are less useful as screening instruments, but are valuable in the diagnosis of specific disorders. Narrow-band questionnaires include those for depression, anxiety, ADHD, obsessive-compulsive behaviour, tics and autism spectrum disorders. If a manifest psychological disorder is suspected by history, clinical observation, exploration and broad-band questionnaires, a child psychological or psychiatric assessment is recommended. Short, medium and long screening questionnaires are available.

Conclusion: screening questionnaires are effective to diagnose comorbid behavioural disorders (LoE:2)

Recommendation: screening questionnaires are recommended to diagnose behavioural disorders (GR:B)

6.1.1. Short broad-band screening questionnaires

The ‘Parental Questionnaire – Enuresis/Urinary Incontinence (PQ-EnU)’, a parental questionnaire which has been used widely in clinical care and research, has been validated (84). It contains yes/no questions regarding nocturnal enuresis (NE) (12 items), daytime urinary incontinence (DUI) (10 items), voiding and stool habits (19 items), as well as behavioural problems (10 items). In the validation sample of 496 patients, a high correlation of .723 to .778 with diagnoses of incontinence (NE, DUI and faecal incontinence -FI) could be demonstrated. A factor analysis of the Behavioural Problem Scale (BP) revealed three factors: “attention and school deficits“ (Cronbach’s α =.665), “impulsive-aggressive behaviour“ (Cronbach’s α =.731) and “internalising problems“ (Cronbach’s α =.409). These factors showed significant correlations with Child Behaviour Checklist (CBCL – see below) total, internalising and externalising scales (.351 to .608). In summary, the PQ-EnU is a valid questionnaire to examine children with incontinence and can be used as a screening for psychological symptoms. It can be downloaded without charge (3).

The ‘Short Screening Instrument for Psychological Problems in Enuresis (SSIPPE)’ is a comparable instrument available in appendix of Van Hoecke et al. (85). It is a validated parental questionnaire, based on the Child Behaviour Checklist (CBCL) (86). It has three

scales including 7 Items for emotional problems, 3 Items for attention symptoms and 3 Items for hyperactivity/impulsivity symptoms. The authors recommend that if more than two yes answers are given for any of the 3 problem areas (emotional, attention, hyperactivity/impulsivity), this should be followed by a more detailed questionnaire such as the CBCL. If the CBCL T-scores are in clinical range (or many problem items are answered with a "2"), then a detailed child psychiatric assessment should follow.

6.1.2. Medium-length broad-band screening questionnaire

The Strengths and Difficulties Questionnaire (SDQ) is a medium-length behavioural screening questionnaire about 3-17 year olds (14). Parent and teacher versions are available, as well as self-reports for 11-17-year-old children and adolescents. It exists in several versions to meet the needs of researchers, clinicians and educationalists. In addition to the standard version, one version additionally assesses impact and incapacitation, while another version is useful for follow-up. Official translations are available in 77 languages.

All versions of the SDQ ask about 25 attributes, some positive and others negative. The items are scored on a three-point scale: not, somewhat and certainly true. The 25 items are divided between 5 scales: emotional symptoms (5 items), conduct problems (5 items), hyperactivity/inattention (5 items) and peer relationship problems (5 items) – these 4 scales form the total difficulties score. A fifth scale measures prosocial behaviour (5 items).

The Strengths and Difficulties Questionnaires, whether in English or in translation, are copyrighted documents that may not be modified in any way. Paper versions may be downloaded and subsequently photocopied without charge by individuals or non-profit organizations provided they are not making any charge to families. The questionnaires, scoring instructions, norms and related articles can be down-loaded free of charge at following website: www.sdqinfo.org

6.1.3. Long broad-band screening questionnaires

The family of Achenbach questionnaires covers the age groups from 1 1/2 years to 30 years – with self-informant-, parent- and teacher versions (86). The parental Child Behaviour Checklist (CBCL/6-18) is one of the most widely used questionnaires worldwide with translations in many different languages (over 90) and with national norms.

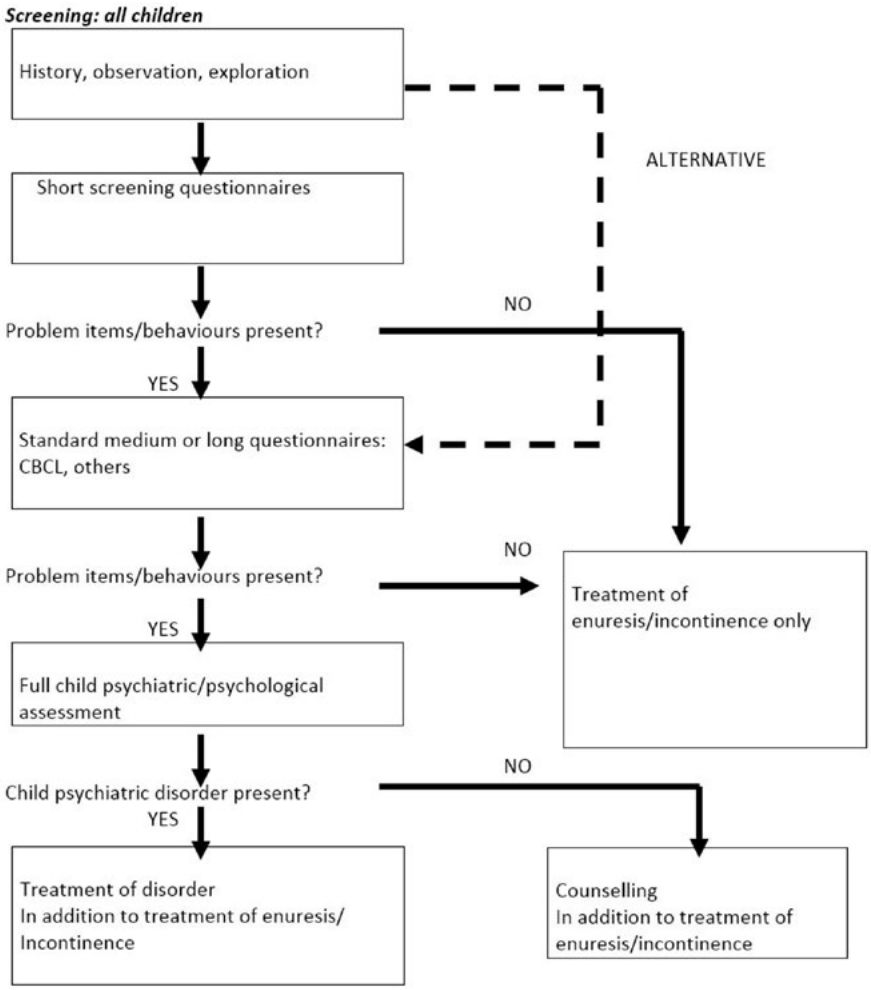

Figure 1: Flow chart for assessment of psychological symptoms (subclinical) or disorders (clinical). The specific treatment for enuresis / incontinence is the same for all children including those with symptoms requiring counselling, and those with disorders needing treatment (7)

As the name implies, the CBCL/6-18 is a parental questionnaire for the age groups of 6 to 18 years. It consists of a 113 problem items, which are scored on a three-point scale: 0= not true; 1= somewhat or sometimes true; 2= very true or often true. Three composite scales can be calculated (total score, internalizing, externalising behaviour). For these composite scales, the clinical cut-off is at the 90th percentile and the borderline cut-off at the 85th percentile. In addition, 8 other syndrome scales can offer valuable information.

The CBCL is one of many questionnaires within the Achenbach family of instruments: these aim at the pre-schoolers (1 ½ - 5 years), school age children (6-18 years), young adults (18-30 years), adults (18-59 years) and older adults (60-90 years). Self-report, parent and teacher versions exist, so that behaviour can be assessed in different contexts. All Achenbach questionnaires (such as the CBCL), manuals and related materials can be ordered under: www.aseba.org

In the ICCS documents, a general screening for emotional and behavioural problems in all settings (paediatric, urologic, child psychiatric, etc.) with a validated and standardised parental behavioural questionnaire is recommended because of the high rate of comorbid disorders in 30-50% of children (8). This can be done in two steps: using a short screening questionnaire first, followed by a long questionnaire; or in one step: using a validated, medium of long questionnaires. If many problem items are checked, a child psychological or psychiatric assessment should follow. If comorbid disorders are present, counselling or treatment, if necessary, is recommended (see figure 1).

One construct of special interest in children with incontinence is that of health-related quality of life (HQOL). In their standardisation document, the ICCS recommends to screen for changes of health-related quality of life (HrQoL) and specifically recommends using the PinQ-questionnaire, which is by far the best condition-specific HrQoL for children with incontinence (8, 88).

Generic HrQoL questionnaires can be useful in research in comparison with healthy controls and with children affected by other chronic medical conditions (89-91). Self-report versions for different age-groups, as well as proxy-report versions exist. The youngest age for self-report is 4 to 6 years, with reliable results available from 8 years onwards. The most commonly used proxy report is by parents, but caregivers, nurses and doctors can fill out these questionnaires, as well. Parental and child appraisal of HrQoL can differ. In research, comparison of child and own parental QoL can be interesting (91,92), but is usually not feasible in clinical practice.

In general, as HrQoL is a multidimensional construct, different aspects are assessed such as physical functioning, psychological well-being, social relationships, everyday life activities, satisfaction, discomfort, etc. These questionnaires can also be useful in monitoring the effects of therapy – in research, as well as in clinical practice. HrQoL-questionnaires are not useful in screening for psychological disorders, i.e. the information is not sufficient to decide if a disorder could be present or not.

6.2. Child psychiatric assessment

A child psychiatric assessment is a professional procedure with the goal of coming to a categorical decision: to see if a diagnosis, according to the standardised classification schemes (ICD-10 or DSM-I5) is present in the child or not (10,11).

The first step is a detailed developmental, behavioural and family history in much greater detail than provided in the outline in the appendix. The next step is to observe the child as well as the parent-child-interaction, followed by an active exploration of the child. The information gained from history, observation and exploration forms the basis of the mental state examination. This is a descriptive, phenomenological assessment of mental and behavioural signs and symptoms (for example: CASCAP-D) (94).

Questionnaires are always an essential part of a child's psychiatric assessment. They are a time-efficient way to gather information from different informants. They can contribute towards but do not provide a diagnosis. Behavioural questionnaires can again be divided into general and specific questionnaires. The best known, most widely used general parental questionnaire is the Child Behaviour Check List, which has been translated into many languages (CBCL/6-18) (86). In the meantime, Achenbach and co-workers have produced a whole "family" of questionnaires for different age groups (infants, children – adolescents, young adults) and different informants (parents, teachers and for children themselves starting from age 11). In addition, other specific questionnaires address circumscribed areas such as depressive symptoms or ADHD problems.

An intelligence test is not routinely indicated in the assessment of children with elimination disorders, as the IQ is in the normal range for most children with wetting, as well as soiling problems. However, the rate of elimination disorders is clearly increased in children with general developmental disorders, including those with mental and physical handicaps (6). If a lower intelligence is suspected, one-dimensional tests (such as the CFT or CPM/SPM tests) or multidimensional tests such as the Kaufman or the Wechsler tests can be performed. If specific developmental disorders such as dyslexia or dyscalculia are suspected, specific tests for these circumscribed disorders are indicated. Disorders of speech or language (such as articulation, expressive and receptive speech disorders) require a detailed assessment by an audiologist and speech therapist. Motor disorders can be assessed clinically by including soft neurological signs in the physical examination of children.

After the diagnostic process has been completed, the child's disorder is diagnosed according to standardised classification schemes. The two standard classification systems are the ICD-10 (10), which is widely used in Europe and in other parts of the world and the DSM-5 (11) employed in the United States. The ICD-11 has not been issued yet, but will be in use in the coming years.

In child psychiatry, a multi-axial classification is used. Six different axes denoting different domains are used, including:

1. Axis: clinical psychiatric diagnosis (such as anorexia nervosa, depressive episodes, etc.)
2. Axis: specific developmental disorders (such as dyslexia)
3. Axis: intelligence (such as dyslexia, speech and motor disorders)
4. Axis: somatic diagnosis (such as epilepsy and other paediatric diagnoses)
5. Axis: psychosocial risks occurring within the last six months (such as distorted intra-familial interaction, isolated family and other stressful life events)
6. Axis: the global severity of a disorder (ranging from mild incapacitation to disorders requiring constant supervision and guidance)

Only after the diagnostic process has been completed and discussed with parents and children, should therapeutic interventions be planned.

6.3. General principles: treatment of psychological disorder

For most children with elimination disorders, a symptom-orientated approach is sufficient. If, however, another, co-occurring child psychiatric disorder is present, additional types of treatment will be necessary. In these cases, a differential indication for therapy is mandatory. The question is: which treatment is most effective for this child in this family at this moment?

For some disorders (such as ADHD), medication plays a major role. For most others, psycho-therapeutic interventions are the first-line treatment. There can be no doubt that psychotherapy in children is effective. In one of the best and largest meta-analysis of 150 studies, Weisz et al. (94) conclude that "psychotherapy with young people produces positive effects of respectable magnitude "(i.e. effect sizes in the medium to large range - 0.5 to 0.8). It has been estimated that over 500 different types of psychotherapies exist in the USA for children and adolescents alone (95). Of those which have been evaluated, three basic schools of psychotherapy can be differentiated:

1. Depth psychology (or psycho-analysis), which addresses and works with unconscious aspects of the psyche;
2. Family therapy, which focuses on the interaction between family members but not the individual person;
3. Cognitive-behavioural therapy, focusing on cognitions and observable behaviour, which has become the most important and effective mode of treatment for many disorders in children and adolescents.

Before initiating any psychotherapy, a differential indication for therapy as to be made. The first basic question should be: is treatment needed at all? In many cases counselling of parents and child is all that is required. In other cases, changes in the child's environment (such as changing school) or help from social services can be more useful than psychological treatment in the narrower sense.

The modality should be considered. Although parents are nearly always included, the focus can be on an individual, group or family therapy. The intensity and duration should be addressed: is a short focal therapy focused on one specific problem needed, or a longer more general treatment? The age of the patient plays an important role: while older children and adolescents can be reached verbally, younger children require play or other non-verbal media in their therapy.

Psychotherapies can be combined with other methods, such as pharmacotherapy, but also by using speech, occupational, physiotherapy, music and other types of therapies – if indicated. The decision should no longer be based on personal inclinations. Instead, empirically based "practice parameters" or "guidelines" have been developed in many countries. These interventions are usually performed on an out-patient basis. Day clinic treatment can be indicated in more severe disorders, which require a more intense approach and management. Finally, in-patient child psychiatric treatment is indicated in severe disorders, in which a more intense type of treatment is possible.

6.4. General principles

6.4.1. Urotherapy

A major part of therapy of incontinence in children is non-pharmacological and non-surgical. The term urotherapy is used in some countries. It is an umbrella term which has been defined as a "type of training which makes use of cortical control of the bladder, teaching children to recognise and employ conscious command over their lower urinary tract." Its main ingredients are information about normal lower urinary tract function and the specific dysfunction in the child, instruction about what to do about it and support and encouragement to go through with the training programme (96). Standard and specific urotherapy can be differentiated.

Although not a psychotherapy in a narrow sense, it employs many psycho-therapeutic techniques borrowed especially from counselling and cognitive-behavioural therapies. As these approaches have been shown to be most effective, basic principles and findings shall be outlined. Details of the general principles and practice of urotherapy can be found in a recent ICCS-document (96). Specific approaches for children with neurodevelopmental disorders are outlined in another ICCS-document (77).

6.4.2. Non-specific approaches

The first step in any diagnostic and therapeutic process is to create a good relationship with both the child and the parent. One should enquire and talk about all relevant facts, signs and symptoms openly. It is also important to ask about the subjective meanings and connotations. Next, the provision of information is essential, because many facts are not known. It is often forgotten that not only parents but each child needs information, as well. This should be provided in words and concepts that a child understands and in a format that is attractive. Increasing motivation and alleviation of stress and guilt feelings are also part of all patient contacts.

Conclusion: creating a good relationship , providing information, increasing the motivation and alleviation of stress and guilt feelings are effective non-specific approaches essential in the diagnostic and therapeutic process in children with nocturnal enuresis, daytime incontinence and faecal incontinence (LoE:4)

Recommendation: creating a good relationship , providing information, increasing the motivation and alleviation of stress and guilt feelings are recommended in the diagnostic and therapeutic process of children with nocturnal enuresis, daytime incontinence and faecal incontinence (GR:B)

6.4.3. Counselling

Counselling is already part of the treatment process, which has been defined as the provision of assistance and guidance in resolving personal, social, or psychological difficulties. For many children, even with psychological disorders, counselling is, in fact, sufficient. Sometimes, it can be helpful to enhance the verbal counselling by other techniques. One simple technique is that of "demonstration", e.g. actively showing how an alarm works. In "coaching", parents and children take an even more active role, e.g. they set and activate an alarm themselves. They can be observed and corrected. Other techniques might include "modelling" and "role-playing". The learning effect is much greater in these active forms of teaching than in solely verbal counselling.

6.4.4. Cognitive –behavioural therapy

Cognitive-behavioural therapy (CBT) is a subtype of psychotherapy that has shown to be effective for many disorders. Cognitive therapy focuses on irrational, dysfunctional conditions, thoughts and beliefs. Cognitive therapy encompasses a whole variety of techniques such as "self-monitoring" (observation and registration), "activity scheduling" (organisation of activities) and "labelling" (using positive suggestive statements). Behavioural therapy concentrates on observable behaviour, which it aims to modify with a variety of techniques. These include "classical conditioning" and "operant conditioning", which basically means learning by success, which

can be achieved by different strategies using positive or negative reinforcement.

6.4.5. Baseline and observation

Baseline and observation are effective techniques used in cognitive-behavioural therapy. Children (and parents) are advised to observe a defined symptom. Different parameters such as frequency (how often it occurs), severity (how marked it is), symptomatology (in what form it occurs) and in which situation (associated factors) can be registered, e.g. in an observation chart. The mere observation and registration has a therapeutic effect and many symptoms diminish if they are simply observed.

In nocturnal enuresis, children are asked to fill out a calendar or chart depicting the wet and the dry nights symbolically for two to four weeks (3). These non-specific measures have been shown to be successful and are associated with fewer wet nights (3). In one clinical trial, for example, 18% became dry after an 8-week baseline (98).

In urgency incontinence, the cognitive aspects are stressed in treatment: children are asked to register feelings of urgency, refrain from using holding manoeuvres, to void and register the voiding (or any wetting) in a chart (3). For children with voiding postponement, timed voiding 7 times a day and registration in a chart is recommended (3,41).

For all children with faecal incontinence, stool regulation is an essential part of treatment. Children are asked to sit on the toilet three times a day after meal-times in a relaxed mode for five to ten minutes (4). This is documented in a chart and can be reinforced positively. If constipation is present and a large amount of faecal mass has accumulated, disimpaction has to be performed at the beginning of treatment. Oral disimpaction is the preferred method. To avoid re-accumulation of faecal masses, maintenance therapy with oral laxatives, such as polyethylenglycol (PEG) is recommended for at least six, and up to twenty-four months (99). The preferred oral laxatives are osmotic laxatives such as PEG.

Conclusion: baseline and observation are effective techniques in the cognitive-behavioural therapy of children with nocturnal enuresis, daytime incontinence and faecal incontinence (LoE:2)

Recommendation: it is recommended to use baseline and observation techniques in the cognitive-behavioural technique of children with nocturnal enuresis, daytime incontinence and faecal incontinence (GR:C)

6.4.6. Biofeedback

Biofeedback has been shown to be effective in some elimination disorders such as dysfunctional voiding (100). It is defined as a variety of techniques, by which physiological activity is registered, enhanced and presented to the patient in real time by visual and acoustical signals). In faecal incontinence, biofeedback is no more effective than standard behavioural techniques in faecal incontinence both with (101) and without constipation (102).

Conclusion: biofeedback is effective in the treatment of dysfunctional voiding (LoE:3)

Recommendation: Biofeedback is recommended in children with dysfunctional voiding (GR:C)

6.4.7. Alarm treatment

Alarm treatment for nocturnal enuresis is also a type of cognitive behavioural therapy. It works by positive reinforcement, as well as aversive, negative experiences and has been shown to be highly effective and was introduced by Mowrer and Mowrer (103).

It is the most effective form of treatment of nocturnal enuresis with the best long-term results (grade I level of evidence according to reviews and meta-analyses). Houts et al. (104) compiled a systematic review and meta-analysis on 78 randomised studies on nocturnal enuresis. 62% were dry at the end of treatment and 47% at follow-up. The authors conclude that “urine alarm treatments should not only be considered the treatment of choice, but the evidence from this review suggests that cure rather than management is a realistic goal for the majority of children suffering from nocturnal enuresis”. Therefore, when indicated, alarm has been endorsed as a first line curative treatment by various guidelines and by the new ICCS document on enuresis (105).

In a recent retrospective study of nearly 3000 children, who underwent alarm treatment, 76% achieved continence with a mean duration of therapy of 9 weeks. 23% of children had relapses and some children needed several courses of alarm therapy (106).

The effect of alarm treatment can be enhanced by adding additional behavioural components to the treatment. Programmes that include alarm in addition to other behavioural components showed following general effects: 72% of children became dry at the end of treatment, and 56% remained so at follow-up (meta-analysis) (104).

These specific programmes including alarm are all essentially cognitive-behavioural techniques. Arousal training is a simply and easily performed (107,108). Children are instructed to turn off the alarm within three minutes, go to the toilet and reset the alarm. This goal is reinforced positively with two tokens. If the goal is not reached, one token has to be returned. The initial success rate (89 %) and the rate of dryness after 2 ½ years (92 %) were higher than with alarm treatment alone (73 % and 72 % respectively).

Finally, alarm treatment can be combined with pharmacotherapy, although the evidence for combination treatment is conflicting. The combination of desmopressin and alarm treatment has been reported in several studies (108,109). The combination with anticholinergics plays an important part in clinical practice, but has not been investigated systematically. However, when alarm treatment fails, the ICCS recommends switching to desmopressin alone (110).

Conclusion: alarm treatment is effective in nocturnal enuresis (LoE:1)

Recommendation: alarm treatment is recommended in nocturnal enuresis (GR:A)

Conclusion and summary

This review summarised the most important psychological aspects in children with enuresis, urinary incontinence and faecal incontinence.

The rate of comorbid clinical behavioural disorders is increased. Children with DUI are more affected than those with NE. Children with secondary and non-monosymptomatic NE have especially high rates of comorbid psychological disorders. The most common single diagnosis is ADHD, but other disorders such as de-

pression, anxiety disorders and autism spectrum disorders can exist and must be considered.

Children with DUI have mainly externalising behavioural disorders. Children with urgency incontinence have a low comorbidity, those with voiding postponement are characterised by oppositional behaviour. Children with FI have the highest rate of associated disorders – both internalising and externalising.

These disorders will not disappear upon attaining dryness. They must be addressed, as they will interfere with the incontinence therapy due to low compliance. Even if comorbid disorders are not present, children and parents are highly stressed by the incontinence. These subclinical symptoms will often recede upon successful treatment. Children with special needs, especially those with ID, have very high rates of incontinence. Assessment and treatment of incontinence should be offered to all affected children.

Questionnaires are useful as screening instruments in the assessment process. It is recommended that questionnaires are used as a general screening procedure for emotional and behavioural problems routinely in all settings. If a psychological disorder is suspected, a full child psychiatric assessment and subsequent treatment is needed. The basic principles, including those of psychotherapy, are outlined. Psychotherapeutic techniques are used in urotherapy, especially cognitive-behavioural elements. Non-pharmacological and non-surgical techniques are most effective for most forms of incontinence. Therefore, it is important that psychological aspects are integrated into the treatment of children with incontinence problems.

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VIII. URINARY INCONTINENCE IN CHILDREN WITH SPECIAL NEEDS

1. INTRODUCTION

Children with special needs, i.e. intellectually and/or motor disabled, suffer lower urinary tract symptoms (LUTS) more than the normal population. Several studies have shown that nocturnal enuresis, daytime urinary incontinence and faecal incontinence are more frequent in children with special needs. Moreover, incontinence has a higher likelihood to persist during adolescence and adulthood. Although LUTS are associated with poor quality of life and health status, they are often less important to parents and physicians who are mainly focusing on physical rehabilitation. Literature on this topic is limited, but illustrates that adequate treatment improves quality of life significantly.

2. CHILDREN WITH SPECIAL NEEDS: GENERAL INFORMATION

2.1. Intellectual disability

Intellectual disability, the former mental retardation, is defined by the American Association on Mental Retardation (AAMR) as a disability characterised by significant limitations both in intellectual functioning and in adaptive behaviour as expressed in conceptual, social and practical adaptive skills. The disability originates before 18 years of age. Limitations in intellectual ability correspond to an IQ less than 70 to 75.

According to DSM -V (Diagnostic and Statistical Manual of Mental Disorders 5th edition. American Psychiatric Association (2013) Washington, DC) intellectual disability involves impairments of general mental abilities that impact adaptive functioning in three domains, or areas. These domains determine how well an individual copes with everyday tasks:

- The conceptual domain includes skills in language, reading, writing, math, reasoning, knowledge, and memory.
- The social domain refers to empathy, social judgement, interpersonal communication skills, the ability to make and retain friendships, and similar capacities.
- The practical domain centres on self-management in areas such as personal care, job responsibilities, money management, recreation, and organising school and work tasks.

In DSM-V intellectual disability is two standard deviations or more below the population mean, which equals an IQ score of 70.

Severity was defined in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders 4th edition. American Psychiatric Association (2000) Washington, DC) based on IQ ranges:

- Mild: 50-55 to 70
- Moderate: 35-40 to 50-55
- Severe: 20-25 to 35-40
- Profound: < 20-25

2.2. Motor disability:

Motor disabilities affect a person's ability to learn motor tasks such as walking, running, skipping, sitting, handwriting and others. To be considered a disability, the problem must cause a person to have motor coordination that is significantly below what would be expected for age, and the problem must interfere with activities of learning and daily living.

Although Intellectual disabilities and motor disabilities can stand on their own, in a considerable number of patients, a combination of both is diagnosed.

Intellectual disability is a common problem. Up to 10% of the school-aged children are learning impaired and as many as 3% of children in the US manifest some degree of mental retardation. The prevalence of mild mental retardation is about 1/77 (1.2%) and that of severe mental retardation is 1/300 (0.33%). For the clear majority of individuals with mental retardation (45-63%) no aetiology is identifiable. More than 800 syndromes are associated with mental retardation, of which Trisomy 21 or Down's syndrome is the best known. In addition, environmental factors, such as Foetal Alcohol Syndrome and peri- and postnatal conditions, such as CMV, rubella and hypo-ischaemic encephalopathy, may also be responsible for mental retardation.

The second most important cause of developmental disability is cerebral palsy (CP). Cerebral palsy encompasses a group of disorders of the development of movement and posture, causing activity limitation, which are attributed to non-progressive disturbances occurring in the developing foetal or infant brain [1]. Often disturbances of sensation, cognition, communication, perception and/or behaviour, and/or seizure disorders accompany the motor disorders. CP is a non-progressive injury of the brain occurring in the perinatal period and persisting through the lifespan.

The incidence of cerebral palsy is about 1.5 per 1000 births.

Twenty percent of the intellectually disabled individuals suffer cerebral palsy and 50% of the cerebral palsy patients are intellectually disabled.

3. LOWER URINARY TRACT SYMPTOMS IN CHILDREN WITH SPECIAL NEEDS: PREVALENCE

Von Wendt et al. published that 7-year-old children with mild intellectual disability differ relatively little from healthy children with respect to enuresis, (11.1% versus 9.8%), but suffered significantly more daytime urinary incontinence (16.7%) than the normal population (3.4%). The more severe the intellectual disability the higher the risk of persisting enuresis and daytime urinary incontinence [2].

Although LUTS are associated with poor quality of life and health status [3], urinary incontinence in children with CP is often considered a normal, unavoidable or minor problem. Yildiz et al. found 80 % of adult CP patients had never been referred to a physician due to urinary problems and 60 % had never been asked about urinary problems by any physician. An even higher rate of patients never had a urinary system ultrasonography, post-void residual urine measurement or urodynamic testing up until adult age.

Continence can be achieved spontaneously [4], but the continence process will be delayed and LUTS or abnormal urodynamic findings can be present at a young age [5]. In children with CP 55.5% suffer LUTS, of which urinary incontinence is the most frequent with a prevalence rate ranging between 20% and 94%. Urgency and frequency, with a respective prevalence of 38.5% and 22.5%, are also very common in CP patients. Urinary incontinence, urgency and frequency are significantly more common in children with CP compared to a healthy population.

Storage symptoms are more prevalent than voiding symptoms, with a prevalence of hesitancy in children with CP of 16.5%. Urinary tract infections (UTI), with a prevalence rate of 8.5%, are also more common in CP children than in the normal population [6].

Patients with Down's syndrome also show an impaired ability to become continent. Several studies have illustrated that children with Down's syndrome have a delay in toilet training and are more prone to incontinence afterward. One fifth of the children with Down's syndrome are not toilet trained at the age of five and nearly 50% of the toilet trained children will have incontinence, that even can persist into adulthood [7]. Niemzcyk et al. noted a significant gender difference for daytime incontinence prevalence rates, with male patients demonstrating more incontinence [8].

LUTS are also more common in children with Down's syndrome, with a prevalence around 27 %, and symptoms are also more common in male than in female patients [9]. These LUTS decrease with age, and patients with Down's syndrome older than 10 years have a five times lower chance of LUTS compared to those who are ten years or younger [10]. Kitamura et al. found LUTS to be very common in children with Down's syndrome, but remarkably neither the children nor their environment seemed to be aware of it [9].

Von Gontard reviewed the association of nocturnal enuresis, daytime urinary incontinence and faecal incontinence in children with intellectual disability in general and in patients with specific syndromes of intellectual disability including Rett's, Angelman's, Fragile-X, Prader Willi, Noonan's and Williams' syndrome. He concluded that people with profound intellectual disability have the highest rate of incontinence, whereas syndromes with mild intellectual disability have much lower rates [11-16].

Not only intellectual capacity, but also motor capacity is correlated with the development of continence. The more immobile the higher the prevalence of urinary incontinence. Motor disability, especially the degree of mobility, rather than intellectual disability seems to be the dominant factor determining urinary continence [17].

4. PATHOPHYSIOLOGY OF LUTS IN CHILDREN WITH SPECIAL NEEDS

4.1. Urodynamic findings

Samijn et al. found in their review on LUTS and Urodynamic Findings in CP patients that 84.5% had an abnormal videourodynamic study. Neurogenic detrusor overactivity (NDO) is the most common urodynamic abnormality, with an average prevalence rate of 59% [6]. The finding of NDO on urodynamics is not synonymous for the prevalence of LUTS. Several authors found pathological urodynamic findings in both symptomatic and non-symptomatic children with CP and vice versa [18-21]. Therefore, some authors stress the need for urodynamic examination in this population to discover silent bladder dysfunction or risk factors for upper urinary tract dysfunction (UUTD).

Abnormal uroflow patterns, especially staccato pattern, were found in 36.5% to 66% of CP patients [17,22,23]. Van Laecke et al. could not establish a correlation between uroflow pattern and urinary incontinence, whereas Silva et al. reported a significant correlation between abnormal uroflow patterns and the presence of LUTS [17,22].

The average prevalence rate of detrusor sphincter dyssynergia (DSD) is 11% [6].

Comparing urodynamic studies with uroflowmetry showed more pathological findings on urodynamics than on uroflow, which can be explained by the fact that uroflowmetry only measures the voiding phase.

The high prevalence of NDO can be explained by the fact that CP is caused by a cerebral insult, with lesions in the suprapontine circuitry, disturbing the inhibitory control over the pontine micturition centre [20]. Overactivity of the pelvic floor and the urethral sphincter is not expected in patients with a cerebral lesion, and may suggest a lesion of the lumbosacral cord. Severe hypoxia might be the cause of this in CP patients [24-26].

In children with CP, hesitancy is more prevalent than DSD, which may indicate that other factors than DSD contribute to overactivity of the pelvic floor. Mayo et al. suggested that hypertonia is the cause of the inability to relax the pelvic floor muscles during micturition, resulting in an increased rate of hesitancy [27]. One might conclude that children with spasticity may suffer pelvic floor overactivity as a voluntary reaction to an overactive bladder.

De Medeiros Francilaide Campos et al. found similar results in children with microcephaly and congenital zika syndrome[28]. Urodynamic evaluation demonstrated mostly immature and reflex bladder or detrusor overactivity.

Kitamura et al. found in their study that a significantly lower number of children with Down's syndrome had a normal bell-shaped uroflow pattern (18%) than age-matched control children (60%). They concluded that the non-bell-shaped uroflow patterns are due to functional and not to anatomical or organic abnormalities. [9]

4.2. Bladder capacity:
Reduced bladder storage ability is a major factor in the pathophysiology of urinary incontinence in children with special needs. Several studies illustrated that 73.5% of the CP subjects have a small bladder capacity compared to the expected bladder capacity for age (EBC). Mean bladder capacity is 58.5% of the EBC. [6] Bladder capacity can be negatively influenced by involuntary bladder contractions, characteristic for NDO, inadequate fluid intake due to swallowing problems and inadequate hydration [5, 17, 29-31]. Constipation, which can be due to restricted fluid intake, can negatively influence reduced bladder capacity [32]. Samijn et al. demonstrated maximum voided volume, a measurement for bladder capacity, significantly associated with incontinence in a population of children with CP [33].

4.3. Inadequate fluid intake
Van Laecke et al. found that only 9.9% of the children with a special need included in their study had a normal fluid intake. Although some of these children suffer swallowing problems, the major problem was found to have inadequate drinking. Increasing the fluid intake to a normal level of 1500ml/m² resulted in a significant increase in continence and maximum voided volume [17, 31].

Consistent with these results, oral fluid intake was found to be an important predictive factor for incontinence in children with CP [33]. Although children with and without incontinence did not drink enough, regression analysis demonstrated that an increase of fluid intake equal to one percent of the recommended fluid intake could have a considerable effect on the odds of incontinence.

4.4. Post-void residual
In CP patients, due to the low prevalence of DSD and hesitancy, the finding of pathologically increased post-void residual is low [18, 22, 23, 32, 33]. Similar results were found in children with microcephaly and congenital zika syndrome. [28]. In Down's syndrome patients, increased post-void residual was demonstrated in 7% [9].

4.5. Intellectual disability and motor dysfunction.
Von Gontard noted intellectual disability (i.e. IQ < 70) as a major risk factor for incontinence, with increasing rates as IQ decreased. [35]. Prevalence rates for incontinence or LUTS in general in patients with intellectual disability further depends on the syndrome and disorder.

However, LUTS are less influenced by intellectual disability than by moderate to severe motor dysfunction [17, 33, 36, 37]. With respect to children with CP, continence is less often achieved in subjects with low intellectual capacity combined with spastic quadriplegia than in subjects with high intellectual capacity combined with hemi- or diplegia [4]. The combination of both intellectual disability and spasticity has a bigger influence than both factors independently. Bross et al. concluded that urinary symptoms and pathological urodynamic findings increase along with the degree of motor function impairment [18].

Involuntary spasticity of the pelvic floor, which may be part of a general spasticity, may cause LUT dysfunction [30,38]. This can also explain the potential to acquire pelvic floor hyperactivity in reaction to NDO in children with spasticity [18, 27].

In subjects with quadriplegia, LUTS and abnormal urodynamic findings are found more often than in patients with diplegia, illustrating that not only lower limb impairment, but also upper limb impairment plays a role in achieving continence [4]. The plasticity of the central nervous system enables the unaffected side to assume more control over the bladder during development. This could explain the lower prevalence of LUTS and disturbed urodynamic findings in children with hemiplegia [37].

Poor mobility is an important factor in achieving continence, as children can be faced with both organic incontinence due to their underlying disorder and functional incontinence due to the inability to reach the toilet and adequately get on the toilet [35]. Difficulties in consuming enough will influence both urinary incontinence and constipation. Moderate to severe functional impairment (GMFCS III or higher) and the spastic subtype with quadriplegic distribution will negatively influence the ability to become continent. [6].

5. COMORBIDITY

5.1. Constipation and faecal incontinence
Constipation is an important comorbidity relating to urinary incontinence in children with special needs. There is a proven correlation between constipation and urinary incontinence, detrusor overactivity, dysfunctional voiding and UTI [39]. Intellectually disabled children are more prone to constipation and faecal incontinence. Up to 70% of these children suffer constipation [40]. Up to 90% of the children with CP suffer constipation and 47% faecal incontinence, though most of them to a minor degree [41]. In children with Down's syndrome, a systematic review demonstrated bladder bowel dysfunction in 75-96% of children with LUTS. Functional constipation was most frequently seen and included 90% of the children with bladder and bowel dysfunction [42].(Level of Evidence 2a-b)

5.2. Neuropsychiatric disorders
ADHD and autism are more frequent in intellectually disabled children and there is a proven correlation between ADHD and urinary incontinence [43,44].

5.3. Sleep disorders
There is increasingly more evidence that there is a relationship between nocturnal enuresis and sleep disorders in otherwise healthy children [45-47]. Sleep is a complex neurological function. In children with brain damage, the autonomic nervous system, which is involved in pineal melatonin secretion and sleep regulation might be affected [48]. Sleep is also vulnerable to several other factors common in CP. Muscle spasms, decreased ability to change body position during sleep, epilepsy and glossoptosis, which can induce sleep disorder breathing, may be the cause of disturbed sleep in these children [49,50]. Sleep disorders like delayed insomnia, dis-

rupted sleep, early awakening or a combination of these are frequently reported in patients with CP. Newman et al. found that 44% of the patients presented at least one clinically significant sleep disorder. Nearly 50% of the children with CP have some kind of sleep problem. These problems are reported more in non-walkers (72%) than in walkers (36%) [51]. Also in patients with Down's syndrome sleep disturbances are more common [7].

6. EVALUATION OF THE SPECIAL NEED CHILD SUFFERING LUTS

Of the children with CP who are dry at adult age, most achieve continence by the age of five years old [4, 52]. Therefore, Reid and Borzyskowski suggest children with CP can merit early urological evaluation [5]. ICCS guidelines recommending urologic evaluation when LUTS are present after the age of five years old should also be used in children with special needs [53]. After the age of five years spontaneous achievement of continence drastically decreases and parents and physicians should not assume lower urinary tract dysfunction as a normal feature in these children. (Level of Evidence 1b)

In general, all the assessment principles and tools for incontinence in typically developing children apply to those with special needs. [35]. Multimodal urological, paediatric and child psychiatric skills are needed to ensure optimal treatment in many cases.

6.1. History

History taking in children with special needs is often challenging, and mainly relies on hetero-anamnestic data. It is important that not only parental information but also information from the care givers should be considered, as many of these patients spend a lot of their time in specialised institutions. The questions should include items on nocturnal enuresis, urinary incontinence, lower urinary tract symptoms and bowel function. Attention should also be paid to intellectual and motor development, family disorders, the child's psychosocial and familial situation, neurological and congenital anomalies, urinary tract infections, relevant medication and surgery. Special emphasis should be given to fluid intake and food habits.

A voiding and drinking diary, and a dry-wet calendar are essential in determining the child's voiding frequency and voided volumes, to evaluate the number of enuresis and incontinence episodes, to determine the degree of nocturnal diuresis and to evaluate the quantity and quality of fluid intake. The same should be done for stool, registering defaecation frequency, stool consistency and soiling.

6.2. Physical examination

Theoretically, physical examination should include the assessment of perineal sensation, the perineal reflexes supplied by the sacral segments S1-S4 and anal sphincter tone and control. Practically, as this is discomforting for the child, this part of the physical examination is restricted to those where there is a suspicion of neuropathy.

Special attention should be paid to signs of neuropathy such as: spine deformity, abnormal gait, abnormal deep tendon reflexes, asymmetrical atrophy of the feet, high plantar arches, hammer toes, and signs of occult dysraphism, i.e. skin discolouration, dimples, hairy tufts, subcutaneous lipoma, asymmetrical buttock, legs or feet and oblique gluteal cleft [54]. The abdomen should be palpated to asses a full bladder, full sigmoid or descending colon and flank masses. The external genital region must be inspected for vaginitis and vulvitis, meatal web and a hymen that covers nearly the complete vaginal introitus in girls, and for penile anomalies and meatal stenosis in boys. In motor disabled children the locomotor system has to be evaluated according to muscle power, mobility, stability and spasticity. In intellectually disabled children the IQ and the functional autonomy has to be estimated.

6.3. Laboratory tests

Urine analysis to exclude pyuria, proteinuria, glycosuria, haematuria, calciuria and bacteriuria should be done at the first office visit. Urine osmolality and electrolytes should be determined in case of monosymptomatic enuresis with persistent therapy resistant polyuria.

6.4. Uroflowmetry

Uroflowmetry in children with special needs is often a problem. Intellectually disabled children are often too anxious to perform a uroflowmetry and motor disabled children are often incapable of performing a non-disturbed micturition because of their unstable position on the flow chair. ICCS guidelines recommend ensuring relaxation of the pelvic floor muscles by using foot support [55]. A standardised adequate position should be used carefully as this could have an effect on the outcome parameters. This is reinforced by the recommendation of the ICS, which stated that testing should be performed in the preferred usual position [56]. Therefore uroflowmetry, especially in moderate and severe patients, should be preferably performed in their own environment on their personally adapted toilet chair. Implementation of a correct toilet posture with maximal potential of pelvic floor relaxation during micturition is important and should therefore be trained as the natural voiding position to ensure accurate interpretation of uroflowmetry.

ICCS guidelines mention voided volumes less than 50 % of expected bladder capacity for age (EBC) are not reliable to interpret [53]. As 73.5% of the subjects with CP exhibit a reduced bladder capacity compared to EBC [6], this could further influence accurate interpretation of uroflowmetry in children with CP.

Samijn et al. tried to evaluate uroflow/EMG results in children with CP, but interpretation of pelvic floor activity was only possible in eighteen of the 79 (23%) evaluated children [33]. With six out of nine children (67%) demonstrating pelvic floor overactivity in both the continent and incontinent group, it could be suggested that pelvic floor overactivity is equally present in continent and incontinent children. However, not being able to void on uroflowmetry was defined as a significant risk factor for incontinence and could also be the result of the inability to relax the pelvic floor to start micturition.

6.5. Ultrasound

Ultrasound is used to evaluate the upper and lower urinary tract in children with LUTS especially when they are suffering from a UTI. It can also be used to measure the post-void residual.

6.6. (Video-) Urodynamic examination

These urodynamic investigations are invasive, especially in children with special needs who often lack the intellectual capacity to understand what is going to happen, or are physically unable to undergo the examination in a comfortable way. Although some authors are convinced that urodynamics should be performed in the majority of moderate and severe patients to rule out the silent bladder dysfunction or risk factors for UUTD,it is recommended that this examination should be reserved for those patients suffering therapy resistant urinary incontinence and/or recurrent UTI or when obstructive lower urinary tract problems are suspected.(GR B)

7. TREATMENT OF URINARY INCONTINENCE IN CHILDREN WITH SPECIAL NEEDS

7.1. Non-pharmacological treatment

7.1.1. Urotherapy

Urotherapy in children with special needs does not differ fundamentally from that used in normally developing children. The aim is also to achieve normalisation of the micturition pattern by a combination of patient education and cognitive, behavioural and physical therapy methods. Some previous studies have tried to implement parts of urotherapy [25, 31, 37], but none have administered urotherapy as instructed by the ICCS for typically developing children [53, 57].

Often the use of pharmacotherapy is seen as starting point of incontinence treatment. Decter et al. used a frequent voiding schedule and behavior modification with or without biofeedback in respectively eight and six children, whereas 47 children received pharmacotherapy [25]. A more recent study applied a combination of toilet posture, biofeedback and spasticity management of the pelvic floor when pelvic floor overactivity was present. When neurogenic detrusor overactivity was present, pharmacotherapy was initiated [37].

The first cornerstone of urotherapy is patience. Treating these children will certainly take more effort and time as compared to unaffected individuals, but even in severe patients it may lead to an significant improvement or cure of urinary incontinence. Discrepancy between effective and expected results could influence adherence to therapy, as primary focus of the child, parents and caregivers often lies with being dry. Communication is crucial to avoid frustration resulting from therapy not meeting expectations. Therapy should be interdisciplinary and feasible for the child and social environment.

The second is adequate fluid intake. Although often time-consuming, the results are remarkably positive as illustrated in the study of Van Laecke et al. [31]. Fluid intake does not only positively influence maximum voided volume and continence, but also contributes to an important amelioration of constipation.

The third cornerstone of urotherapy is correct toilet position. Adequate relaxation of the pelvic floor can only be achieved when sitting in a stable position. In many children with CP this can only be the case when using a personal adapted toilet chair.

The environment of the child can be adapted to decrease the influence of negative prognostic factors. An adapted toilet chair could be used to optimise pelvic floor relaxation, whereas an adapted drinking cup could influence fluid intake. The use of mobility aids could improve transfer to and on the toilet and ease of removing appropriate clothing could decrease time needed to reach the toilet.

Recommendation: Urotherapy with special emphasize to, patience, fluid intake and adequate toilet position is essential in the treatment of children with special needs suffering urinary incontinence (GR:B)

7.1.2. Treatment of Bowel Dysfunction

Constipation and faecal incontinence are common comorbidities in children with special needs. Adequate management of both constipation and faecal incontinence are recoommended for successful treatment of urinary incontinence in these patients. (GR:A)

Vande Velde et al. published a flowchart for a suggested experience based stepwise approach of constipation in children with CP [58]. First line treatment should include normal fibre intake and mobility stimulation. A fixed defaecation moment with toilet sitting is included as second line treatment and could be implemented in urotherapy interventions. In case of functional constipation, stool masses need to be evacuated with laxatives or enemas. Afterwards laxatives should be continued together with behavioural therapy and dietary interventions for months or even years [59].

7.1.3. Alarm treatment

As in normally developing children, alarm therapy can be used to treat either nocturnal enuresis or daytime urinary incontinence in children with special needs [57, 60, 61]. In the treatment of daytime incontinence, it can be used to achieve active continence, but in some therapy resistant cases it can also be used to achieve passive continence by introducing timed voiding [62]. Again, one should be aware of the fact that using an alarm in this population will be more challenging and time consuming.

Conclusion: daytime alarm is an effective treatment of daytime incontinence (LoE:3)

Recommendation: in therapy resistant patients the daytime alarm can be used (GR:C)

7.2. Pharmacological treatment

7.2.1. Antimuscarinics

If standard urotherapy fails to achieve urinary continence, antimuscarinics are the mainstay of treatment in patients with overactive bladder (OAB). Oxybutynin remains the only FDA approved antimuscarinic for OAB treatment in children. The major problem with oxybutynin is the side effects; dry mouth, constipation, blurred vision, psychologic and personality changes are common side effects, causing up to 10% of the children to stop their treatment [63]. Especially in children with special needs these side effects are more problematic as tooth decay, constipation, mood disturbances and intellectual delay, which are already relatively common in this population, can get even worse. Therefore, newer, more bladder specific antimuscarinics, only approved for adults, such as solifenacin and tolterodine are used off-label in these patients. Propiverine, which is suggested to be better tolerated than oxybutynin, has been approved in some countries for use in children [64]. When using antimuscarinics, strict follow-up with special attention to side effects and post void residual is necessary.

7.2.2. Desmopressin

In the case of monosymptomatic enuresis with proven nocturnal polyuria, as in normally developing children, desmopressin is a first line treatment [65]. This treatment should be used with care as excessive fluid intake shortly before or quickly after administration of desmopressin can cause a life-threatening water intoxication with hyponatraemia and convulsions.

7.2.3. Botulinum toxin

Botulinum toxin has been used off-label successfully for the treatment of children with neuropathic bladder and non-neurogenic bladder dysfunction [57, 66-68].(LoE 3) In accordance with treatment in normally developing children, in children with special needs it can only be considered in patients suffering OAB or urinary incontinence in whom other treatment options have failed.(GR:C)

7.3. Surgery

Children with Down's syndrome have a significantly increased risk of anterior urethral obstruction and posterior urethral valves [69]. In Down's syndrome children, where there is suspicion of obstruction of the LUT, cystoscopy under general anaesthesia with possible incision of the obstructive element should be performed. In those patients with a neuropathic bladder, refractory to conventional therapy, bladder augmentation, i.e. ileocystoplasty with or without continent catheterisable stoma (Appendico-vesicostomy, Monti, etc.) can offer the final, non-reversible, solution to achieve continence and to protect the upper urinary tract.

7.4. Clean intermittent catheterisation (CIC)

Some children do need intermittent catheterisation, especially those undergoing a bladder augmentation. Children with cerebral palsy treated with continuous baclofen can also suffer urinary retention needing intermittent catheterisation. The problem with some of these children with special needs is that they have normal genital sensation that makes catheterisation uncomfortable, or even painful. Combined with the reduced intellectual capacities of some this makes CIC nearly impossible. Therefore, an incontinence stoma is sometimes the only solution.

8. CONCLUSION

Although often thought to be a minor problem urinary incontinence remains an important issue for every special needs child. Urinary incontinence can lead to limited self-esteem and independence, and may be a considerable health care challenge. Often it is a multifactorial problem, but with adequate therapy these children are amenable to continence rehabilitation. The majority can become continent, but some will only achieve a passive form of continence.

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COMMITTEE 8

ADULT CONSERVATIVE MANAGEMENT

Chair
Dumoulin, Chantale (Canada)

Members
Booth, Jo (United Kingdom)
Cacciari, Licia (Canada)
Campbell, Pauline (United Kingdom)
Hagen, Suzanne (United Kingdom)
Homsi Jorge, Cristine (Brazil)
Morin, Mélanie (Canada)
Morkved, Siv (Norway)
Nahon, Irmina (Australia)
Pang, Ran (China)
Panicker, Jalesh (United Kingdom)
Vesentini, Giovana (Canada)
Wallace, Sheila (United Kingdom)
Yamanishi, Tomonori (Japan)

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I. INTRODUCTION

Conservative management of urinary incontinence (UI) or pelvic organ prolapse (POP) is defined as any intervention not involving surgical or pharmacological approaches (1). These comprise lifestyle modification, pelvic floor muscle training (PFMT) either alone or with the addition of biofeedback, vaginal cones, electrical stimulation (EStim), magnetic stimulation (MStim), together with tibial nerve stimulation (TNS), scheduled voiding regimens, complementary/alternative medicine and supportive rings/pessaries. In this chapter, we cover studies that provide comparative data between a conservative management approach and the absence of treatment or placebo, between two conservative management approaches or between a conservative management approach and medications or surgery.

Conservative management is considered relatively low cost and non-invasive, with minimal adverse effects. Management is typically guided by a healthcare professional and depends on user participation. Conservative interventions are part of initial management at the primary care level and are also indicated for those for whom other treatments are inappropriate, for example, those unable to undergo surgery and women who plan future pregnancies. Other indications include individuals awaiting surgery or who wish to delay surgery and those whose symptoms are not severe enough for surgical intervention.

Scientific evidence on the effectiveness of conservative interventions is growing. In this chapter, we add to the sixth edition of the International Consultation on Incontinence (ICI) chapter on conservative management, which was published in 2017 (2), integrate new evidence and update the recommendations from the previous edition. We also add a new section on conservative management of UI in patients with neurological conditions.

- The updated literature search covered the period of September 9th, 2015 to December 31st, 2020 inclusively (i.e., from the date of the last search for the sixth ICI to the seventh ICI search cut-off date of December 31st, 2020), according to the following search methods. The searches were conducted between March 1st and 9th, 2021 inclusively. We did not impose any language or other limitations on any of the searches described below.

- **Cochrane Incontinence systematic reviews**

Relevant Cochrane systematic reviews were identified for each section of this chapter, by two of the authors (CD, SW) assessing the full list of reviews (Cochrane Incontinence (3) or upon request). The leads for each section were given lists of these relevant reviews. Additional searches of the Cochrane Incontinence Specialised Register were provided to each section author to bring the review searches up to date or, if there was a gap in review coverage, a full search of the Register was conducted.

- **Additional searches for this ICI chapter**

Electronic searches

We identified relevant trials from the Cochrane Incontinence Specialised Register. For more details on the search methods used to build the Register please see the Group's webpages where details on the Register›s development can be found (4). In brief, the Register contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print, MEDLINE Daily, ClinicalTrials.gov, WHO ICTRP, and includes hand searching of journals and conference proceedings. The search covered:

- For sections covered by existing Cochrane reviews: from the date of the last search for the published version of the review to December 31st, 2020.
- For sections not covered by existing Cochrane reviews – complete search of all contents of the Register covering from the date of last search for the sixth ICI, September 9th, 2015 to the seventh ICI search cut-off date of December 31st, 2020.

The terms used to search the Register for each section are provided in Appendix 1.

Searching other sources

We searched the reference lists of relevant articles for other relevant trials.

In continuity with the last edition of the ICI chapter on conservative management and to ensure consistency throughout the chapter, the primary outcomes reported in this chapter include *patient-reported outcomes*: cure and cure and improvement, UI-specific or POP-specific quality of life (QoL), validated symptoms questionnaire and/or number of leakages (as per the bladder diary). Secondary outcomes considered in this chapter are *clinician-reported outcomes* (pad test, POPQ score, etc.). These were chosen in relation to each subsection's specificity and in continuity with our previous chapter.

Each subsection concludes with the level of evidence, grade of recommendations and factors affecting outcome. Separate chapters in this seventh edition address incontinence management in the frail older persons (Chapter 14), in childhood (Chapter 7), address continence products (Chapter 19) and present conservative management of faecal incontinence (Chapter 15).

Where summary statistics are presented, the raw data from which these are derived can be found in the tables within each subsection, and in trial reports and systematic reviews cited in the chapter. The chapter is intended as a stand-alone document and adds to the comprehensive reports from previous ICI editions.

II. URINARY INCONTINENCE IN WOMEN

1. LIFESTYLE MODIFICATION

A number of lifestyle factors may play a role in the development of UI and other lower urinary tract symptoms (LUTS). Lifestyle modification is the application of interventions in the management of lifestyle-related health problems (1). It is not limited to but includes weight loss, changes in physical activity level, smoking cessation, diet restriction such as caffeine reduction and other changes in life habits. These lifestyle modification interventions may be used to prevent or treat UI in women either combined or as single interventions.

Although lifestyle modification is relatively low cost and low risk, the sixth ICI (2017) cited a lack of evidence on lifestyle interventions to prevent UI. There were also no evidence-based recommendations on lifestyle modification interventions in the prevention of UI. Only a few cohort and case control studies provided low level evidence on the association between physical activity/dietary restriction and UI and suggested that moderate physical exercise and changes in diet decreased the incidence of UI. The sixth ICI noted that a weight loss of 5% of initial body weight was considered to have an impact on the reduction of UI symptoms. This formed the basis of a recommendation for overweight and obese women with UI, based on two randomised controlled trials (RCTs), cohort studies and a metanalysis of cohort studies (2).

This review section updates the evidence on the use of lifestyle modification to improve UI and related symptoms in women. Table 1 shows the number of studies included in the sixth ICI edition and the new studies included in this update (N= 5 trials: 6 comparisons). The characteristics and new data of the individual new trials can be found in Tables 2, 3, 4 and 5 for each lifestyle modification intervention.

We addressed the following questions in this update:

- Are lifestyle modification interventions (e.g., weight loss, increased/decreased physical activity, smoking cessation, dietary or fluid changes) effective in the prevention of UI?
- Are lifestyle modification interventions (e.g., weight loss, increased/decreased physical activity, smoking cessation, dietary or fluid changes) better than no treatment, placebo or control in the treatment of UI?
- Is one lifestyle modification intervention (e.g., weight loss, increased/decreased physical activity, smoking cessation, dietary or fluid changes) better than another lifestyle intervention in the treatment of UI?

Table 1. Lifestyle modification interventions studies included

Lifestyle modification interventions	ICI 2013 and 2016	ICI 2023	Total
Weight loss	5 RCTs, 6 cohort studies, 7 cross-sectional studies,1 retrospective study, 1 meta-analysis	1 meta-analysis, 1 RCT (secondary analysis)	6 RCTs, 1 (one group) non-randomised clinical trial, 8 observational studies, 2 meta-analysis
Physical activity	5 cohort studies 1 case control study	1 RCT, 1 cohort study	2 RCTs, 6 cohort studies, 1 case control study
Smoking	2 case control studies, 1 RCT (pilot, secondary analysis)	-	2 case control studies, 1 RCT (pilot, secondary analysis)
Dietary factors/fluid intake	1 case control study, 1 prospective cohort study, 1 cross-sectional cohort study, 3 observational studies	2 RCTs (1 secondary analysis, 1 pilot study)	2 RCTs (1 secondary analysis, 1 pilot study), 1 case control study, 1 prospective cohort study, 1 cross sectional cohort study, 3 observational studies

Abbreviations: RCT: randomised controlled trial

1.1. Prevention

Are lifestyle modification interventions effective in the prevention of UI?

In this update, one secondary analysis of the Women's Health Initiative (WHI) Dietary Modification Intervention (DM-I), a RCT investigating a lifestyle intervention for prevention of female UI (5) and a prospective study on the association between physical activity and LUTS in parous middle-aged women (6) were included.

1.1.1. Dietary modification intervention

The study conducted by Rogo-Gupta *et al.* (5) aimed to evaluate the effect of a low-fat and high fruit, vegetable and whole grain diet on the risk of developing de novo UI in continent postmenopausal women (Table 2). Participants were randomly assigned to receive the intervention (DM-I) including an intensive behaviour modification programme for a reduction in fat intake and an increase in fruit, vegetable, and whole grain intake. Controls received only health education materials. Despite being a secondary analysis, the strong point of this study is the large sample of 22,852 women randomised to the control arm and 19,541 to the DM-I group. Separate logistic regression models showed that one year after the intervention, continent participants in the DM-I group were less likely to develop UI (all types) compared to controls when adjusting for weight change, age, ethnicity, or hormone replacement use. Interestingly, the study found that a moderately high intake of grain (3-4.3 and 4.3-5.9 grams/day) was an effective modifier for overall UI (OR 0.86, 95% CI 0.76-0.98 and OR 0.78, 95% 0.68-0.89 respectively) and was associated with a lower risk of stress urinary incontinence (SUI) (OR 0.78, 95% CI 0.65-0.92 and OR 0.76, 95% CI 0.64-0.91 respectively). Furthermore, a diet of 1663.6-1909.48 kcal/day was associated with a lower chance of *de novo* SUI (p=0.03). However, there was no statistical difference in *de novo* urgency urinary incontinence (UUI) for the DM-I group compared to controls. Surprisingly a moderately high amount of fat decreased the chance of developing UUI, but the exact mechanism underlying this result is unclear and needs further investigation.

Regarding risk of bias (ROB), information about the main methods of the RCT was extracted from the original RCT. Randomisation was done using a permuted block algorithm. However, there was no information on allocation concealment. The nature of the intervention would not allow participants to be blinded to the intervention and outcome measures were self-reported by the participants. Intention to treat (ITT) analysis was not reported and loss to follow-up was considered to have low ROB. Despite the overall moderate ROB, the substantial number of participants included in this study provided some evidence that advising women to increase their intake of whole grains and adopting a moderate calorie diet may reduce the risk of developing UI, especially SUI.

1.1.2. Physical activity

A study prospectively analysing collected data on parous middle-aged women participating in a longitudinal study of parents and children (6) examined the associations between physical activity and a range of lower urinary tract symptoms (LUTS). At the three-year and 11.5-year follow-ups respectively, 4126 and 2770 women reported if they had symptoms of SUI, UUI or mixed UI. After three years, women in the highest category of physical activity (≥43.2 MET hours/week) were less likely to have UI (adjusted OR (aOR)=0.51; 95% CI 0.32, 0.80) compared to women in the lowest category (0 MET hours/week). After 11.5 years of follow-up, women in the highest category of physical activity were still less likely to have SUI (aOR= 0.56; 95%CI: 0.39, 0.82), UUI (aOR= 0.34; 95%CI: 0.20, 0.67) and mixed UI (aOR= 0.34; 95%CI: 0.19, 0.63) compared to women in the lowest physical activity category.

Summary

A secondary analysis of a large RCT with moderate ROB showed that a dietary intervention with high fruit, vegetable and whole grain content as well as a moderate caloric intake reduces the risk of developing *de novo* UI (all types) symptoms, especially SUI, in continent postmenopausal women. **(Level of evidence: 2)**

A large prospective longitudinal study showed that higher level of physical activity was associated with a reduced prevalence of UI, especially SUI in the medium and long term in continent parous women. **(Level of evidence: 3)**

Recommendations

A dietary intervention with high fruit, vegetable and whole grain content as well as a moderate caloric intake can be recommended to postmenopausal women to prevent UI. **(Grade of recommendation: B New)**

Higher levels of physical activity (≥43.2 MET hours/week) could be recommended to continent parous middle-aged women to prevent UI. **(Grade of recommendation: C New)**

Further high quality RCTs are required to confirm the effect of a dietary intervention with high fruit, vegetable, and whole grain content as well as a moderate caloric intake and physical activity in the prevention of incontinence in women. Finally, high quality cost-effectiveness RCTs are needed to determine the possible benefits of implementing any lifestyle intervention strategies to prevent UI, especially in higher-risk groups, such as postmenopausal, overweigh and obese women.

Table 2. Summary data on prevention

Author, Year	Comparator	N	Study population	Age	Outcomes/Results	Follow up	Notes (side effects, loss to follow-up, risk of bias)
Rogo-Gupta (2017) (5)	Dietary modification versus health education materials	N = 22852 control group and N =19541 intervention group	Postmenopausal women	No information	Participants were grouped into NUI vs. SUI if they reported UI during activity. In a separate analysis, participants were grouped into NUI and urge UUI if they reported UI with urgency. At year 1 and when adjusted, continent participants who underwent dietary modification were less likely to develop UI overall (OR 0.94, 95% CI 0.99-1, p=0.04) or SUI (OR 0.9, 95% CI 0.83-0.98, p=0.014).	12 months	RCT No side effects or loss of follow-up reported
Alhababi (2019) (6)	Highest category of physical activity (43.2 MET hours or more per week) compared to the lowest category (0 MET hours per week).	4126	Women	37.2 ± 4.6 years	Self-reported symptoms of lower urinary tract symptoms. 3-year follow up: women in the highest category of physical activity (43.2 MET hours or more per week) had lower odds of stress incontinence (aOR 0.51, 95% CI 0.32-0.80) than women in the lowest category (0 MET hours per week). After 11.5 years, women in the highest category of physical activity had lower odds of stress incontinence (aOR 0.56, 95% CI 0.39-0.82), urgency incontinence (aOR 0.34, 95% CI 0.20-0.67) and mixed incontinence (aOR 0.34, 95% CI 0.19-0.63) compared to women in the lowest physical activity category.	3 and 11.5 years	Prospective

Abbreviations: NUI: no urinary incontinence; SUI: stress urinary incontinence; UUI: urge urinary incontinence; RCT: randomised clinical trial; MET: metabolic equivalence of task

1.2. Treatment

In relation to lifestyle interventions to treat UI in women, this update includes one new meta-analysis (7) and one RCT (secondary analysis) related to weight loss and physical activity (8). It also includes one RCT (9) about physical activities and one survey about smoking (10). Finally, it includes two RCTs about dietary factors/fluid intake (11, 12).

1.2.1. Weight loss and physical activity

The characteristics of the studies are presented in Table 3. One new systematic review was conducted by the American Urogynecologic Society Systematic Review Group and assessed the impact of both surgical and behavioural weight loss interventions on UI symptoms in overweight and obese women (7). It included a total of 43 publications, mostly (76.7%) observational studies (related to surgical intervention) and 10 reports that used data from 5 RCTs (related to behavioural weight loss (BWL). Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) the authors concluded, that there is high-certainty evidence that BWL, such as diet and exercise, decreases the prevalence of SUI by 15% to 18% and all type of UI by 12% to 17% after 1 to 2.9 years in overweight women. However, the certainty of evidence on the long-term effects (1 to 2.9 years post-intervention) of these interventions was lower and evidence about weight loss on urgency UI was graded as moderate. The RCTs included in this systematic review were all included in the previous editions of this chapter. New data published in 2018 has now been added (8). Secondary analysis of the "Programme to Reduce Incontinence by Diet and Exercise (PRIDE)" study assessed whether the BWL programme (including diet, exercise, and behaviour modification) would improve non-UI LUTS including urinary frequency, nocturia, urgency, at six months compared to a structured education programme (control group) among overweight and obese women with UI. At the six months follow-up, the overall cohort, regardless of group assignment, reported a significant improvement in multiple non-UI LUTS domains. However, LUTS outcomes did not differ between the intervention and control groups and no differences were observed based on either the amount of weight lost (≥ 5% compared to <5%) or physical activity (≥1500 kilocalorie expenditure/week compared to < 1500 kilocalories) (8).

An important limitation of this study is that not all participants in the original RCT had non-UI LUTS. This reduced power and limited the ability to detect changes in LUTS in women without UI. In addition, the multiple comparisons may have increased the risk of type 1 error and the loss to follow-up was 19% in the control group. In contrast, the original RCT found that 96% of the participants provided UI outcome data at the 6- and 18-month follow-ups (13, 14).

Summary

The addition of one systematic review to previous data continues to support BWL in the reduction of UI in women who are overweight or obese. **(Level of evidence: 1)**

BWL does not appear to be better than a structured education programme to improve non-UI LUTS, including urinary frequency, nocturia and urgency at six months among overweight and obese women with UI. **(Level of evidence: 2)**

Recommendations

BWL should be recommended to obese and overweight women with UI. **(Grade of recommendation: A)**

Table 3. Summary data on weight loss

Author, Year	Comparator	N	Study population	Age	Outcomes/Results	Follow up	Notes (side effects, loss of follow up, risk of bias)
Yazdany (2020) (7)	BWL intervention (diet modification, exercise programs, medications, and/or counselling)	-	Overweight and obese women	> 18 years	There is high-quality evidence that BWL results in modest improvements in stress and overall UI in overweight and obese women 1 to 2.9 years after the intervention	-	Systematic review No studies investigating conservative interventions reported any side effects.
Breyer (2018) (8)	BWL intervention (group sessions focused on nutrition, exercise and behaviour change)	338 intervention (N=226) or control (N=112)	Overweight or obese women with UI	Mean age: 53 years	For both groups combined, women experienced significant improvement in nocturia and urgency UI (all P < 0.001). However, lower urinary tract symptoms outcomes at 6 months did not differ between the intervention and control group. Similarly, no differences were observed based on either the amount of weight lost (>5% compared (<5%) or physical activity (> 1500 kilocalorie expenditure/week compared to < 1500 kilocalories).	6 months	Secondary analysis of RCT Losses to follow up: Intervention group: 12 (5%) Control group: 22 (19%) Adverse effects not reported

Abbreviations: BWL: behavioural weight loss; UI: urinary incontinence; RCT: randomised controlled trial

1.2.2. Physical activity

Very few data have been published on either the benefit of moderate physical activity or the adverse effect of strenuous activity on UI in women.

In this update we included one new RCT (9). Summary data are presented in Table 4.

One RCT (9) investigated the effect of a three-month physical activity programme for the reduction of abdominal fat (PRAF) in young overweight women with overactive bladder (OAB) compared to a control group (no exercise programme). The intervention comprised an aerobic training programme, in addition to abdominal muscle strengthening and general stretching exercises but excluded PFM exercises. OAB symptoms were assessed using a voiding diary and questionnaires (OAB-q and PPIUS scales). The study found significant differences in favour of the group of women who exercised [voiding per 24 h: treatment versus control group, baseline 9.1 ± 0.3 versus 8.6 ± 0.3, final 6.9 ± 0.2 versus 8.1 ± 0.2, $p < 0.0001$; mean voided volume per 24 h (ml): treatment versus control group, baseline 154.2 ± 9.1 versus 162.2 ± 9.3, final 201.3 ± 9.3 versus 164.1 ± 9.6, $p < 0.0001$]. A possible confounding factor in this study was the reduction in body mass index (BMI), which could have affected OAB symptoms, including UI. The study had an overall moderate ROB with no blinding of the participants and a high loss to follow-up in both groups, which could have further biased results.

Summary

Previous non-RCT evidence suggests that moderate exercise decreases the incidence of UI. **(Level of evidence: 3)**

One new RCT with moderate to high ROB suggests that a three-month physical activity programme for the reduction of abdominal fat is better than no exercise to reduce LUTS in overweight women with UUI. **(Level of evidence: 2)**

Recommendations

A physical activity programme for the reduction of abdominal fat could be recommended to young overweight women with UUI to reduce LUTS. Further high-quality RCTs are needed to confirm these results. (**Grade of recommendation: C New)**

Table 4. Summary data on physical activity

Author, Year	Comparator	N	Study population	Age	Outcomes/Results	Follow up	Notes (side effects, loss of follow up, risk of bias)
Hagovska (2020) (9)	Control: no exercise program TX: exercise program	70 (36- intervention, 34 – CG)	Overweight women with OAB symptoms	Average age of 26.2 years	The program for reducing abdominal fat significantly reduced the weight of the participants as well as mild symptoms of OAB after 12 weeks.	12 weeks	RCT Side effects were not addressed

Abbreviations: OAB: overactive bladder; RCT: randomised controlled trial

1.2.3. Smoking

The sixth ICI edition reports on data from a pilot RCT investigating the impact of smoking abstinence on overactive bladder (OAB) symptoms. The results showed that participants who were abstinent from smoking at the 12-week follow-up were more likely to reduce their urinary frequency (p=0.042) and ICIQ-OAB score (for more details consult the sixth ICI edition).

No new trial investigating the impact of smoking cessation on UI was found. Although cigarette smoking has been associated with UI in women, the exact mechanism underlying this association is still unknown. It is possible that smoking-induced atherosclerosis can be a pathway influencing the development of LUTS. A recent study screened a total of 10,000 women registered by a web-based internet survey company in Japan to determine the correlation between smoking habits and LUTS (10). The results showed that smoking habit was a risk factor for LUTS in women, increasing daytime frequency, nocturia, urgency and UUI, especially in the younger women (aged <40 years). Urgency and UUI prevalence decreased in correlation with the duration of smoking cessation among young female ex-smokers, but no correlation was found between smoking and the prevalence of urgency and UUI. Limitations of this survey included the study design and the use of a web-based self-administrated questionnaire. The authors reported that the study failed to obtain the satisfactory number of participants calculated by population-based numbers, especially for participants aged 70 and over. The association between cigarette smoking habits and UI suggests that cessation of smoking might decrease the prevalence of UI, especially UUI, however this is low-quality indirect evidence.

Summary

A large new survey showed that the prevalence of UUI decreased in correlation with the duration of smoking cessation among young female ex-smokers. These new data suggesting smoking cessation is related to UI and LUTS prevalence or severity adds to previous findings. (**Level of evidence: 3**)

Recommendations

Although no UI – LUTS recommendation can be made, smoking cessation may be offered to current smokers at initial encounter for the general health benefits. (**Grade of recommendation: D)**

Further high-quality RCTs are needed to confirm the impact of smoking cessation on UI.

1.2.4. Dietary modification

Factors such as diet; and caffeine intake might influence UI. In 2020, a scoping review on caffeine consumption and LUTS was published (15). This review identified 14 interventional studies, with eight RCTs and six cohort studies, all published before 2016. Therefore, no new RCTs about caffeine and fluid intake were included in this update. The scoping review's conclusion points out to a decrease in urgency episodes and in nocturnal enuresis episodes with caffeine reduction (15).

In relation to diet, a secondary analysis of one RCT (11) and one new RCT (12) were included in this update. The dietary interventions investigated were a low-fat and high fruit, vegetable and whole grain diet (11) and supplementation of vitamin D (12). Summarised data are presented in Table 5.

Part of this secondary analysis of the WHI Dietary Modification (DM), (11) is covered in the lifestyle intervention prevention section (section II.1.1.1). In a short abstract, the author studied the impact of dietary intervention (DM-I) on UI symptoms, in postmenopausal women with UI, a subgroup of the main trial. The participants were assigned to receive a dietary intervention (DM-I) including an intensive behaviour modification programme for a reduction in fat intake and an increase in consumption of fruit, vegetable and whole grains. Controls (DM-C) received only health education materials. Participants (48,835) were randomised to DM-C (29,294 (60%)) and to DM-I (19,541 (40%)). Participants who reported urinary leakage were considered to have UI and categorized as SUI if they reported UI during activity and UUI if they reported UI with urgency. The groups were homogeneous at baseline in relation to demographic characteristics. When adjusting for weight change, women in the DM-I group were less likely to report overall UI (OR 0.94, 95% CI 0.9-0.98, p=0.002) or SUI (OR 0.89, 95% CI 0.86-0.93, p< 0.001) one year after the intervention compared to controls but were more likely to report UUI (OR 1.06, 95% CI 1.01- 1.1, p=0.02).

The pilot RCT (12) investigated the efficacy of vitamin D supplementation on the reduction of UUI episodes in community dwelling postmenopausal women. The intervention consisted of 12 weeks of a weekly oral dose of 50,000 IU vitamin D3 or placebo. UUI episodes per 24-hour period decreased by 43.0% with vitamin D3 compared to 27.6% with placebo (P = .22). In obese women, UUI episodes decreased by 54.1% compared to 32.7% with placebo (P = .29). Black women obtained the largest effect of vitamin D supplementation with a 63.2% decrease in UUI episodes compared to 22.9% with placebo (P = .03). Randomisation was performed using a computer 1:1 allocation ratio, although the allocation concealment was not clearly described. Participants and the assessor were blinded to treatment or placebo. The adherence to therapy was high in both arms and the study is one of the few in this chapter to have instigated and reported adverse effects (Table 5). There was no incomplete outcome data and selective reporting, but the study lacked sufficient power to detect differences between groups.

Summary and recommendations

One secondary analysis of an RCT provides evidence that a low-fat and high-fruit, vegetable and whole grain diet have a small effect in decreasing UI symptoms independently of weight change, age, ethnicity, and hormone replacement use and therefore could be recommended. **(Level of evidence: 2; (Grade of recommendation: C)**

Vitamin D supplementation can be recommended to decrease UUI episodes in post-menopausal black women. **(Level of evidence: 2; Grade of recommendation: B)**

The levels of evidence related to other interventions such as fluid intake and reduction of daily caffeine consumption remained the same as no new RCT was added to this update. **(Level of evidence: 2)** Adequate fluid intake and reduction of caffeine consumption can be recommended for people with UI and LUTS symptoms. (**Grade of recommendation: B)**

Further large high-quality RCTs are needed to assess the impact of dietary interventions on the different types of UI in women.

Table 5. Summary data on dietary modification

Author, Year	Comparator	N	Study population	Age	Outcomes/Results	Follow up	Notes (side effects, loss of follow up, risk of bias)
Rogo-Gupta (2017) (11)	Dietary modification versus health education materials only	22.852 control and 19.541 intervention	Postmenopausal women	No information	Patients who reported urinary leakage were considered to have UI. They were categorized as having SUI if they reported UI during activity, and UUI if they reported UI with urgency. Women who received the dietary intervention were more likely to become continent in the 1-year follow-up (OR 1.08, 95% CI 1.01-1.16, p=0.03). They also had no SUI (OR 1.12, 95% CI 1.06-1.18, p<0.001) when adjusted for weight change, age, ethnicity and hormone replacement use. However, I participants receiving the dietary modification intervention were less likely to cure UUI (OR 0.93, 95% CI 0.88-0.98, p=0.01).	12 months	secondary analysis Side effects were not addressed Loss of follow up: not reported
Markland (2019) (12)	Vitamin D versus placebo	28for the intervention group and 28 for the placebo	Community-dwelling postmenopausal women	50 +	Primary efficacy estimate was the percentage change in UUI episodes. Secondary estimates included changes in other lower urinary tract symptoms. UUI episodes per 24 hours day decreased 52.4% with Vitamin D compared to 30.9% with placebo (p=0.09).	12 weeks	RCT Side effects: Palpitations (n=1), transient asymptomatic hypercalcemia (n=2) and Gastrointestinal symptoms (n= not reported) Loss of follow-up: 14%

Abbreviations: UI: urinary incontinence; SUI: stress urinary incontinence; UUI urge urinary incontinence.

1.2.5. Constipation

No new trials on constipation were found. Therefore, the evidence remains the same (small observational studies) suggesting that chronic straining may be a risk factor for the development of UI **(Level of evidence: 3).**

Recommendations

Further research is needed to confirm the role of abdominal straining in the pathogenesis of UI.

2. PELVIC FLOOR MUSCLE TRAINING

Pelvic floor muscle training (PFMT) is defined as exercise to improve pelvic floor muscle (PFM) strength, endurance, power, relaxation, or a combination of these (1). PFMT remains a key factor in the treatment of UI. Because PFM integrity appears to play an important role in the continence mechanism (see Chapter 3: Pathophysiology of urinary incontinence, faecal incontinence and pelvic organ prolapse), there is a biological rationale to support the use of PFMT in preventing and treating SUI in women (16-18). The role of PFMT in the treatment of UUI was determined afterwards (19, 20). More details about the biological rationale regarding the effect of PFMT on SUI and UUI can be found in the 2013 ICI edition of this chapter (21).

PFMT is an intervention that involves understanding PFM activation and repeating a PFM exercise programme over time. Because the effectiveness of PFMT depends on the participant's adherence during the intervention and follow-up (in the maintenance phase), a better understanding of adherence mechanisms and how they can be promoted is of major importance. The 2011 International Continence Society State of the Science Seminar on Adherence produced four papers and a Consensus Statement in 2015, reviewing present literature. They also made recommendations for increasing PFMT adherence that could be useful in both clinical and research settings (22-26).

This section presents evidence for the use of PFMT in the prevention and treatment of UI in women. The questions addressed are:
- Is PFMT effective in the prevention of UI?
- Is PFMT better than no treatment, placebo, or control treatments in the treatment of UI?
- Is one type of PFMT programme better than another in the treatment of UI?
- Is PFMT better than other treatments in the treatment of UI?
- Does the addition of PFMT to other treatments add any benefit in the treatment of UI?
- What factors might affect the outcome of PFMT in the treatment of UI?
- What is the effect of PFMT on other LUTS?

2.1. Prevention and treatment (pregnant and postpartum women only)

This subsection considers PFMT for the prevention and treatment of UI in pregnant and postpartum women (also called childbearing women). As the physiological changes of childbearing can affect PFM function, the effect of PFMT might differ in this group compared to non-childbearing women. Therefore, this group is treated separately. An updated Cochrane review was published in 2020 (27). Since our last ICI chapter (2017), eight new RCTs focusing on the prevention and/or treatment of UI were identified and reviewed for this subsection (28-35), as well as one follow-up study (36) of a previously reported trial (37) (Table 6). Trials in this section were previously grouped into three areas: 1) PFMT for the prevention of UI (performed in women without UI symptoms when randomised); 2) PFMT trials for the treatment of UI; and 3) PFMT trials for the prevention and treatment of UI (participants with and without UI symptoms enrolled). Trials were further separated into those beginning during pregnancy (prepartum) or after pregnancy (postpartum). The primary outcome of interest was self-reported UI (cure, improvement, number of leakage episodes). Other outcomes of interest included adherence measures.

2.1.1. Is PFMT effective in the prevention of UI in childbearing women?

This section addresses the question of PFMT effectiveness for primary and secondary prevention of UI in childbearing women. Clinically, it can be difficult to screen trial participants effectively to ensure that a disease is altogether absent (for primary prevention studies), present although asymptomatic (for secondary prevention). Trials investigating the prevention of UI usually enrol people purely based on the absence of symptoms. Thus, trials represent a combination of primary and secondary prevention effects.

Since the last ICI chapter, one (29) new prevention trial was found (Table 6) adding to the nine trials presented in the previous edition. The study by Sangsawang (29) included 70 continent primiparous women at 20-30 weeks' gestation. All women received antenatal education about PFM function and strengthening and how to perform PFM exercises. The supervised group PFMT programme began during pregnancy. The control group received usual antenatal care from health professionals, obstetricians, or midwives (who were not involved in the study). They received information on diet, sleep, breast feeding and antenatal exercise (which may have included advice on PFMT), from their maternity caregivers. They did not receive information about stress UI during pregnancy and performance of correct PFMT was not assessed.

Quality of data

This was a two-arm RCT. Allocation concealment and randomisation were adequate. However, the outcome assessors were not blinded. The total dropout rate was 10%: 2/35 in the intervention and 5/35 in the control group. Outcomes were measured at baseline (20-30 weeks' gestation) and the primary endpoint was 38 weeks' gestation. The trial did not report ITT analysis and adverse events.

Results

The primary outcome was self-reported UI (defined as involuntary leakage of urine during sneezing, coughing, effort or physical exertion, ≥ once per week). Significantly fewer women in the PFMT group reported SUI compared to the control group (OR 3.05, 95% CI 1.07–8.70, $P = 0.018$), and a significantly smaller amount of leakage was reported in the PFMT group (P=0.03). The authors concluded that PFMT was effective in preventing SUI in late pregnancy.

Summary

One new study was found assessing the preventive effect of PFMT. Together with previous trials, this RCT supports the effectiveness of PFMT during pregnancy to prevent SUI in late pregnancy and up to mid post-partum period. (**Level of evidence: 1)**

Recommendations

Continent, pregnant women should be offered a supervised PFMT programme (including regular health professional contact) that is intensive and aimed at strengthening PFMs to prevent antepartum and postpartum UI (up to 6 months) UI. **(Grade of recommendation: A)**

Additional trials with long-term follow-up (more than 12 months postpartum) are needed to determine long- term benefits of antenatal PFMT. Furthermore, the only study including multiparous women is a quasi-randomised trial (38). Thus, large, good-quality RCTs are needed to investigate the effects of antepartum PFMT on preventing postpartum UI in multiparous women.

2.1.2. Is PFMT effective in the treatment of UI in childbearing women?

Since the sixth ICI one new trial assessing the effects of pre- or postpartum PFMT in the treatment of UI was found (Table 6), adding to the previously reported trials.

Sigurdardottir (2020) (32) recruited 84 primiparous women with UI six to 10 weeks after delivery, who were randomised to a PFMT group (supervised by a physical therapist) and a control group (no instructions). The intervention started at ~9 weeks postpartum and consisted of 12 weekly individual sessions of PFM strength training with a physiotherapist. Adherence to the PFMT protocol was reported using exercise diaries.

Quality of data

This was a two-arm RCT. Allocation concealment and randomisation were adequate. The outcome assessors were not blinded. The total dropout rate was 16%: 8/41 in the intervention and 5/43 in the control group. Analyses were per protocol.

Results

The primary outcome was rate of UI, and the primary endpoint was six-months postpartum. A statistically significant difference in UI in favour of the intervention group was found six months after delivery (RR 0.7 (95% CI 0.51-0.96) p=0.03), but not at 12 months. However, adherence to exercise at this time point was low. No adverse effects were reported.

Summary

Data from previous trials and this new trial showed a significantly superior treatment effect of supervised PFMT on UI compared to the control group. The addition of the new trial does not change the level of evidence. **(Level of evidence: 1).**

Recommendations

PFMT should be offered as first line conservative therapy to women with persistent UI symptoms, two to three months after delivery. **(Grade of recommendation: A).**

An 'intensive' PFM strength training programme (in terms of supervision and exercise content) can be recommended as it increases the treatment effect. **(Grade of recommendation: B).**

Research recommendations

There is a need for one large, pragmatic, well-conducted and explicitly reported trial with long-term follow-up (more than five years) that investigates the effect of an 'intensive' PFM strength training programme.

2.1.3. Is PFMT effective in the mixed prevention and treatment of UI in childbearing women?

Since the last ICI, six new mixed prevention and treatment trials which assessed the effect of PFMT on symptoms of UI (28, 30, 31, 33-35) and on quality of life (QoL) (31, 34) were found, adding to the 16 previously reported trials. One follow-up study was also published (36).

Four trials included pregnant women (28, 31, 33, 35) and two included postpartum women (30, 34).

The PFMT interventions, intervention periods, outcome measures related to UI and primary endpoints varied (Table 6):

Antepartum PFMT versus usual care or no PFMT

Szumilewicz (2019) (31) compared a general group exercise programme in pregnant women that included PFMT to one without PFMT. The main outcome measure was change in neuromuscular activity in the PFMT. The original intervention, in the follow up study by Johannessen (2020) (36), compared a similar intervention to standard care and reported on UI three months after delivery.

Combined ante- and postpartum PFMT versus usual care or no PFMT

Three trials assessed the effect of instructions and home PFMT during both pregnancy and after delivery (28, 33, 35). Sut (2016) (28) and Sacomori (2019) (33) compared PFMT instructions with no instructions, while Hyakutake (2018) (35) compared PFMT instructions and pelvic floor health with usual care (most likely including information about PFMT). The primary endpoint was at the early postpartum period (28, 33, 35), while Sut (2016) (28) also reported outcomes in late pregnancy.

Postpartum PFMT versus usual care or no PFMT

Yang (2017) (30) compared three groups: two groups received a home PFMT programme with and without additional EStim and the control group had no PFMT instructions. UI was reported at three months postpartum. Lin (2020) (34) compared a control group receiving routine postpartum rehabilitation nursing (unclear if this included PFMT), and an intervention group receiving one-to-one nursing intervention with postpartum PFMT. The intervention took place over six months and the primary endpoint was after the six-months intervention (34).

Quality of data

Antepartum PFMT

Szumilewicz (2019) (31) published a RCT with adequate random sequence generation, but no information on allocation concealment and thus had unclear risk of selection bias. There was no blinding of participants or personnel (participant bias) or assessors (detection bias), and outcome data were incomplete (attrition bias). The method of collecting patient-reported UI symptom data was not blinded. Loss to follow-up was 38% in the intervention and 51% in the control group, and was related to medical issues and other reasons. The quality of the follow-up trial by Johannessen (2020) (36) has been presented in a previous edition of this chapter by Stafne (2012) (37).

Combined ante- and postpartum PFMT

Sut (2016) (28) and Hyakutake's (2018) (35) RCTs were two-armed while the Sacomori study (2019) (33) was a cluster RCT. Sut (2016) (28) randomised 64 parous pregnant women in their third trimester to a home PFMT programme during pregnancy and postpartum, while the control group received no PFMT instruction. Hyakutake (2018) (35) included 100 nulliparous women, who were randomised to two groups. The PFMT group attended a single pelvic floor health workshop. The control group received routine prepartum care with their existing maternity care provider, which most likely included advice on PFMT.

Sacomori (2019) (33) conducted a two-arm cluster RCT, including 202 primiparous women immediately after giving birth. The PFMT group received instructions in a home training programme, while the control group had no instructions.

The trials by Sut (28) and Sacamori (33) had unclear risk of selection bias. Hyakutake (35) had adequate random allocation generation and concealment, but incomplete outcome data. The method of collecting patient-reported incontinence symptoms was not blinded in any of the trials. The proportion of participants lost to follow-up was 5.4% (28), 26% (35) and 34.7% respectively (33). Losses to follow-up in intervention and control groups were quite similar in all trials, but ITT analyses were not reported.

Postpartum PFMT
Yang (2017) (30) used a random number table to randomise 240 primiparous women into three groups (control, PFMT and PFMT plus EStim) after delivery. The risk of selection bias was low, and researchers were blind to group allocation. However, outcome data were incomplete, and the proportion lost to follow up was 21.3%, but quite similar in all groups. ITT analysis was not reported. Lin (2020) (34) randomised 97 postpartum women to an intervention and a control group while in hospital. The randomisation procedure was not described and risk of selection bias unclear. Outcome data were mainly self-reported (incidence of SUI, ICIQ-SF, I-QOL). No losses to follow-up were reported.

Results

Antepartum PFMT
Szumilewicz (2019) (31) assessed UI specific QoL (IIQ-7) in late pregnancy. Only 1/55 in the control group and 9/111 in the intervention group reported symptoms initially, and accordingly, 2/27 and 9/70 reported symptoms after the six-weeks intervention RR 1.74 (95% CI 0.4, 7.52, *P*=0.46). Johannessen (2020) (36) reported a significant (RR 0.75, 95% CI 0.61-0.93, *P*=0.008) reduction in UI in the intervention group compared to control group three months after delivery. Adherence was reported in both trials.

Combined ante- and postpartum PFMT
Symptoms of UI were registered in the subscales of the questionnaires used (28, 33, 35). It is important to note that none of the PFMT interventions included regular supervision of the exercises. Adherence was reported by Hyakutake (2018) (35), Sacomori (2019) (33) but not by Sut (2016) (28).

In the trials by Sut (2016) (28), Hyakutake (2018) (35) and Sacomori (2019) (33) there was no difference in UI symptoms between groups. The primary endpoint was 6-8 weeks' postpartum. The results in the trial by Sut (28) showed that the frequency and urgency levels in both groups significantly decreased between late pregnancy and early postpartum, according to voiding diary levels. However, changes between groups were not significantly different. Hyakutake (2018) (35) and Sacamori (2019) (33) reported no significant difference between groups at six weeks postpartum, using the UDI-6 (bladder subscale).

Postpartum PFMT
Yang (2017) (30) found that significantly more women reported no UI in the PFMT group and in the PFMT plus EStim group, compared to the control group. UI was also measured by using a urine pad test, and the results showed that significantly more women in the control group leaked urine compared to the two PFMT groups (PFMT alone and with EStim). In the combined PFMT group, 66/129 reported UI compared to 56/60 in the control group, giving a RR 0.55 [0.46,0.66] (*P*<0.00001). Adherence was reported.

The results by Lin (2020) (34) showed that the incidence of SUI and ICIQ-SF scores were significantly lower in the intervention group than in the control group (*P*<0.05) and that the I-QOL scores were significantly higher (*P*<0.05).

Summary

None of the new trials specified self-reported UI prevalence, cure, or improvement as an outcome. However, symptoms of UI were registered in subscales of questionnaires used. It is also important to note that only one (34) of the interventions used to prevent or treat UI, included regular supervised PFMT sessions. It is possible that for the other trials, absence of supervision could have tempered the results. The overall quality of most of the new trials was low.

The only new antepartum mixed prevention and treatment trial on the effects of PFMT on symptoms of UI was inconclusive; however, the trial quality was low (31). In contrast, the high-quality follow-up study by Johannessen (2020) (36) showed that the antepartum PFMT programme still influenced UI symptoms three months after delivery. The three trials combining ante- and postpartum PFMT did not find significant differences between groups on postpartum symptoms of UI (28, 33, 35).

However, both postpartum treatment trials - Yang (2017) (30) and Lin (2020) (34) - found that significantly fewer women reported UI in the PFMT intervention groups compared to the control group.

It is difficult to draw conclusions on the effect of antepartum PFMT or postpartum PFMT on prevention and treatment of UI. The overall quality of many of the new trials was low, and none of the trials had UI symptoms, cure or improvement specified as an outcome measure. Moreover, the control interventions were not always compared to supervised, intensive PFM strength training, as has been previously recommended.

The characteristics of previous trials - all methodologically robust - demonstrated reduced UI prevalence in late pregnancy and six months postpartum and had high adherence to a supervised PFM strength training programme and home exercises. Similar results were demonstrated in two new mixed prevention and treatment trials assessing the effect of postpartum PFMT. **(Level of evidence: 2)**

Nevertheless, one trial using the recommended training protocol in postpartum women did not show any differences between groups (39). Even if the combined results from the published trials still are inconclusive, the benefit of ante- and postpartum PFMT to prevent and treat UI shown in most of the higher-quality studies and the lack of adverse effects of PFMT should be taken into consideration.

Recommendations

Health providers should carefully consider the costs and benefits of population-based approaches, such as professionally taught antepartum or postpartum PFMT. PFMT should be provided to all pregnant or postpartum women by a health professional regardless of their current or prior continence status.

(Grade of recommendation - antepartum PFMT: A)

(Grade of recommendation - postpartum PFMT: B)

For population-based approaches, the 'best' evidence to date suggests recommending: (a) an intervention comprising of a daily home PFMT and weekly physiotherapist-led exercise classes for 12 weeks, starting at 16-24 weeks' gestation for pregnant women, and (b) an individually taught strengthening PFMT programme that incorporates adherence strategies for postpartum women who have had a forceps delivery or a vaginal delivery of a large baby (4000g or more). **(Grade of recommendation: C)**

Table 6. PFMT on pregnant and postpartum women

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Hyakutake (2018) (35)	2-arm RCT Control group (n = 50): Routine prepartum care, likely to have received advice on PFMT. Intervention group (n=50): Instructions on PFMT + home PFMT	100	Nulliparous women with singleton gestation. Incontinence at recruitment was not reported. Single centre Canada.	A single 2-hour long pelvic floor health workshop; information pack to take home; and encouraged to contact a local PF physiotherapist. Women were instructed to perform PFMT three times daily at home starting with 5 contractions (1-sec hold) progressing to 10 contractions (10-sec hold), for the rest of their lives. No PF examination performed.	UI-specific quality of life: CG: 7.3 (12.6) IG: 5.3 (12.8) Std. Mean difference -0.16[-0.61,0.3] UDI-6 (bladder subscale): CG: Mean 15.1, SD 18.7 IG: Mean 11.2, SD 18.2 Mean difference -3.90 (95% CI -12.31 to 4.51)	Primary endpoint: 6 weeks postpartum	Losses to follow-up: 26% CG:13/50 IG:13/50 Adherence: 58.34% of women in the IG and 22.9% of the CG had done PFMT at least daily. ITT analyses not reported Adverse effects: Not reported
Johannessen (2021) (36) Follow up study	2-arm RCT Control (n=426): standard care, not discouraged from PFMT Intervention (n= 429): 12 weeks group PFMT	855	Multiparous pregnant women between 16-24 weeks gestation. With and without UI at inclusion. Multi Centre Norway	12-week exercise class led by a PT between 20 and 36 weeks of pregnancy, including general exercises and specific PFMT. Additional home PFMT: 3 x 10 max. contractions at least 3x per week. Correct VPFMC checked at enrolment	Primary outcome was presence of UI: CG 38% IG 29% p=0.01	3-month follow-up	Loss to follow up: 16% CG:82/426 TG:45/429 ITT analyses reported Adverse effects: None

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Lin (2020) (34)	2-arm RCT Control group (n=48): routine postpartum rehabilitation nursing. Unclear if this included PFMT Intervention group (n=49): Individual PFMT	97	Postpartum women with singleton pregnancies. Incontinence at recruitment not reported. Single centre China	One-to-one nursing intervention in postpartum PFM rehabilitation and more for 6-8 weeks. PFMT 3 x per day, 30 min. each set. Not specified if a correct PFM contraction was confirmed.	Lower incidence of SUI in IG than in CG, p<0.05 Significantly lower ICIQ-SF scores in IG than CG, and higher I-QOL scores in IG than CG, p<0.05	Primary endpoint was 6 months	No losses to follow up reported. Adherence not reported. ITT analyses not reported Adverse effects: Not reported
Sacomori (2020) (33)	2-arm cluster-RCT. Control group (n =104): no PFMT Intervention group (n=98): Home PFMT program	202	Primiparous and multiparous postpartum women included immediately after giving birth to a live child. Incontinence prior to pregnancy: PFMT 10.4%, control 9.2%. Incontinence by third trimester: PFMT 62.7%; control 63.1%. Single centre Brazil.	Home PFMT program performed 2x per day: -10 repetitions of 10 sec holds -10 repetitions of 5 fast and strong contractions -'the knack' (a contraction before and during a sneeze or cough) Correct PFM contraction was assessed.	UI 3 months postpartum: CG: 9/67 IG: 4/65 RR 0.46 [0.15,1.41] UI-specific quality of life (ICIQ-SF): Mean difference not calculable Primary outcome: adherence, classified according to the length of time dedicated to the exercises.	Third trimester Primary endpoint: 3 months' postpartum.	Losses to follow-up: 34.7% CG: 39/104 IG: 31/98 A cluster-RCT with no apparent adjustment for the effect of cluster. Adherence: 55 (85.1%) women reported overall adherence to PFMT. 21 (31.3%) performed PFMT for 3 months postpartum, others for around 2 months. ITT analyses Adverse effects: None reported

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Sangsawang (2016) (29)	2-arm RCT Control group (n=35): usual prenatal care including information about PFMT Intervention group (n=35): Supervised group PFMT	70	Pregnant primiparous women between 20-30 weeks' gestation. No incontinence at recruitment Single centre Thailand	IG followed a supervised group PFMT program (45 min, held once every 2 weeks, group of 4-5 women) led by a midwife, for a duration of 6 weeks(a total of 3 sessions). The ability to contract the PFM was assessed using the stop test (stop or slow urinary flow for 1-2 sec). Women were instructed to perform 20 sets of exercises twice per day at home in different positions, at least 5 days per week.	Primary outcome: UI in late pregnancy: CG:53.3% IG: 27.3% OR 3.05, 95% CI 1.07–8.70, P = 0.018. Secondary outcomes: Self-reported amount of leakage. p=0.03 in favour of the IG Perceived severity on VAS Mean difference -2.0 (95% CI -3.4 to -0.6), in favour of the IG.	Primary endpoint at 38 weeks' gestation	Losses to follow-up at 38 weeks' gestation: 10% CG: 5/35 IG: 2/35 Adherence: No women were excluded for failing to perform the PFMT for < 28 (of approximately 42) days. ITT analyses not reported Adverse effects: Not reported
Sigurdardottir (2020) (32)	2-arm RCT Control group (n=43): no instructions after initial assessment Intervention group (n=41): Individual PFMT for 12 weeks	84	Women with UI; symptoms at 9 weeks after delivery. Single centre Island	12 weekly individual sessions from 9 weeks postpartum: 45-60 minutes sessions with physical therapist with gradual progression of PFMT-exercises + home exercises 3x10 close to maximal PFM contractions.	Primary outcome measure UI postpartum: Endpoint, 6 months postpartum: C:31/38, I:21/37 (p=0.03) Follow up, 12 months postpartum: C:34/42, I:28/38 (p=0.6)	6 months postpartum 12 months postpartum	Total loss to follow up:13/84 (16%) CG: 5/43 IG: 8/41 33/41 (80%) in the IG attended all 12 PFMT sessions. Adherence at 6 months: 11/36 (31%) Adherence at 12 months: 8/38 (21%) ITT analyses not reported Adverse effects: None

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Sut (2016) (28)	2-arm RCT Control group (n =32): no instruction was given Intervention group (n=32): Home PFMT program	64	Pregnant women at 28 weeks gestation. UI at recruitment was not stated. Statistically significant difference (P = 0.018) in vaginal deliveries between groups. Single centre Turkey.	Intervention: Home exercise program during pregnancy and postpartum, 3 sets of 10 exercises, 3x per day. Did not report whether correct execution of contractions was confirmed. Women were phoned at two-week intervals to remind them to perform their exercises.	Severity of UI (3-day voiding diary) in late pregnancy between the groups. Mean difference 0.2 (95% CI -0.35 to 0.75). UI-specific quality of life early postpartum period (0-3 months): CG: 0.3 (1.7) IG: 1.7 (6.4) RR 0.3 [-0.21,0.8]	36-38 weeks' gestation and 6-8 weeks' postpartum.	Losses to follow-up: 5.4% IG: 2/32 CG: 2/32 Adherence not reported ITT analyses not reported Adverse effects: Not reported
Szumilewicz (2018) (31)	2-arm block RCT Control group (n = 55): did not receive biofeedback, verbal instruction on how to contract the PFM or any exercise program. Intervention group (n=111): Supervised group exercise sessions including PFMT	166	Pregnant nulliparous women. Incontinence at recruitment: CG: 3.7% IG: 12.9% Women who were unable to perform a PFM contraction (assessed with EMG) and did not report good quality of life at the pre-intervention assessment were also excluded. Single centre Poland	Supervised group exercise sessions (60 min, 3x per week), led by a certified pregnancy and postpartum exercise specialist over a 6-week period (18 sessions in total). Sessions included a progressive PFMT program incorporated into high and low-impact aerobic activity (25 min) and strengthening exercises (25 min), stretching and breathing exercises and relaxation (10 min). PFM contraction was confirmed by EMG and women received one session of verbal instruction about PFM contraction and relaxation with biofeedback.	Symptoms of UI initially CG: 1 IG: 9 and in late pregnancy CG: 2 IG: 9 RR 1.74 [0.4,7.52] Primary outcome was changes in neuromuscular activity of PFM (EMG).	Late pregnancy, after the 6 weeks intervention.	Losses to follow-up at late pregnancy: CG: 30/55 (of these 14 were excluded prior to no PFMT). IG: 41/111 (of these 26 were excluded prior to PFMT) Data on losses to follow-up in CONSORT flowchart are incongruent. Adherence: IG group attended 13±3 exercise sessions (from a maximum of 18), which constituted 71±19% of the planned exercise program. ITT analyses not reported Adverse effects: None

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Yang (2017) (30)	3-arm RCT Control group (n=80): No PFMT, unclear whether they were instructed not to perform PFMT. Postpartum routine guidance. Intervention group 1 (n=80): Home PFMT program Intervention group 2 (n=80): Home PFMT program + electrical stimulation Note: groups IG 1 and IG 2 were combined as the IG for comparison with controls	240	Primiparous women, with an episiotomy or second-degree tear. Incontinence at recruitment was not reported. Single centre China.	IG 1: unsupervised home exercise program from 2 days to 3 months postpartum, 2-3 times per day. Taught by two specialised staff members at 2 days postpartum (each training session went for 20 min with the exercises perform 6 times per min). Correct PFM contraction confirmed. IG 2: in addition to home PFMT, this group received electrical stimulation administered by 2specialised staff, 30 min, 3x per week, beginning at 6 weeks postpartum (15 sessions in total).	UI in early postpartum period: CG: 56/60 IG 1 and 2: 66/129 RR 0.55[0.46,0.66] Loss of urine under stress test: CG: 15/60 IG 1 and 2: 17/129 OR 0.46 [0.21,0.99]	3 months postpartum	Losses to follow up: 21.3% CG 60/80 IG 1 66/80 IG 2 70/80 Adherence: three cases failed to complete the PFMT in accordance with the prescribed frequency and timing in the training group. ITT analyses not reported Adverse effects: None

Abbreviations: RCT: randomised controlled trial; PFMT: pelvic floor muscle training; PF: pelvic floor; PFM: pelvic floor muscle; ITT: intention to treat; PT: physiotherapist; IG: intervention group; CG: control group; ICIQ-SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form.

2.2. Prevention (other women)

Although there are multiple trials of PFMT for prevention of UI in peripartum women (see section II.2.1.1), there is little research on PFMT for prevention of UI in non-childbearing women. We found five new trials to add to the one trial from the previous edition. Two (40, 41) were workshops on incontinence awareness and education including PFMT and are out of the scope of this chapter. Please refer to chapter 20 on *Primary prevention, continence promotion, models of care and education* for more details on educational workshops on incontinence. Three more trials on PFMT for UI prevention were found (42-44).

PFMT details

Two trials involved post-menopausal women (42, 43) and the other one, young volleyball players (44). All three trials involved a PFMT programme supervised by a physiotherapist one to two times per week, for 12-16 weeks in addition to home PFM exercises compared to an inactive control. More details about the exercise programmes are presented in Table 7.

Quality of data

Of the three trials, one was of moderate size (43) and the two others were small (42, 44). All three presented a clear randomization method, but only one reported a clear method of concealment, blinded outcome assessors and intent-to-treat analysis (43). Loss to follow-up was moderate (20% and up) and when reported, side effects were minor. The overall ROB was considered to be low in one trial (43) and moderate in the others (42, 44), mainly due to blinding of the assessor and attrition bias.

Results

Prevalence of UI was based on quantifiable measures (pad test) (44) or on or UI-specific validated questionnaires (42, 43). In all three trials, prevalence of UI was lower in the treatment group than in the controls immediately after the intervention, supporting the effect of PFMT in the prevention of UI. No longer-term effect was reported.

Summary

PFMT could be effective in the prevention of UI in younger athletes and menopausal women, immediately after the intervention. (**Level of evidence: 2)**

Supervised PFMT can be offered to prevent UI in women **(Grade of Recommendation: B New)**.

Larger size RCTs with longer follow up are needed.

2.3. Treatment (other women)

2.3.1. Is PFMT better than no treatment, a placebo, or a control group treatment?

- This updated literature review identified 13 new trials that compared PFMT to no treatment, a sham treatment, or a control treatment (45-57). Two of the new trials were merged as they are reports from the same study (51, 56). Therefore, 13 reports of 12 new trials were included. The new identified trials were diverse and included studies from 11 countries (See Table 7). Samples involved adult women, with one trial specific to obese elderly women (57). Results from the studies added in this update are integrated with the conclusions drawn from previously reviewed studies.

PFMT details

Like in previously reviewed studies, most new trials proposed a 12-week (three-month) PFMT intervention. In some trials, the intervention was shorter, lasting from four to eight weeks (47, 48, 54, 56, 57) or longer, lasting up to 15 weeks in one trial (46). Of the 12 new trials, only six stated that a correct voluntary PFM contraction was confirmed prior to training using vaginal examination (47-50, 52, 56). Seven trials involved supervised PFMT by a physiotherapist or nurse (47-50, 54, 56, 57), and four included a regimen of home-based exercises (47-50). In four trials, supervised PFMT was delivered on an individual basis (47-49, 54), while in the other three, PFMT was conducted in group classes (50, 56, 57). Unsupervised PFMT was delivered with the aid of written and/or audio material in five trials (45, 46, 52, 53, 55). In three trials, the unsupervised programme was given in a single education session, delivered either individually (52, 53) or in groups (45). Of note, one study tested a smart phone application with no face-to-face contact with the participants (46). This application was previously tested in women with SUI (58) and this time it was applied in women with UUI or mixed urinary incontinence (MUI) (46). Furthermore, in five trials, PFMT was embedded in a multi-component programme with other behavioural or exercise components (45, 46, 49, 50, 53), but in all cases, PFM-specific exercises for the treatment of UI were considered as a main component of the intervention.

Quality of data

Of the new trials, four included more than 100 women (45, 46, 50, 56) of which two included over 400 participants (45, 50), five included 50-100 women (52-55, 57), and three involved fewer than 50 participants (47-49). Ten new trials presented a clear randomisation method (45-47, 49, 50, 52, 53, 55-57), eight reported concealment (45-47, 49, 50, 52, 56, 57), and four reported using blinded outcome assessors (45, 55-57). Four trials reported ITT analysis (45, 46, 52, 53). Loss to follow-up was low (below 10%), balanced between groups and unrelated to the study intervention in four trials (46, 50, 52, 53). When reported, side effects were minor and did not differ between groups (45, 46, 49, 50, 52, 55). The overall ROB was considered to be low in four trials (45, 46, 50, 52) and unclear in the remaining eight trials, mainly due to selection and attrition bias (47-49, 53-57). None of the newly included trials were considered to have high ROB.

Results

Similarly to the previously reviewed trials, the new added trials based their results on a variety of outcome measures, including patient-reported outcomes: cure (45, 46, 50, 55), improvement (45, 46, 52, 53, 55), UI-specific QoL or symptoms-validated questionnaires (45-49, 51-57), and number of leakages (as per the diary) (46, 48, 50, 55). Other outcomes included generic QoL or symptoms-validated questionnaires (50, 51) and clinician-reported measures, such as the 24-hour pad-test (45), PFM function (45, 47, 48, 52), and irisin (57) or myostatin (56) concentration. Cure and improvement were based on quantifiable measures such as a bladder diary (45, 46, 50, 55) or UI-specific validated questionnaires (45, 46, 52). One trial showed UI improvement based on UI-specific validated questionnaires, but only for the treatment group (53). The International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF) was the most used UI-specific questionnaire (45-47, 49, 52-55), followed by the Revised Urinary Incontinence Scale (RUIS) (51, 56, 57) and the King's Health Questionnaire (KHQ) (51, 53).

When reported, cure rate favoured treatment in all trials, including the new and the previously reviewed trials. Three trials presented similar cure rates, where 32% to 55% of the participants reported

being cure (46, 50, 55). The cure rate was considerably lower in one trial compared to the other three, where only 4% of the treatment group versus 1.5% of the control group were cured (45). This difference might be related to the specificity of each intervention protocol. Particularly for the trial with lower cure rate, the intervention consisted in three months of unsupervised PFMT followed by a two-hour group class on bladder health. Additionally, no specific PFM assessment was reported to confirm whether participants performed a correct PFM contraction, which raises the possibility that not all participants were able to follow exercise instructions, and lack of supervision may have affected adherence to PFMT. Reported improvement rates varied widely, between 33% to 87% and consistently favoured treatment in new and previously reviewed trials (45, 46, 52, 53, 55, 58, 59). In the trials added to this chapter, improvement rates varied according to the definition used: Higher rates (71-87%) were reported in trials considering improvement as "a little better" to "very much better" on the Patient Global Impression of Improvement (PGI-I) questionnaire (46, 53), or as 50% reduction in UI episodes (46, 55). Lower rates (33-47%) were seen when improvement was considered as only "much better" to "very much better" on the PGI-I (53); when there was a 70% reduction in UI episodes (45); or, in one case, when improvement was based on a four-points category system using the ICIQ-UI SF total score (52).

Results favoured the treatment group in most of the trials that reported on UI-specific QoL or impact questionnaires. In this update, improvements were related to treatment in eight (45-48, 52-54, 56) out of 11 added trials that reported UI-specific QoL outcomes. Only three trials reported no difference between PFMT and control groups after the intervention (49, 55, 57). In one trial, post treatment outcomes were assessed at four weeks only in obese elderly women with UI (57), a population that may require a longer intervention time because of the increased pressure on the pelvic floor. The other two comprised a small pilot study with a high attrition rate, with 10 out of 22 participants concluding the trial (49), and an unsupervised low intensity PFMT programme (*'3-min exercise before going out'*) (55). Other outcomes that consistently favoured treatment across trials included number of leakages (46, 48, 50, 55) and pad test measured urinary loss (45). Overall better outcomes, including higher adherence and maintenance of results were observed in trials involving intense (8- to 12-week long) and supervised PFMT protocols (48, 50, 54, 60). Of note, two trials presented longer-term follow-ups (one year) that supported maintenance of results (45, 60).

Summary

PFMT is effective as a stand-alone therapy, as part of multi-component therapies embedding PFMT with concomitant behavioural strategies and lifestyle changes, and as part of general physical exercise programmes to improve physical function in women. Results expand the evidence base to include PFMT implemented by mobile technology, with a potentially broader reach, cost savings, and impact on rural health. New evidence from two high quality trials suggests the results were maintained in the longer term (one-year). Benefits are shown across age cohorts and UI type, in various cultural contexts, using several different training regimens, and assessed by multiple outcome measures. **(Level of evidence: 1)**

Recommendations

Supervised PFMT should be offered as a first line conservative therapy for women of all ages with UI. **(Grade of recommendation: A)**

Table 7. Summary of PFMT vs no treatment

Author, year	Comparator	N	Study population/ Country	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Prevention							
Alves (2016) (42)	RCT PFMT vs no treatment	42	Post-menopausal women (at least 5 years) Brazil	PFMT: 12 supervised PFMT 2x week during 30 minutes performed in group of 8-10 participants including pelvic mobility, stretching and straightening and relaxation exercises in different positions + PFMT with fast and slow contractions Control: one session of general exercises	Outcomes: primary outcome was measured using ICIQ-UI SF and ICIQ-OAB Key findings: There was a significant decrease in UI symptoms in PFMT group when compared to control for both ICIQ-UI (p=0.03) and ICIQ-OAB (p<0.001).	NR	Publication: FT Dropouts: 3/21 women in PFMT did not receive the intervention;9/21 women in the control arm did not complete the follow-up assessment AE: NR

Author, year	Comparator	N	Study population/ Country	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Antônio (2018) (43)	RCT PFMT vs no treatment	99	Post-menopausal women (at least 5 years) Brazil	PFMT: supervised PFMT sessions in group of up to 4 participants with 10 maximal voluntary contractions maintained for at least 6 seconds + 5 fast contractions with intervals of 6 seconds. The sets were performed in four positions: lying in lateral decubitus, sitting, kneeling on all fours and standing 2x week for 12 weeks. Participants were also instructed to perform home PFMT Control: no treatment	Outcomes: Prevalence and severity of UI was measured by the ICIQ-UI SF Key findings: There was a significant greater effect on prevalence of UI symptoms in PFMT group compared to control group (p=0.028). However, no differences on severity of UI were observed between groups (p=0.37).	Baseline and 12 weeks	Publication: FT Dropouts: 4/51 women in PFMT did not receive the intervention; 7/48 women in the control arm did not complete the follow-up assessment AE: NR
Pires (2020) (44)	RCT PFMT vs no treatment	14	Elite female volleyball athletes Portugal	PFMT: supervised PFMT during 16 weeks. The exercises consisted of three phases: awareness/stabilization, strength training and power. The participants were also instructed to perform daily PFMT at home. Control: no treatment	Outcomes: Urine loss using Pad Test and QoL using KHQ. Key findings: Between-groups showed significant difference (p=0.039) in pad test favouring PFMT group. The KHG showed no difference between groups in all domains.	Baseline and 4 months	Publication: FT Dropouts: 0/7 women in PFMT; 1/4 women in the control arm did not complete the follow-up assessment AE: NR
Treatment							
Al Belushi (2020) (52)	PFMT vs no Tx (lecture with no PFMT).	N=73 Tx:36 CG:37	Adult women with SUI (20-50 years; mean 35 years) Oman	12 weeks of unsupervised PFMT after one individual education session. Home progressive training: 5 sessions per day including endurance and speed exercises in different body positions with the aid of compliance cards and weekly phone calls	Patient-reported outcomes Improvement (based on ICIQ-UI SF total score): favoured Tx, 47% Tx vs 5% CG, p=.001 UI-specific QoL or impact (ICIQ-UI SF): favoured Tx (mean difference of change 2.9 [1.9, -3.8], p<.001)	Post Tx. (12 weeks)	Side effects: mild lower abdominal pain (first 2 weeks), which disappeared spontaneously (n=2) Loss to follow-up: 3 (2 Tx, 1 CG); ITT analysis
Bertotto (2017) (47)	(1) PFMT (2) No Tx (waitlist) (3) BF	N=49 Tx:16 CG:16 BF:17	Postmenopausal women with SUI (50-65 years; mean 59 years) Brazil	4 weeks of supervised PFMT, 20-min, twice per week. Home exercises twice a day. Progressive training in different body positions: sustained and phasic contractions + guided imagery (US) training	Patient-reported outcomes UI-specific QoL or impact (ICIQ-UI SF): favoured Tx (mean difference -5.70 [-8.69, -2.71], p<.001)	Post Tx (4-6 weeks)	Side effects: N.R. Loss to follow-up: 3 (1 Tx and 2 CG), reasons unknown, no ITT analysis Note: no between group comparison reported for most outcomes

Author, year	Comparator	N	Study population/ Country	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Diokno (2018) (45)	PFMT vs no Tx	N=463 Tx:232 CG:231	Older women with UI (>55 years; mean 64 years) USA	3 months of unsupervised PFMT, 2-hour bladder health class with written and audio material. No further details on PFMT program provided.	Patient-reported outcomes Cure (ICIQ-UI SF=0): 4% Tx vs 1.5% CG Improvement (70% reduction in UI and PGI-I): 35% Tx vs 22% CG and 64% vs 11% (much better and very much better) UI-specific QoL or impact (ICIQ-UI SF and MESA): favoured Tx across all time points, p<.001 Clinician-reported outcomes favoured Tx: 24h pad-test	3, 6, 9 and 12 months	Side effects: minor and not different between groups Loss to follow-up: 42 (23 Tx and 19 CG) post Tx, 65 (37 Tx and 28 CG) at 12 months, reasons unknown, ITT analysis Note: 2h class including other Tx modalities (bladder health)
Firra (2013) (48)	(1) PFMT (2) No Tx (waitlist) (3) PFMT + electrical stimulation	N=38 Tx:19 CG:19 ES:26	Women with SUI or UUI (≥ 21 years; mean age 58 years) USA	8 weeks of supervised PFMT, twice weekly sessions + home exercises; progressive training with submaximal and Maximal sustained and short PFM contractions in different positions	Patient-reported outcomes UI-specific QoL or impact (YIPS) favoured Tx, p<.05 Number of leakages (3-days BD): favoured Tx, p<.05	Post Tx (8 weeks)	Side effects: N.R. Loss to follow-up: 5 (1 Tx and 4 CG) post Tx, no ITT analysis Note: results provided separately by UI type (SUI and UUI)
Fu (2020) (53)	PFMT vs no Tx (waitlist)	N=50 Tx:24 CG:26	Older women with UI (≥ 55 years, mean age 70 years) UK	Self-management package including one individual session and 12 weeks of unsupervised PFMT, BT and lifestyle interventions with aid of brochure. Optional 1-h support session. No further details on PFMT program provided.	Patient-reported outcomes Improvement (PGI-I from Tx only): 71% considering a little better to very much better or 33% considering much better to very much better UI-specific QoL or impact (KHQ, ICIQ-UI SF, incontinence impact and severity scale) favoured Tx Generic anxiety and depression scale (HADS): favoured Tx for the depression but not anxiety sub-scale	Post Tx (12 weeks)	Side effects: N.R. Loss to follow-up: 1 (CG), ITT analysis Note: Self-management package includes other Tx modalities (bladder health)
Ilgun (2013) (54)	PFMT vs no Tx (waitlist)	N=60 Tx:30 CG:30	Women between 18-60 years with UI Turkey	8 weeks of supervised PFMT with BF, twice weekly, 20-min sessions. No further details on PFMT program provided.	Patient-reported outcomes UI-specific QoL or impact (ICIQ-UI SF and I-QOL): mean difference -3.1 [-5.45, -0.75], p=.01 and -5.2 [-2.6, 13], p=0.2	Post Tx (8 weeks)	Side effects: N.R. Loss to follow-up: 0 every patient who withdrew from the study was replaced by a new patient Note: no between group comparison reported

Author, year	Comparator	N	Study population/ Country	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Okayama (2019) (55)	(1) PFMT (2) No Tx (3) Supportive underwear (SU)	N=89 Tx:50 CG:50 SU:50	Women with SUI (30-59 years; mean 44 years) Japan	12 weeks of unsupervised PFMT using audio guide, 3-min exercise before going out (Takumi Vision Co., Kyoto, Japan), twice per day. The intervention includes 26 PFM contractions in 3 min.	Patient-reported outcomes Cure (7-days BD =0): 55% Tx vs 18% CG improvement (50% leakage reduction on 7-days BD): 74% Tx vs 25% CG UI-specific QoL or impact (ICIQ-UI SF) not different between groups (p=.08) Number of leakages (3-days BD): favoured Tx	Post Tx (12 weeks)	Side effects: none Loss to follow-up: 61 (19 Tx, 22 CG, 20 SU), either due to lack of consent or absence of UI at baseline, no ITT analysis
Radziminska (2018) (56) Weber-Rajek (2020) (51)	(1) PFMT (2) No Tx (3) EMI	N=128 Tx:44 CG:40 EMI:44	Older women with SUI (>60 years; mean age: 69 years) Poland	4 weeks of supervised group PFMT (5-6 participants) consisting of 45-min sessions 3x per week. Progressive and tailored protocol including fast and slow contractions in different body positions + posture and breathing exercises	Patient-reported outcomes UI-specific QoL or impact (RUIS, GSE, KHQ): RUIS favoured the Tx (median, IQR: 6 [5] Tx vs 9 [5] CG, p=.0008), GSE not different between groups, KHQ favoured Tx for the domain physical limitations, social limitations, personal relationships and emotions (p<.05)	Post Tx (4 weeks)	Side effects: N.R. Loss to follow-up: 13 (4 Tx, 6 CG, 7 EMI), no ITT analysis Note: publications merged considered as two reports from the same study.
Solberg (2016) (49)	(1) PFMT (2) No Tx (waitlist) (3) AC	N=34 Tx:10 CG:12 AC:12	Women with MUI (>60 years; median 64 years) Norway	12 weeks of supervised PFMT, once per week, 45-min, including general exercises (20-min) and home training (10 min)	Patient-reported outcomes: UI-specific QoL or impact (ICIQ-UI SF) not different between groups (p=0.12)	Post Tx (12 weeks)	Side effects: worsening of UI that disappeared spontaneously (n=1) Loss to follow-up: 12 (4 Tx, 6 CG, 4 AC), no ITT analysis Note: ICIQ-UI SF different at baseline, high attrition rate
Wadensten (2021) (46)	PFMT vs Very brief information on PFMT, BT, psychological topics related to UUI and summarized lifestyle advice	N=123 Tx:60 CG:63	Women with UUI or MUI (>18 years; mean 58 years) Sweden	15 weeks of unsupervised PFMT (smart phone app); progressive and tailored protocol including PFMT, BT, psychoeducation, and lifestyle advice. No face-to-face contact	Patient-reported outcomes: Cure (32% Tx vs 8% CG) Improvement (50% reduction in UI [2-day BD] and PGI-I [a little better to very much better]): 68% Tx vs. 30% CG and 87% Tx vs 30% CG UI-specific QoL or impact (ICIQ-UI SF, ICIQ-LUTSqol and Incontinence Catastrophizing Scale) favoured Tx Number of leakages (2-day BD): favoured Tx, p<.001	Post Tx (15 weeks)	Side effects: inguinal hernia (n=1) likely not related to Tx and increased UI with decreased UUI (n=1) Loss to follow-up: 5 (3 Tx, 2 CG), ITT analysis Note: no face-to-face contact, CG had access to some information on PFMT

Author, year	Comparator	N	Study population/ Country	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Wagg (2019) (50) Haque (2020) (60)	PFMT vs Bladder-health education without PFMT training/practice and mobility exercises	N=579 Tx:298 CG:281	Older women with UI (60-75 years; mean 65 years) Bangladesh/ Canada	12 weeks supervised group PTMT, twice weekly 60-min group sessions + 30-min brisk walking. Sessions included fitness (breathing, global relaxation, strengthening) and bladder-health education. Daily home exercise for 24 weeks	Patient-reported outcomes Cure (3-days BD): 41% Tx vs. 0 CG post Tx and 62% at 12-months (Tx only subsample, n=130) Number of leakages (3-days BD): favoured Tx (mean difference –7.7 [–10.6 to –4.8]) Other generic outcomes measures on health state, depression and QoL also favoured Tx: CES-D-10, EQ5D	Post Tx (12 weeks) 12 months for a subsample of 130 treated women	Side effects: none Loss to follow-up: 22 (15 Tx and 7 CG); cluster analysis (by village) Note: Tx included other modalities (brisk walking); control group included some education and exercise
Weber-Rajek (2019) (57)	PFMT vs no Tx	N=62 Tx:32 CG:30	Obese elderly women with UI (>60 years; BMI >25; median age 64 years) Poland	4 weeks of supervised group PFMT (5-6 participants), 3x week 45-min sessions Progressive and tailored protocol including fast and slow contractions in different body positions + posture and breathing exercises	Patient-reported outcomes UI-specific QoL or impact (RUIS) not different between groups Clinician-reported outcomes also not different between groups: irisin concentration and BMI	Post Tx (4 weeks)	Side effects: N.R. Loss to follow-up: 17 (4 Tx, 6 CG, 7 EMI), no ITT analysis

Abbreviations: ICIQ-UI SF: International Consultation on Incontinence Questionnaire – urinary incontinence short form; PGI-I: Patient Global Impression: Improvement; MESA: Medical, Epidemiologic, and Social Aspects of Aging; YIPS: York Incontinence Perceptions Scale; KHQ: King's Health Questionnaire; HADS: Hospital Anxiety and Depression Scale; I-QOL: Incontinence Quality of Life Questionnaire; RUIS: The revised Urinary Incontinence scale; CES-D-10: Centre for Epidemiologic Studies Depression Scale; EQ-5D-5 L: The five-dimensional EuroQoL Questionnaire; GSE: Geriatric Self-Efficacy index; Tx: Treatment group; CG: control group; PFMT: Pelvic floor muscle training; ITT: intention-to-treat; SUI: stress urinary incontinence; UI: urinary incontinence; UUI: urgency urinary incontinence; QoL: quality of life; BD: bladder diary; BT: Bladder training; BF: biofeedback; PFM: pelvic floor muscle; IQR: interquartile range; MUI: mixed urinary incontinence; BMI: body mass index; EMI: Extracorporeal magnetic innervation.

2.3.2. Is one type of PFMT programme better than another?

Several factors can influence the outcome of a PFMT programme, such as the way it is taught and/or supervised, the parameters of the actual exercises as well as the adherence to the training regimen. But what is the most effective PFMT programme? This updated search revealed 29 new potentially eligible RCTs to address this question through 12 pre-defined comparisons. Of these, three were excluded because they did not report any incontinence outcomes (61-63). Three additional studies were not considered as they were already included as abstracts in the previous ICI, and the findings remained unchanged in the full manuscripts (64-66). Table 8 shows the studies included in the previous edition as well as the 23 eligible trials identified in this update (47, 67-88). Characteristics of each new RCT are presented in Table 9.

Table 8. Studies comparing different PFMT programs included in previous reviews and the current update (7th ICI)

	Studies included in previous ICI reviews	New studies identified in this update (7th ICI)
1. Supervision of training: amount of contact with health professionals	10	2
2. Supervision of training: individual versus group supervision	8	2
3. Exercise program: direct versus indirect exercises	8	2
4. Exercise program: generic versus individualised exercises	1	0
5. Exercise program: submaximal versus near maximal contractions	1	0
6. Exercise program: daily versus three times per week	1	0
7. Exercise program: addition of upright exercise position	1	0
8. Exercise program: addition of strength training to motor learning	1	1
9. Exercise program: addition of abdominal or hip muscle exercises	4	4
10. Exercise program: addition of an intravaginal resistance device	5	1
11. Exercise program: addition of an adherence strategy	2	2
12. Exercise program: addition of biofeedback	15	9

Abbreviations: ICI: International Consultation on Incontinence

Quality of data

Of the 23 RCTs included, 15 provided sufficient details supporting adequate randomisation and allocation concealment methods (47, 67-70, 72-75, 77-79, 81-83). Six trials were randomised but did not provide information about treatment concealment (71, 76, 80, 84, 86, 87). Two studies did not report sufficient information on randomisation and concealment methods (85, 88). Nine RCTs stated that the outcome assessors were blinded (69, 72-75, 77, 78, 80, 86). Four studies used self-reported outcomes and participants were not blinded to treatment allocation (47, 68, 82, 83). For the remaining 10 RCTs, the assessors were not blinded, or insufficient information was presented (67, 70, 71, 76, 79, 81, 84, 85, 87, 88). Regarding the sample size, seven trials were small, including less than 20 participants per group (47, 75, 80, 83, 85, 87, 88). Nine studies included between 23 and 37 participants per comparison group (67, 68, 70, 71, 73, 76-79) and five had nearly 45 participants per group (72, 74, 81, 84, 86). Only two RCTs had a larger sample size, involving a total of 362 (69) and 600 women (82) (i.e., ≥178 per group). In four RCTs, the dropout rate ranged from 35% to 43% (70, 79, 83, 87) and hence the results of these RCTs should be interpreted with caution.

Results

- **Comparison 1. Supervision of training: amount of contact with health professionals**

Subgroup 1.1: additional group supervision

No further studies investigated the effect of adding an additional supervised group exercise session.

Subgroup 1.2: additional phone calls

No new studies investigated the effect of adding supervisory phone calls to PFMT programmes.

Subgroup 1.3: individual supervision versus no supervision

Two new RCTs were included in this comparison (67, 68). The PFMT programmes evaluated differed with regards to the amount of health-professional contact but were similar in type and quantity of PFM exercises.

For objective cure, the study by Fitz et al. (67), which was included as an abstract in the previous ICI edition, is considered in this update due to the new outcome in cure rate based on the pad test. Women in the supervised group presented a higher cure rate than women in the unsupervised group.

For improvement, the study by Mateus-Vasconcelos (68) showed that supervised PFMT resulted in a greater improvement in the ICIQ-UI scores than unsupervised training.

- **Comparison 2. Supervision of training: individual versus group**

Two new RCTs were included in this comparison. Both studies compared the same PFMT programme which differed only in the type of supervision (group versus individual) (69, 70). Dumoulin et al. (69) conducted a non-inferiority RCT comparing group to individual PFMT in women 60 years and older with SUI or MUI. In a superiority trial, Figueiredo et al. (70) investigated women with a mean age of 51 years. They were randomised to receive either individual PFMT, individual PFMT progressing into group training or group PFMT. It should be highlighted that in both studies, an individual assessment of the PFM was conducted prior to training to teach all women how to perform a proper PFM contraction. Dumoulin et al. (69) also offered women in the group arm the possibility to have an individual supervised session to verify that they were doing their contractions properly.

Dumoulin et al. (69) reported no significant differences between the two treatment arms for UI–specific symptoms and QoL outcomes (ICIQ-UI and ICIQ-LUTS QoL) at one year. Figueiredo et al. (70) found a non-significant difference between group and individual PFMT using the KHQ.

For leakage episodes, Dumoulin et al. (69) showed an average percentage reduction in UI episodes at one year of 70% in individual compared with 74% in group-based PFMT intervention. The differ-

ence between groups fell below the noninferiority margin of 10%, supporting noninferiority of group-based PFMT.

- **Comparison 3. Exercise programme: direct versus indirect exercises**

This comparison encompassed six subgroups evaluating direct versus indirect training. In "direct" PFMT, women specifically performed voluntary contractions of the PFMs, while in the "indirect" PFMT, women focused on other muscle groups to facilitate or stimulate PFM contractions. Of note, these comparisons are often affected by differences in the amount of contact time with health professionals or result from a small sample size, which makes difficult detection of clinically significant differences.

Subgroup 3.1: PFMT versus sham/imitation

No new studies were found comparing PFMT to sham or imitation PFMT treatments (e.g., crossing the ankles and pulling the legs apart).

Subgroup 3.2: PFMT versus the 'Paula method'

No further evidence was available.

Subgroup 3.3: PFMT versus the 'Sapsford' approach

One trial (71) examined the efficacy of PFMT compared to abdominal training using the Sapsford approach and found a non-significant difference between groups. However, the two treatment arms differed in the number of supervised sessions and no sample size calculation was provided. Hence caution is required when interpreting the data.

Subgroup 3.4: PFMT versus Pilates

No new RCTs were found evaluating Pilates treatments in comparison to PFMT.

Subgroup 3.5: PFMT versus hip rotator training

No further evidence was available.

Subgroup 3.6: PFMT versus hypopressive training

Our search revealed two new RCTs comparing PFMT to hypopressive training (72, 73). In the study by Jose-Vaz *et al.* (72), women with SUI received either PFMT or hypopressive training. The study by Navarro-Brazález *et al.* (73) included women with various pelvic floor disorders including SUI and MUI, and investigated three treatment arms (PFMT, PFMT plus hypopressive training and hypopresive training alone).

For improvement, Jose-Vaz *et al.* (72) showed higher changes in the PFMT group compared to the hypopressive group, while Navarro-Brazález *et al.* found non-significant differences in the Pelvic Floor Distress Inventory (PFDI) and Urogenital Distress Inventory (UDI) scores between the two groups (73). For leakage episodes, Jose-Vaz *et al.* (72) reported that women who received PFMT had significantly fewer UI episodes than women in the hypopresive training group.

- **Comparison 4. Exercise programme: generic versus individualized exercises**

No further evidence.

- **Comparison 5. Exercise programme: submaximal versus near maximal contractions**

No further evidence.

- **Comparison 6. Exercise programme: daily versus three times per week**

No further evidence.

- **Comparison 7. Exercise programme: addition of upright exercise position**

No further evidence.

- **Comparison 8. Exercise programme: addition of strength training to motor learning**

One trial compared the effects of PFMT to PFMT combined with PFM reflex activation during functional activities, such as running and jumping, in women with SUI and MUI (74). This study revealed no benefits of adding a motor learning programme to PFMT. No significant differences were found between the two groups regarding changes in ICIQ-UI scores and pad test results.

- **Comparison 9. Exercise programme: addition of abdominal or hip muscle exercises.**

This comparison encompassed two subgroups evaluating the addition of either abdominal muscle (subgroup 9.1) or hip muscle (subgroup 9.2) training to PFMT.

Subgroup 9.1: PFMT versus PFMT plus abdominal muscle exercises

Three new RCTs evaluated the efficacy of adding abdominal muscle exercises to PFMT in women with SUI (68, 75, 76). In two of the trials, the same amount of health-professional supervision was given to each group (68, 75) whereas in the other trial, limited information was available on the similarity in treatment dosage (76).

For improvement in the study by de Souza Abreu *et al.* (75), a larger reduction in the Incontinence Severity Index (ISI) scores was found in the combined group compared to the PFMT group alone, while a no significant difference was observed in the Patient Global Improvement Indices (PGI-I). The study by Kucukkaya *et al.* (76) showed a superior effect in the Urinary Distress Inventory, Short Form, (UDI-6) scores for the group combining PFMT with abdominal exercises compared to PFMT alone. In contrast, the findings of Mateus-Vasconcelos *et al.* (68) favoured PFMT alone over PFMT combined with abdominal exercises when considering differences in the ICIQ-UI scores.

For leakage episodes, the study by de Souza Abreu *et al.* (75) showed a higher reduction in UI episodes in the combined group compared to the PFMT group.

In the study by Kucukkaya *et al.* (76), fewer positive cough tests were found in the group combining PFMT with transverse abdominal exercises at four weeks of treatment. All participants in both groups were considered continent at the cough test at the three-month follow-up.

Subgroup 9.2: PFMT versus PFMT plus hip muscle exercises

The study by Marques *et al.* (77) was considered in the current update even though it was included as an abstract in the previous edition (89). The complete manuscript provided additional incontinence outcomes and included a larger sample. A non-significant group x time interaction was found between the PFMT group and the PFMT plus hip exercise group for the ICIQ-UI and KHQ scores as well as for the frequency of urinary leakage (3-day bladder diary).

- **Comparison 10. Exercise programme: addition of an intravaginal resistance device**

The study by Orhan *et al.* (78) investigated the efficacy of PFMT compared to PFMT combined with resistance training (i.e., using a tampon that was pulled out) in women with stress-predominant incontinence. No-significant differences between groups were found for self-reported improvement, Incontinence Severity Index (ISI) score, frequency of incontinence episodes and pad test results.

- **Comparison 11. Exercise programme: addition of adherence strategy**

Two trials investigated the addition of adherence strategies to PFMT training (83, 84). The two trials employed the same PFMT protocols across the study arms. In the study by Araujo *et al.* (83), a mobile application with reminders, which was not connected to any intra-vaginal probe, was used in conjunction with PFMT compared to PFMT alone in women with predominant SUI. The study by Sacomori et al. (84) employed adherence and self-efficacy strategies using discussions, videos and reminders in women with SUI, UUI or MUI.

In the two studies, significant improvements were found in all groups for ICIQ-UI scores, but no-significant differences between groups were also observed (83, 84). Higher adherence was observed in the group using the application combined with PFMT compared to PFMT alone in Araujo's study (83), whereas Sacomori *et al.* (84) reported a no significant difference between the groups.

- **Comparison 12 Teaching programme: addition of biofeedback (BF)**

Nine RCTs (five published manuscripts (47, 79-82) and four abstracts (85-88)) examined the efficacy of adding biofeedback to PFMT. Of these, three trials are not further described because no between-group statistical comparisons were presented (81, 85, 88). Comparison groups were similar with respect to the amount of supervision and intensity of training; they differed only in the addition of biofeedback (47, 80, 82, 86). Similarity treatment dosage was difficult to assess in the abstract by Ngai *et al*. (87) and treatments appeared to differ in the study by Fitz *et al.* (79). Four RCTs investigated **clinic-based** biofeedback using pressure perineometry (79, 80), ultrasound imaging (87) and electromyography (47, 80). Three trials included women with SUI or stress-predominant UI (47, 79, 80), while the abstract by Ngai *et al.* (87) did not specify the type of UI. Duration of treatment ranged from eight weeks (47, 80) to three months (79). Only one RCT evaluated **home-based** biofeedback using a Kegel-Q device (86) in women with SUI. The non-inferiority trial by Hagen *et al.* (82) investigated the addition of **both home-based and clinic-based electromyography biofeedback** compared to PFMT alone in 600 women with MUI and SUI.

No data were provided assessing self-reported cure. For improvement, three trials reported a non-significant benefit of adding clinic-based biofeedback, which was assessed using the ICIQ-UI (47) and Urogenital Distress Inventory (UDI) (87). With regard to home-based biofeedback, the abstract by Lee *et al.* (86) reported greater improvements in the biofeedback group for the Sandvik frequency and severity index. In the study by Hagen *et al.* (82) no-significant differences between the two groups were found for the ICIQ-UI and PGII.

For leakage episodes, two studies found no significant differences between the clinic-based biofeedback group and PFMT group (79, 87).

Pad and paper towel tests: Fitz *et al.* (79) reported a non-significant benefit of adding clinic-based biofeedback to PFMT based on pad-test measurements. Conversely, Özlü *et al*. (80) showed superior effects in pad test results in the two groups using biofeedback (electromyography or pressure biofeedback device) compared to PFMT alone. As for home-based biofeedback, Lee *et al.* (86) showed superior effects in pad test results when adding biofeedback, whereas a no significant difference was reported when categorising the pad test results as cured versus uncured.

Summary

Evidence synthesis

PFMT with regular (e.g., weekly) supervision is better than PFMT with little or no supervision. **(Level of evidence: 1)**

Supervised group PFMT (including verification of adequate PFM contraction) appears to provide similar benefits to individual PFMT. **(Level of evidence: 1)**

'Indirect' methods of PFMT (e.g., the 'Paula method', 'Sapsford' approach and hypopressive training) are no better than direct PFMT for treating UI. **(Level of evidence: 2)**

The combination of PFMT with other treatment modalities, such as motor learning, intra-vaginal resistance devices and adherence strategies, does not appear to provide additional benefits. **(Level of evidence: 2)**

There is conflicting evidence as to whether the combination of PFMT with abdominal or hip muscle training could increase its efficacy. **(Level of evidence: 4)**

The benefit of adding biofeedback to PFMT for improvement of UI symptoms and pad test results, in either home or clinic setting remains unclear. (**Level of evidence: 2**)

There was no statistically significant difference between groups undergoing in-clinic and home-based EMG biofeedback-assisted PFMT or non-biofeedback PFMT for SUI self-reported cure and improvement. **(Level of evidence: 1)**

Recommendations

Clinicians should offer and provide the most intensive health professional-led PFMT programme possible within service constraints. **(Grade of recommendation: A)**

Supervised individual or group PFMT with confirmation of adequate PFM contraction can be considered in postmenopausal women with SUI and MUI. **(Grade of recommendation: B New)**

Direct PFMT as opposed to indirect PFMT can be recommended **(Grade of recommendation: B New)**

There is no clear benefit for adding other modalities (i.e., motor learning, abdominal or hip muscle training, intra-vaginal resistance devices and adherence strategies) to PFMT, and therefore they cannot be routinely recommended. **(Grade of recommendation: B)**

There is no clear benefit for adding clinic- **(Grade of recommendation: B changed)** or home-based biofeedback (**Grade of recommendation: B) or both (Grade of recommendation: A New)** to a PFMT programme. However, biofeedback may be considered for sub-groups of women presenting an important PFM weakness or atrophy, or reduced proprioception.

No robust recommendation can be made about the type or specification of training (i.e., generic versus individualised exercises, submaximal versus near maximal contractions, daily versus three times per week, addition of upright exercise position).

Implications for research

Comparisons of PFMT approaches are, *de facto*, comparisons of two active treatments. It is therefore difficult to determine which approach is best unless (a) the differences in outcomes are large or (b) the RCTs are designed with sufficient sample sizes to detect small to moderate differences. Finding the best PFMT approach remains among the highest research priorities. Future studies should be sufficiently powered to detect clinically important differences or assess non-inferiority when a less costly intervention is compared to a gold standard.

Although, most new comparisons presently include few trials, they integrate new interventions such as posture rehabilitation, stabilisation exercises and general body exercises. These new comparisons will be added to our next chapter update.

Table 9. Summary of data on different PFMT programmes comparisons

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Araujo (2019) (83)	PFMT (16) vs. PFMT+App (17)	33	Women with predominant SUI	PFMT: Written PFM exercises. 8s hold/8s rest followed by 3 phasic PFM contractions, repeated 8x, for a total of 32 contractions. Performed twice a day (sitting, lying down or standing) for 3 months. PFMT+App: Same as PFMT (no vaginal probe) with the visual aids from the app. The app used an alarm reminder. A tool to improve adherence is presented in the manuscript.	Sign. changes in ICIQ-UI and QUID in both groups from baseline to 1,2,3 months of tx but no sign. difference btw groups. Adherence: Sign. difference in adherence btw the two groups at 2 months and 3 months in favour of the PFMT-App group.	1, 2 and 3 months of tx.	Randomisation and concealment adequate Assessor blinded Dropouts: PFMT 7/16 PFMT+App 5/17 Adverse events: not documented Dose: same PFMT programme Sample size calculation based on adherence.

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Bertotto (2017) (47)	PFMT (16) vs. PFMT + BF (17) vs. Control (no tx) (16)	49	Postmenopausal women with SUI	PFMT: Two 20-min sessions per week for a total of 8 sessions. PFMT in various positions combined with guided imagery. Home exercises performed twice a day on non-study training days. PFMT+BF: Same PFMT protocol but with BF (in-clinic EMG-BF). Same home exercises without BF. Control: No tx	ICIQ-UI QoL: Sign. improvement from baseline to post-tx in the intervention groups (both p<.0001), but not for the control group. Sign. difference btw the control group and the two intervention groups No sign. difference btw PFMT+BF and PFMT in post-tx.	Post-tx	Randomisation and concealment adequate Assessor blinded Dropouts: PFMT 1/16 PFMT+BF 1/17 Control 2/16 Adverse events: not documented Dose: same PFMT protocol in the intervention groups No sample size calculation provided
Chiu (2018) (71)	PFMT (24) vs. Abdo (23)	47	Women ≥ age 45 y with at least one episode of SUI or MUI per month	Before the exercise sessions started, oral instructions about the human anatomy of PFMs, physiology regarding the mechanism of continence and bladder hygiene were given to both groups. Abdo: Abdominal muscle exercises for 6 training sessions over 12 weeks – diaphragmatic breathing, PFM activation, tonic activation, muscle strengthening, functional expiratory patterns (e.g., blowing nose, coughing, etc.), impact activity. **also includes PFM exercises** PFMT: 2 exercise sessions – session 1 included basic PFM exercises combined with diaphragmatic breathing. Session 2 included the advanced application of PFM contractions during daily activities. The participants were asked to perform at least 10 repetitions of PFM contractions for 5-10 s, 3-5 times per day (30-50 contractions) for 12 weeks.	The ISI, 1-hour pad test, and 3-day voiding diary improved sign. after the interventions within each group (p<.017); no sign. difference was found btw the groups (all p>.05).	Post-tx	Randomisation adequate Concealment not reported Assessor not blinded Dropouts: PFMT 4/24 Abdo 3/23 Adverse events: No participant had any adverse effects during the study. Dose: not the same - Abdo had 6 sessions, PFMT only had 2 No sample size calculation provided

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
de Souza Abreu (2017) (75)	PFMT (20) vs. PFMT + Lumbopelvic (20)	40	Women with SUI (confirmed by cough-provocation test)	PFMT: Individual sessions of approx. 30 min each with a physiotherapist, 2x per week for 5 weeks (total of 10 sessions) + home exercises: same protocol of exercises daily, during the 5 weeks. PFMT+Lumbopelvic: Individual sessions of approx. 30 min twice a week for 5 weeks (total of 10 sessions). Same PFMT exercises as PFMT group + lumbopelvic stabilisation exercises (4 stages according to degree of complexity). Home exercises: same protocol of exercises, performed daily over the 5 weeks.	Sign. reduction in ISI from baseline to post-tx in both groups, but no sign. difference btw groups in post-tx (p=0.50). At 3-month follow up, PFMT+Lumbopelvic group presented sign. lower values compared to PFMT group (p<.006) Sign. reduction of both diurnal and nocturnal UI episodes (bladder diary) from baseline to post-tx in both groups. No sign. difference btw groups at post-tx (p>0.49). At 3-month follow up, PFMT+lumbopelvic group presented a sign. lower frequency of UI episodes compared to PFMT group (p<.001). Impression of improvement (PGI-I): nonsign. difference was found btw the two groups at post-tx (p=.18). At 3-month follow up, PFMT-lumbopelvic was superior to PFMT (p<0.001).	Post-tx and 3-month follow up	Randomisation and concealment adequate Assessor blinded Dropouts: PFMT 3/20 PFMT+Lumbopelvic 4/20 Adverse events: none reported Dose: same PFMT protocol
Dumoulin (2020) (69)	Individual PFMT (184) vs. Group PFMT (178) Non inferiority RCT	362	Women ≥60 years old with SUI or MUI ≥ 3 times/week, for ≥ 3 months	All women were taught to properly perform a PFM contraction using vaginal palpation. Individual PFMT: Weekly 1-h sessions supervised by a physiotherapist for 12 weeks, including 15 min of education (lifestyle intervention and PFM precontraction), 45 min of PFM exercises assisted by BF (strength, rapidity, endurance and coordination) and lower extremity strength and functional exercises (dance) btw PFM exercises. Home PFM exercises 5x per week. Group PFMT: Same as individual PFMT but conducted in a group of max. 8 patients. Women who reported difficulty with their exercises were offered short individual sessions with their physiotherapist to confirm correct PFM contractions. Home PFM exercises 5x per week.	Sign. reduction in leakage episode frequency (7-day bladder diary) in both groups from baseline to post-tx and 1-year follow up (p<.001). At 1 year (primary time point), the median percentage reduction UI episodes in individual PFMT was 70% vs. 74% in the group-based intervention (within the non-inferiority margin suggesting non meaningful difference btw groups). Both groups showed sign. improvement for all outcomes (micturition, nocturia, pad test 24-h, ICIQ-UI) from baseline to 1-y follow up, but no sign. differences were found btw groups.	Post-tx and 1-year follow up.	Randomisation and concealment adequate Assessor blinded Dropouts: Individual 19/184 Group 24/178 Adverse events: Individual PFMT: 6 reported vaginal spotting and 21 reported vaginal discomfort while using intravaginal BF Group PFMT: 5 reported vaginal discomfort Dose: Same PFMT protocol

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Figueiredo (2020) (70)	Individual PFMT (30) vs. Individual PFMT to group training (IPGT) (30) vs. Group training only (30)	90	Women with SUI	All groups had a 30-min session once per week for 12 weeks. All groups were educated about PFM and proper contractions. The same exercise protocol as they performed with the physiotherapist, was performed at home, every day, over the 12 weeks of supervised training. Individual PFMT: 12 individual sessions with a physiotherapist (with vaginal palpation for the first 4 sessions). IPGT: 4 individual sessions (with vaginal palpation for first 4 sessions) followed by 8 group sessions. Group training: 12 group sessions	The severity measured with the KHQ improved in all 3 groups (p<.001) from baseline to post-tx. No sign. difference btw groups (p=.56). The benefits of the intervention were maintained 3 and 6 months after the end of the supervised training (p<.001) (non-sign. difference btw groups). The IPGT group had a sign. Improvement. in PFM function when compared to the other groups post-tx (P < .001). Bladder diary assessed, but statistics not provided for within- or btw-group comparisons.	Post-tx, 3 and 6-month follow up	Randomisation and concealment adequate Assessor not blinded Dropouts: Individual 12/30 IPGT 6/30 Group 12/30 (all dropouts were replaced) Adverse events: none mentioned Dose: same
Fitz (2017) (79)	PFMT (37) vs. PFMT +BF (35)	72	Women with predominant SUI symptoms ≥2g leakage (pad test) and with capability to contract the PFM properly	PFMT: 24 outpatient sessions of PFM exercises without BF (40-min sessions with 10 repetitions each, 2x per week). Exercises were performed in the supine position (1st month), sitting (2nd month) and standing (3rd month) with a physiotherapist + home PFM exercises for 3 months. Home programme: 3 sets of 10 repetitions daily for 3 months. PFMT +BF: 24 outpatient/in clinic sessions of PFMT using BF (40-min sessions with 10 repetitions each, twice a week). Exercises were performed in the supine position with BF. Home exercise program: 3 sets of 10 repetitions daily for 3 months. The positions in which the exercises were performed were progressive. The protocol was personalised and based on initial evaluation of PERFECT. Each patient was evaluated for adjustment and progression on a monthly basis	Sign. changes in the number of leakage episodes (bladder diary) from baseline to post-tx and follow ups. No sign. difference btw groups. Sign. changes in severity of SUI (20-min pad test) (g) from baseline to post-tx and follow ups. No sign. difference btw groups. Cure of SUI (<2g on 20-min pad test): Sign. difference btw groups at post-tx (p=0.018), but not at 6-month follow up (p=0.358) Subjective cure: No sign. difference btw groups at post-tx or 6-month follow up.	Post-tx as well as 3- and 6-month follow up	Randomisation and concealment adequate Assessor not blinded Dropouts: PFMT+BF 10/35 PFMT 13/37 Adverse events: none documented Dose: Not exactly comparable. Same home programme and exercises in outpatient sessions, but BF group did exercises in supine position only and PFMT group progressed from supine -> sitting -> standing (during outpatient sessions). + Each patient had their own personalised programme based on the results of the PERFECT score.

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Fitz (2019) (67) This article was included in the previous ICI as abstract, but the article revealed new findings	PFMTsup (34) vs. PFMT (35)	69	Women with a predominance of SUI and ≥2g of leakage in pad test who are able to properly contract their PFMs.	PFMTsup: 2 supervised sessions per week for a total of 24 sessions. 3 sets of 30 contractions followed by 3 fast-twitch contractions PFMT: Same exercise protocol, monthly appointment for exercise adjustment, including one set of PFM exercises under supervision (total of 3).	Objective cure based on the 20-min pad test (<2g of leakage): Cure was superior in the supervised group (62%, n=21/34) compared to the unsupervised group (28%, n=10/35) (p=.011) Sign. improvement in both groups for the 20-min pad test from baseline to post-tx. Higher improvements were found in the supervised group compared to the unsupervised group (p=.031). Sign. improvement in both groups in the mean number of leakages (7-day bladder diary) from baseline to post-tx. No sign. difference btw groups in post-tx (p=0.703) Compliance rate and frequency of home exercises: Sign. difference btw groups in 1st month (p=0.015), but no sign. difference btw groups in 2nd and 3rd months (p≥0.067). Satisfaction: No sign. difference btw groups.	Post-tx	Randomisation and concealment adequate Assessor not blinded Dropouts: PFMTsup 6/34 PFMT 7/35 Adverse events: Not documented Dose: same home PFMT programme

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Hagen (2020) (82)	PFMT (300) vs. PFMT+BF (300)	600	Women with SUI or MUI	Both groups had 6 appointments with a continence therapist over 16 weeks PFMT: Women received supervised PFMT (60 min for the first session, then 30 min for subsequent sessions), and a home PFMT programme (3 sets of exercises daily, recorded in an exercise diary). Behaviour change techniques, bladder and bowel management information and lifestyle advice were provided as necessary. PFMT+BF: supervised PFMT as in the PFMT group and a home PFMT program. The tx incorporated EMG-BF during clinic appointments and at home.	ICIQ-UI (at 6, 12 and 24 months post-tx): No sign. difference btw groups at 6 months (mean difference 0.39, 95%CI -0.33 to 1.12), 12 months (0.57, 95%CI -0.17 to 1.31) or 24 months (-0.09, 95%CI -0.92 to 0.75). No sign. difference btw groups in cure rate (based on 2 questions of the ICIQ-UI), improvement (reduction >3 points on the ICIQ-UI) or PGII at 24-month post-tx. Exercise adherence: Proportion exercising at least once per week was 52% in the PFMT+BF group and 46.3% in the PFMT group. PFM strength: No sign. difference btw groups at 6 months.	6, 12, and 24 months post-tx	Randomisation and concealment adequate Assessor blinded (self-reported measure non-blinded) Dropouts (at 24-months post-tx): PFMT 62/300 PFMT+BF 70/300 Adverse events: Of the 48 participants who had non-serious adverse events, only 23 were possibly related to tx: PFMT 2 PFMT+BF 21 Dose: same tx regimen

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Jose-Vaz (2020) (72)	PFMT (45) vs. Hypopressive (45)	90	Women with SUI	Both groups underwent 24 sessions over 12 weeks Hypopressive: Abdominal hypopressive techniques were split into 3 phases of 4 weeks each– Phase 1: 3x8 reps in different postures (ex: lying supine with legs bent, cat position etc.) Phase 2: 3x10 reps of various exercises – lying with alternating leg flexion, etc. Phase 3: 3x12 reps in different postures ex: kneeling, etc. PFMT: 3x8-12 PFM contractions per session. Also 3 phases of exercises: all phases included 3 exercises; 2 lying, one sitting - Phase 1: 3x8 reps lasting 6 sec + 3 fast contractions in a row Phase 2: 3x10 reps lasting 6 sec + 3 extra contractions Phase 3: 3x12 reps lasting 6 sec + 4 extra contractions	Both groups reduced their urinary leakage episodes (7-day bladder diary) from baseline to post-tx. PFMT group showed higher changes compared to hypopressive group (p<.001, mean diff. -1.27, IC95% −1.92 to −0.62). ICIQ-UI sign. improved in both groups from baseline to post-tx. The PFMT group showed greater changes compared to the hypopressive group (p<.001, mean diff. -4.7, IC95% −6.90 to −2.50). Manometry also presented improvement after tx for both groups with a mean difference of 11 (95% CI 6.33-15.67) in favour of PFMT.	Post-tx	Randomisation and concealment adequate Assessor blinded Dropouts: PFMT 8/45 Hypopressive 9/45 Adverse events: none mentioned Dose: same for both groups
Kucukkaya (2020) (76)	PFMT (32) vs. PFMT+transverse (32)	64	Women with SUI	PFMT: Maximal PFM contractions performed sitting or in the supine position (3 sets of 10 contractions, 3x/day) according to Sut et al. PFMT + transverse: Addition of abdominal training exercises according to Jung et al. For both groups: Exercises were performed at home individually for 8 weeks, with prior teaching at clinic, and distribution of a brochure explaining the exercises and healthy lifestyle behaviours. Diaries were completed every day (3 times a day). Weekly follow-up phone calls were made to participants to maintain motivation.	The UDI-6 score sign. improved in both groups from baseline to post-tx (p<.001). The changes in the PMFT+transverse group were sign. higher than the PFMT group from baseline to 4 weeks (p<.001) and from baseline to post-tx (p=.047) The percentage of negative cough stress tests at week 4 was sign. higher for PFMT+transverse than PFMT(p<.001). At post-tx, the stress test was negative in all participants in both groups.	During tx (on week 4 of the programme) and post-tx (after 8 weeks of tx)	Randomisation adequate Concealment not reported Blinding of assessor not reported No dropouts Adverse events: not documented Dose: Limited information to ascertain that the PFMT protocol is the same in both groups given that the references are different.

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Lee (2018) (86) Abstract	PFMT (45) vs. PFMT + BF (45)	90	Women with SUI	PFMT: 12-week exercise protocol (repetitions of fast and sustained contractions) performed at home twice a day for 9 minutes. PFMT+BF: Same 12-week exercise protocol as PFMT group but performed with the KegelQ device (BF). Exercises performed twice a day.	Objective cure rate based on the pad test: No sign. difference btw groups post-tx: PFMT (48.9%) vs PFMT+BF (64.4%) p=.136 Sign. more improvement from baseline to post-tx was found for PFMT+BF compared to PFMT: I-QoL (p=.026), Sandvik frequency and severity index (p≤.033), Change of 1hr pad amount (p=.038) and PFM strength (manometry) (p≤.006).	Post-tx	Randomisation adequate Concealment: no details provided Assessor blinded Dropouts: PFMT 7/45 PFMT+BF 7/45 Adverse events: none reported Dose: Same PFMT protocol
Luginbuehl (2021) (74)	PFMT (48) vs. PFMT + involuntary reflexive training (48)	96	Women with SUI or MUI with stress predominance	Both interventions lasted 16 weeks and included 9 physiotherapy sessions and 78 home training sessions PFMT: Voluntary PFM contractions performed in a slow to moderate to fast speed of movement PFMT+involuntary reflexive training: Voluntary pelvic floor muscle contractions performed explosively as well as involuntary PFM contractions from exercises such as running on the spot, counter-movement jumps, and drop jumps. These exercises result in an explosive, reactive, and reflexive speed of movement in terms of power training of PFMs.	ICIQ-UI: Sign. decrease from baseline to post-tx in both groups. No sign. difference btw groups. 20-min pad test: Sign. difference from baseline to post-tx in both groups. No sign. differences btw the groups.	Post-tx (after 16 weeks of tx)	Randomisation and concealment adequate Assessor blinded (the authors mentioned that patients were also blinded but it seems unlikely) Dropouts: PFMT 5/48 PFMT + involuntary reflexive training 7/48 Adverse events: none mentioned Dose: comparable

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Marques (2020) (77) *was included in ICI 2015 as an abstract	PFMT (23) vs. PFMT+hip (24)	47	Women with SUI	PFMT: At each session, PFM contractions were performed: 10 x 5 s, 15 x 3 s, 20 x 2 s, 20 x 1 s (same amount of rest time), and 5 maximal contractions while coughing (1-min interval). Exercise position progressed (supine, sitting, standing) for 20 sessions over 10 weeks. PFMT+ hip: same PFMT programme + 20 min of hip strengthening exercises (adductors, gluteus maximus and gluteus medius)	Mean frequency of urinary leakage (3-day diary): Sign. changes from baseline to post-tx in both groups, but no sign. difference btw groups (p=0.81). Daily frequency of urine leakage (monitoring form): Sign. changes from baseline to post-tx. The author reported a group effect (p<.001) (and concluded in the superiority of PFMT+hip) but a nonsign. group x time interaction (p=.880) ICIQ-UI severity and QoL: Sign. changes in both groups from baseline to post-tx, but no sign. difference btw groups (p>.12). QoL (KHQ): Sign. changes in both groups from baseline to post-tx, but no sign. difference btw groups (p>.39).	Post-tx (after 10 weeks of tx)	Randomisation and concealment adequate Assessor blinded Dropouts: PFMT 2/23 PFMT+hip 2/24 Intention-to-treat analysis not performed Adverse events: none Dose: same PFMT regimen for both groups

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Mateus-Vasconcelos (2018) (68)	PFMTsup (34) vs. PFMT+ posterior pelvic tilt (34) vs. EStim (33) vs. PFMT w/o sup (33)	134	Women with PFM function graded at 0 or 1 using the Modified Oxford Scale (MOS)	Duration for all groups: 8 weeks. Everyone was treated by the same physical therapist. PFMTsup: Supervised PFMT with palpation. Physical therapist performed by digital vaginal palpation to provide proprioceptive stimulation and to examine the PFM contractions (3 sets of 10 contractions of 6 s each and a rest period of 6 s btw each contraction). At the end of each set, 6 quick contractions were performed. No training at home. Tx once per week. PFMT + posterior pelvic tilt: Protocol same as PFMTsup with a posterior pelvic tilt movement during the PFM contractions. No training at home. Tx once per week. EStim: Intravaginal EStim in the supine position with lower limbs extended. Current was a symmetrical biphasic, rectangular pulse. Stimulation parameters: frequency 50 Hz, pulse time 200 ms, contraction time 5 s, relaxation time 10 s and current intensity defined by the motor threshold and adjusted according to occurrence of accommodation. Total ES time: 20 min. Women were instructed not to voluntarily contract their PFM while they were receiving the ES. No training at home. Tx once per week. PFMT w/o sup: PFMT without supervision. Instructed once to do daily PFM contractions at home (3 sets of 10 contractions held for 6 s with 6 s rest btw contractions) followed by 6 quick contractions. No supervision other than instructions on day 1.	ICIQ-UI: Sign. improvement in all groups from baseline to post-tx: PFMTsup (14.55±4.94 to5.79±5.58, mean difference 8.76, 95%CI 5.80 to 11.71; p<.0001) PFMT+ posterior pelvic tilt (14.24±5.35 to 8.85±6.93, mean difference 5.39, 95%CI 2.43 to 8.35; p=.0004) ES (14.12±5.59, to 9.42±7.09, mean difference 4.70 95%CI: 1.77 to 7.65; p=.002) PFMT w/o sup (14.15±6.25 to 10.52±7.37, mean difference 3.64, 95%CI 0.68 to 6.59; p=.016) As for btw-group comparisons, sign. differences were found only btw the following groups: PFMTsup > EStim (p=0.02) PFMTsup > PFMT+ posterior pelvic tilt (p=0.04) PFMTsup > PFMTw/o sup (p=0.01)	Post-tx (after the 8 weeks of tx)	Randomisation and concealment adequate Non-blinded for self-reported outcomes Dropouts: PFMTsup 1/34 PFMT+ posterior pelvic tilt 1/34 ES 0/33 PFMT w/o sup 0/33 Adverse events: None reported

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Navarro-Brazález (2020) (73)	PFMT (33) vs. Hypopressive (33) vs. PFMT+Hypopressive (33)	99	Women 18-70 with stress or mixed UI, AI, and/or diagnosis of stage 1 or 2 POP	All programmes lasted 8 weeks with 2 visits per week. All groups were given the same educational component, and instructions about lifestyle interventions and the knack manoeuvre. PFMT: PFM exercises based on components of the PERFECT scheme. At-home exercises: 1-3 sets of 5-10 reps of PFM exercises in supine, sitting or standing position, 1-3 times per day Hypopressive: Hypopressive abdominal exercises based on Caufriez's method. 5-10 hypopressive exercises performed each session. Participants instructed not to voluntarily contract their PFMs nor their abdominal muscles during each exercise. Women given at-home hypopressive exercises to perform 1-3 times per day. PFMT+hypopressive: same intervention as PFMT and hypopressive groups. Women performed at-home exercises prescribed to both groups, alternating btw days.	Sign. decreases in the PFDI-20, the UDI subscale, and the PFIQ-7 were found in all groups from baseline to post-tx and follow ups. There were no sign. differences btw groups. The only sign. difference btw groups observed was in favour of the PFMT-hypopressive compared to the PFMT group at the follow-up assessment (p=.0248).	Post-tx, and at 3, 6 and 12 months follow up	Randomisation and concealment adequate Assessor blinded (self-reported measure non-blinded) Dropouts: PFMT 1/33 Hypopressive 2/33 PFMT+hypopressive 2/33 (due to pregnancy and not completing follow-up) Adverse events: PFMT+Hypopressive: 1 back pain exacerbation Hypopressive: pain during exercises Dose: same
Ngai (2015) (87) Abstract	PFMT (17) vs. PFMT+BF (US) (16)	33	Women with UI ≥ 3 months	PFMT monitored with palpation PFMT+BF: PFMT taught with transperineal ultrasound	Sign. improvements were found in incontinence severity, UI episodes/week, UDI, and self-rating improvement in both groups. No sign. differences btw groups.	Post-tx and 3-month follow up	Randomisation adequate Concealment and blinding of assessor: no details provided Dropouts: PFMT 6/17 PFMT+BF 0/16 Adverse events: Not documented Dose: unable to judge

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Orhan (2019) (78)	PFMT (24) vs. PFMT+resistance (24)	48	Women with SUI predominance.	All patients had 12 weeks of tx with biweekly visits. All received information sheet about PFMT + exercise diary PFMT: Standardised PFMT programme included one set of 10 fast and 10 sustained voluntary contractions. The number of repetitions was increased after each supervised session. Exercises in different positions: supine, sitting, standing and semi-squatting PFMT+resistance: Same as PFMT group + resistance exercises provided by pulling an intra-vaginal tampon. 2 sets of 15 repetitions of vaginal tampon exercises were performed 5 days per week (2 days with physio and 3 days by themselves).	No sign. difference in self-reported improvement (4-item scale; worse, same, better, cured) btw groups at any time point (p≥.62). No sign. difference btw groups in pad test (categorized as no UI/mild/moderate/severe) at any time point. Sign. changes in ISI score from baseline to 4,8,12 weeks of tx in both groups (p<.05), but no sign. difference btw groups at any time point (p≥.26). Sign. changes in UI episodes (bladder diary) from baseline to 8 and 12 weeks of tx in both groups (p<.05), but no sign. difference btw groups at any time point (p≥0.55). Tx adherence (VAS): No sign. difference btw groups at any time point (p>0.05)	4, 8 and 12 weeks of tx	Randomisation and concealment adequate Assessor blinded Dropouts: PFMT 3/24 PFMT+Resistance4/24 Adverse events: not documented Dose: same PFMT programme in both groups
Özengin (2015) (88) (Abstract in English and article in Turkish)	PFMT (14) vs. PFMT + BF (17)	31	Obese women with UI	Limited info provided PFMT: home programme for 8 weeks PFMT+BF: 3x per week for 8 weeks.	UI (pad test): Sign. decrease from baseline to post-tx for PFMT+BF group (p<.001) No stats provided for the PFMT group or btw-group comparison.	Baseline and post-tx	Randomisation & concealment: no details provided Blinding of assessor: no details Dropouts: Not documented Adverse events: not documented Dose: no details provided

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Özlü (2017) (80)	PFMT (18) vs. PFMT+PBF (intravaginal pressure biofeedback) (17) vs. PFMT+EMG-BF (perineal electromyographic biofeedback) (18)	53	Women with SUI (confirmed with urodynamic testing) and PFM strength ≥3/5	All patients visited the physician to be familiarised with the location of the PFM and pelvic anatomy + exercise training was shown in practice at least once. PFMT: PFM home exercises for 8 weeks - Week 1-2: 2 sets of 5 repetitions of 5s contractions and 10s relaxation. Performed daily. - Week 3-4: 2 sets of 10 repetitions of 10s contractions and 20s relaxation. Performed daily. - Week 5-8: 3 sets of 10 repetitions of 10s contractions and 20s relaxation in 3 different positions (supine, sitting, standing). PFMT+PBF: PFM home exercises (same as PFMT group) + hospital-supervised intravaginal PBF-assisted PFM exercise programme (3x per week for 8 weeks) PFMT-EMG-BF: PFM home exercises (same as PFMT group) + hospital-supervised perineal EMG-BF-assisted PFM exercise programme (3x per week for 8 weeks) with surface electrodes positioned at perianal region.	Severity of UI (1h pad-test): Sign. changes from baseline to 4 and 8 weeks of tx for all groups. Sign. difference in all groups compared to baseline at all times (week 4 and 8): PFMT (pre: 11.47±11.57, 4 weeks: 8.52±8.07, 8 weeks: 7.70±7.33, p<0.05), PFMT+PBF (pre: 11.02±6.96, 4 weeks: 4.55±4.85, 8 weeks: 3.85±4.74, p<0.05) and PFMT+EMG-BF (pre: 11.02±12.74, 4 weeks: 5.11±8.59, 8 weeks: 3.97±6.59, p<0.05). Sign. difference btw groups at 8 weeks (p=0.031), but not at 4 weeks (p=0.092). At 8 weeks: PFMT+PBF > PFMT (p=.012), PFMT+EMG-BF > PFMT (p=.013) and PFMT+PBF = PFMT+EMG-BF (p=.919) Cure (pad test <2g) and improvement (≥50% improvement in pad weight) rate: Sign. difference btw groups at 4 and 8 weeks (p=.033) (PFMT+PBF and PFMT+EMG-BF > PFMT) Tx satisfaction: No sign. difference btw groups at 4 weeks (p=.062). Sign. difference btw groups at 8 weeks (p=.033) (PFMT+PBF and PFMT+EMG-BF > PFMT)	Weeks 4 and 8 of tx	Randomisation adequate No information on concealment Assessor blinded Dropouts: PFMT 1/18 PFMT+PBF 0/17 PFMT+EMG-BF 1/18 Adverse events: None Dose: Similar (same home exercise programme for all groups and same exercises during outpatient sessions for PBF and EMG-BF groups)

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Rizvi (2018) (81)	BT (50) vs. PFMT (50) vs. PFMT+BF (50)	150	Women with OAB	Tx duration was 12 weeks for the 3 groups BT: urge suppression techniques, self-monitoring (bladder or voiding diaries), lifestyle modifications (i.e., eliminating bladder irritants from diet, managing fluid intake (with bladder diary), weight control, bowel regulation, high fibre diet, smoking cessation and time voiding), and delayed voiding techniques. Educational leaflets about good bladder habits. Programme provided by physicians AND incontinence nurse. PFMT: At-home PFM exercises without any devices, according to PERFECT scheme. 5 submaximal to maximal contractions held for 6 s as well as 10 fast contractions/session. Exercises are done 3x per day, either lying, standing, or sitting. Assessed for improvement during subsequent visits. PFMT+BF: intravaginal electromyogram probe used 2x per week with physiotherapist. Contract/relax following audio-visual signals. PERFECT to assess muscles pre- and post-sessions.	UDI-6: Sign. improvement in all groups from baseline to post-tx: BT (8.38±4.3 to 4.77±5.5, mean difference 3.61±7.4 95%CI: 1.43 to 5.798; p=.002) PFMT (9.10±6.2 to 5.44±7.2, mean difference 3.66±9.1 95%CI: 0.935 to 6.385, p=.010) PFMT+BT (7.16±4.7 to 4.46±6.2, mean difference 2.70±7.7; 95%CI: 0.516 to 4.884, p=.016). IIQ-SF7: Sign. improvement in BT (8.30±5.7 to 5.34±5.8, mean difference 2.95±7.5, 95%CI 0.769 to 5.146; p=.009) and PFMT+BF (9.24±5.4 to 4.52±7.3, mean difference 4.72±9.8, 95%CI 1.918 to 7.522; p=.001), but no sign. difference in PFMT (8.92±6.9 to 6.34±6.5, mean difference 2.58±9.1; 95%CI -0.017 to 5.177; p=.051). BT is the only group with a sign. decrease in urinary frequency from baseline to post-tx. All groups had a sign. difference in leak accidents and urgency scores. Btw-group comparisons not reported for any outcome.	Post-tx (after 12 weeks of tx)	Randomisation and concealment adequate Non-blinded (self-reported outcomes) Dropouts: BT 3/50 (due to no effects of tx) Adverse events: PFMT+BF 1 (Unspecified pelvic pain during intervention period. No medical attention needed but led to discontinuation of tx. Case was investigated: interstitial cystitis, which was treated.) Dose: PFMT differed btw the two groups.

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Sacomori (2015) (84)	PFMT (43) vs. PFMT+ adherence (43)	86	Women with SUI, UUI or MUI with mini-mental score >24	PFMT: 3 individual sessions with a physiotherapist including PFMT, instructions on how to deal with UI (e.g. knack), and instructions to perform PFMT every day at home. PFMT+ adherence: Same PFMT combined with strategies to promote self-efficacy and adherence, including a structured discussion on accomplishments and goals, a 9-minute video with testimonials, and a reminder.	Adherence (questionnaire and diary): No sign. difference btw groups at 15, 30 or 90 days of tx for adherence score, duration of exercises, number of repetitions or number of exercising days/week. ICIQ-UI: Sign. changes from baseline to day 15, 30 and 90 for both groups. Sign. difference btw groups at day 30 (p=.035) in favour of the PFMT+adherence group, but no sign. difference btw groups at day 15 and day 90. Self-efficacy: No. sign. difference btw groups.	15, 30 and 90 days of tx.	Randomisation adequate No concealment Assessor not blinded Dropouts : PFMT 7/43 PFMT+adherence 7/43 Dose : same PFMT protocol for both groups
Wilson Edwards (2016) (85) Abstract	PFMT (6) vs. PFMT+BFpericoach (4)	22 (ongoing) Partial data available	Women with SUI and MUI (with stress predominance)	Limited details provided. All patients are trained to perform PFM exercises as per standard clinic practice. PFMT+BF Pericoach: same tx protocol with the peri Coach device.	Only descriptive results presented (no statistical analysis performed) Both groups improved on the 24-h pad test, number of pads per day, leakage episodes (diary), and ICIQ-UI at 4-weeks of tx.	Week 4 of tx	Randomisation and concealment: No details Assessor blinding: not reported Dropouts: No details Adverse events: not documented Dose: no details

Abbreviations: AI: anal incontinence; BF: biofeedback; BT: bladder training; btw: between; dx: diagnosis; EMG-BF: electromyographic biofeedback; eval: evaluation; ICIQ-UI: International Consultation on Incontinence Questionnaire - Urinary Incontinence; IIQ-SF7: Incontinence Impact Questionnaire – Short Form 7; ISI: Incontinence Severity Index; KHQ: King's Health Questionnaire; MUI: mixed urinary incontinence; nonsign.: nonsignificant; OAB: overactive bladder; OAB-Q: Overactive Bladder Questionnaire; PBF: intravaginal pressure biofeedback; PFDI-20: Pelvic Floor Distress Inventory-20; PFIQ-7: Pelvic Floor Impact Questionnaire-7; PFM: pelvic floor muscles; PFMT: pelvic floor muscle training; PFMTsup: supervised pelvic floor muscle training; PGI-I: Patient Global Impression of Improvement; POP: pelvic organ prolapse; QoL: Quality of Life; QoL (KHQ): Quality of Life (King's Health Questionnaire); QUID: Questionnaire for Urinary Incontinence Diagnosis, sign.: significant(ly), SUI: stress urinary incontinence, sup: supervision, Tx: treatment, UDI-6: Urogenital Distress Inventory Short Form-6; UDI: Urogenital Distress Inventory; UI: urinary incontinence

Table 10. Studies comparing PFMT to another treatment included in previous ICI reviews and the current update (7th ICI)

	Studies included in previous ICI reviews	New studies identified in this update (7th ICI)
PFMT vs VC (section III)	14	0
PFMT vs EStim	10	1
PFMT vs BT	4	2
PFMT vs drug therapy	9	1
PFMT vs surgery	2	1
PFMT vs continence pessary	1	0

Abbreviations: PFMT: pelvic floor muscle training; VC: vaginal cone; EStim: electrical stimulation; BT: bladder training

2.3.3. Is PFMT better than other treatments?

Trials comparing PFMT to another stand-alone intervention such as vaginal cones (VC), bladder training (BT), drug therapy, surgery, and continence pessaries are included. As shown in Table 10, previous ICI reviews included a total of 40 RCTs. Our search revealed four new studies comparing PFMT to EStim (68), BT (81, 90), drug therapy (81), and surgery (91). Characteristics of these studies are presented in Table 11 and Table 9 (some studies had more than two arms and assessed other treatment comparisons).

Quality of data

Randomisation and adequate allocation concealment were reported for three RCTs (68, 81, 90). In the study by Bergman *et al.* (91), randomisation was adequate but group allocation was not concealed. The four studies employed self-reported questionnaires and the participants were not blinded to group assignment (68, 81, 90, 91). Azuri *et al.*'s study (90), used a bladder diary and indicated that the assessor was blinded to treatment allocation. Sample sizes ranged from 70 to 164 women and involved 33 to 50 participants per study arm. Very low dropout rates were reported in three studies: Bergman *et al.* (91) had no dropouts, Mateus-Vasconcelos *et al.* (68) reported only one dropout out of 134 participants, and Rizvi *et al.* (81) had three dropouts in the BT group out of 150 participants. Azuri *et al.* (90) reported higher dropout rates, which could be explained by the four-year follow up period. The dropout rate was the highest in the group receiving Tolterodine (42%; n=18/42), but lower in the BT, PFMT and combined treatment groups (range 14%; n=6/41 – 27%; n=11/40).

Results

i. **PFMT versus VC:** *No further evidence available.*
ii. **PFMT versus EStim:** *In the study by Mateus-Vasconcelos et al. (68), women with weak PFM (grade of 0 and 1 on the modified Oxford scale) were randomised into four groups: 1) Supervised PFMT (with palpation); 2) PFMT without supervision (verbal instruction); 3) PFMT with supervision and posterior pelvic tilt movements; and 4) Intra-vaginal EStim. Significant improvements in ICIQ-IU were found in all groups from baseline to eight weeks post-treatment. However, EStim was found to be less effective than supervised PFMT.* **Note:** *women receiving EStim were instructed not to voluntarily contract their PFM.*
iii. **PFMT versus BT:** *The study by Azuri et al. (90) is the four-year follow-up of Kafri et al. (92), which examined the effects of PFMT alone and BT alone using a four-arm design. Findings from the follow-up study agree with the original study. Significant improvements were observed in all groups on all outcomes (i.e., cure rate, number of voids/24-hour, incontinence episodes per week and I-QOL score), but no significant differences between groups were found. In the three-arm study by Rizvi et al. (81), women with an overactive bladder were randomised to BT, PFMT or PFMT plus BT. Significant improvements in the UDI-6 and the Incontinence Impact Questionnaire-7 (IIQ-7) were found in all groups. However, between-group comparisons were not reported. Only the BT group showed a significant decrease in urinary frequency (collected with a bladder diary) from baseline to post-treatment, which was not observed in the other groups.*
iv. **PFMT versus drug therapy:** *Our updated search included a single RCT (90) comparing the efficacy of PFMT to tolterodine using a four-arm design in women with UUI. This study is the four-year follow-up of Kafri et al. (92), included in the previous ICI edition. Findings of the newly added study agree with the original study as significant improvements were observed in all groups on all outcomes (i.e., cure rates, number of voids/24-hour and incontinence episodes per week), but no significant differences were found between groups.*
v. **PFMT versus surgery:** *One trial investigated the effects of surgery-perineorrhaphy with distal posterior colporrhaphy compared to PFMT in women who had suffered a second degree perineal injury and various pelvic floor disorders (91)lored","hb. type":"feature"}}. Findings showed superior effects in the surgery group compared to the PFMT group for patient perceived improvement (PGI-I) as well as for the Pelvic Floor Disability Index (PFDI) and Pelvic Floor Impact Questionnaire-7 (PFIQ-7) total scores and subscales. It should however be highlighted that PFMT included only one to three visits (93).*
vi. **PFMT versus continence pessary:** *No further evidence available*

Summary

VC appear to have similar effects or are inferior to PFMT. **(Level of evidence: 1)** However, VC treatment may be inappropriate in certain cases as some women are unable to use them and because of the potential side effects as reported in four RCTs (i.e., pain, vaginitis, bleeding and a sense of unpleasantness or inconvenience)**.**

EStim had inferior effects for cure rate and improvement compared to PFMT in women with UI according to previous pooled data, as well as to the newly added trial in women with weak PFMs. **(Level of evidence: 1)**

PFMT is a superior treatment to BT for women with SUI **(Level of evidence: 2).** There is no clear evidence supporting a difference in efficacy between PFMT and BT in women with UUI and MUI. **(Level of evidence: 2)**

PFMT is more beneficial than drug therapy for UI. **(Level of evidence: 2)**

Surgery appears to yield superior effects in patient's perceived improvements, incontinence severity, and in other pelvic floor disorder symptoms. **(Level of evidence: 2)**

Data suggest some benefits of PFMT over a continence pessary alone. **(Level of evidence: 2)**

Recommendations

PFMT and VC both appear to be effective as conservative therapies for SUI, although PFMT can be favored because a subset of women is unable to use VC and there are side effects associated with their use. **(Grade of recommendation: B)**

VC with supervised training sessions by a trained health professional can be offered to women with SUI who can and are prepared to use them. **(Grade of recommendation: B)**

PFMT should be preferentially offered over EStim as first line conservative therapy for women with SUI, UUI and MUI. **(Grade of recommendation: A New)**

PFMT can be preferentially offered over BT alone, as a first line conservative therapy for women with SUI, UUI and MUI. **(Grade of Recommendation: B)**

Oxybutynin cannot be recommended over PFMT as a first line therapy in women with UUI and MUI. **(Grade of recommendation: B)**

PFMT can be offered over pharmacotherapy because drug therapy results in more adverse effects and a higher dropout rate. **(Grade of recommendation: B)**

PFMT can be offered as the first line therapy prior to surgical intervention because it is less invasive. Surgery is more effective than PFMT, but the potential benefits should be weighed against the potential adverse events and cost. **(Grade of recommendation: B)**

PFMT and continence pessaries showed significant benefits for women with UI and therefore can be recommended. **(Grade of recommendation: B)**

Table 11. Summary of data on PFMT vs other treatments

Author, year	Comparator	N	Study Population	Modalitity details or parameters	Outcomes/Results	Follow-up	Notes
Azuri (2017) (90) Included in the ICI edition as an abstract in 2013.	DT (42) vs. BT (41) vs. PFMT (40) vs. BT+PFMT+advice (41)	164	Women aged 45-75 who experienced at least 3 UUI episodes per week	DT: Tolterodine SR 4 mg BT, PFMT, BT+PFMT+advice: 4 sessions once every 3 weeks for 3 months BT: education, increasing intervals between voids and positive reinforcement PFMT: contractions in different positions (3 sets of 8–12 slow maximal contractions sustained for 6–8 s) at each session. Daily home-based programme Advice: behavioural advice (bowel education, fluid intake, posture, etc.)	All outcome measures (number of voids/24h, incontinence episodes/week and I-QOL score) sign. improved from baseline to follow up in the four groups (p<.05) No sign. differences were found btw the 4 groups in the number of voids/24h (p=.635), incontinence episodes/week (p=.206) and I-QOL score (p=.354) Cure rates were similar at follow up in the 4 groups (p=.616)	4-year follow-up	Randomisation and concealment adequate Assessor blinded Adverse events: not documented Dropouts: DT 18/42 BT 6/41 PFMT 11/40 BT+PFMT+advice 9/41 Low adherence to the tx and contamination: At follow up, only 14 patients (11.6%) had used DT (DT 7, BT 6, PFMT 0 and BT+PFMT+advice 1) 13 women (10.8%) had practiced PFMT (DT 4, BT 3, PFMT 3, and BT+PFMT+advice 4)

Author, year	Comparator	N	Study Population	Modalitity details or parameters	Outcomes/Results	Follow-up	Notes
Bergman, Westergren Söderberg (2020) (91)	Sx (35) vs. PFMT (35)	70	Primiparous or multiparous women with symptoms related to a poorly healed second-degree perineal injury	Sx: perineorrhaphy w/ distal posterior colporrhaphy PFMT: Patients received initial eval of PFM strength, then were educated about PFM function and taught how to perform proper PFM contractions – BF or EStim used when needed. They were given a PFM exercise program and scheduled for 1-3 follow-up visits.	PGI-I: Sign. more women reported being very much better or much better in the Sx group 26/35 (71%) vs. the PFMT group 4/35 (11%); p<0.01. Regarding within-group changes, all questionnaire scores (PFDI total score and subscales (POPDI-6, CRADI-8, UDI-6) as well as PFIQ total score and subscales (UIQ-7, CRAIQ-7 and POPIQ-7)) among the patients in the Sx group sign. improved (p<.003), whereas the PFMT group improved only in the POPDI-6 subscale (p=.02). As for the btw-group differences, changes from baseline to follow up were sign. higher in the Sx group than in the PFMT group for the PFDI and PIFQ-7 total scores and subscales (p<.02).	6-month follow-up	Randomisation adequate No concealment No blinding (self-reported questionnaire) No dropouts Adverse events: Sx: 5 women had local wound infections and 2 had a re-operation due to postoperative hematoma or bleeding

Abbreviations: BF: biofeedback; BID: twice a day; BT: bladder training; btw: between; CRADI-8: Colorectal-Anal Distress Inventory-8; CRAIQ-7: Colorectal-Anal Impact Questionnaire-7; DT: drug therapy; EStim: electrical stimulation; eval: evaluation; ICIQ-UI SF: International Consultation on Incontinence Questionnaire Short Form; IEF: Incontinence episode frequency; IIQ-7: Incontinence Impact Questionnaire Short Form 7; I-QOL: Incontinence Quality of Life questionnaire; OAB: overactive bladder; PFDI: Pelvic Floor Distress Inventory; PFIQ: Pelvic Floor Impact Questionnaire; PFM: pelvic floor muscles; PFMT: pelvic floor muscle training; PFMTsup: supervised pelvic floor muscle training; PGI-I: Patient Global Impression of Improvement; POPDI-6: Pelvic Organ Prolapse Distress Inventory-6; POPIQ-7: Pelvic Organ Prolapse Impact Questionnaire-7; sign.: significant(ly); SUI: stress urinary incontinence; Sx: surgery; Tx: treatment; UDI-6: Urogenital Distress Inventory Short Form-6; UIQ-7: Urinary Impact Questionnaire-7; UUI: urge urinary incontinence

2.3.4. Does the addition of PFMT to other treatments add benefit?

In this section, the effects of PFMT combined with another therapy (i.e., VC, BT, drug therapy, surgery, and continence pessaries) are compared to the effects of the other therapy alone to address the additive benefits of PFMT. Previous ICI reviews included a total of 12 RCTs (Table 12). Our search revealed six additional studies investigating the addition of PFMT to BT (90, 94, 95), drug therapy (96) and surgery (97, 98). Details on these studies are presented in Table 13 and in Table 11 as one study also assessed other treatment comparisons.

Table 12. Studies comparing PFMT + another treatment vs this other treatment, which were included in previous ICI reviews and the current update (7th ICI)

	Studies included in previous ICI reviews	New studies identified in this update (7th ICI)
PFMT+VC vs VC	2	0
PFMT+Estim vs EStim	1	0
PFMT+BT vs BT	2	3
PFMT+drug therapy vs drug therapy	5	1
PFMT+surgery vs surgery	1	2
PFMT+continence pessary vs continence pessary	1	0

Abbreviations: PFMT: pelvic floor muscle training; VC: vaginal cone, EStim: electrical stimulation; BT: bladder training

Quality of data

Of the six studies retrieved in our updated search, three described adequate randomisation and concealment (90, 97, 98) while the remaining three reported only randomisation (94-96). In five studies, objective measures were collected by an assessor, blinded to group assignment (90, 94, 96-98). Among these trials, four also employed self-reported questionnaires and the participants were not blinded to group assignment (90, 96-98). The study by Schmidt *et al.* (95), published as a short communication, reported that the assessors were not blinded. Four studies had a large sample size ranging from 103 to 480 and involving 40 to 242 participants per study arm (90, 96-98). The two remaining trials included a total of 70 (18 per arm) (94) and 28 participants (14 per arm) (95). In the two trials investigating BT and EStim, dropout rates were low (6%) (94) or not reported (95). For the surgery trials, Sung *et al.* (97) had a small dropout rate of 3.5%, whereas McLean *et al.* (98) reported larger dropout rates of 18% at post-treatment and 65% at the two-year follow-up. In the two studies assessing drug therapy, Hagovska *et al.* (96) reported a dropout rate of 18%, while Azuri *et al.* (90) reported a dropout rate of 42% in the tolterodine group and 14% to 27% in the BT, PFMT and combined treatment groups at the four-year follow-up.

Results

i. **PFMT plus VC versus VC:** *No new evidence available.*
ii. **PFMT plus EStim versus EStim***: No new evidence available.*
iii. **PFMT plus BT versus BT:** *The study by Azuri et al. (90) is the four-year follow-up of Kafri et al. (92), examining the effects of PFMT plus BT and BT alone using a four-arm design in women with UUI. Findings in the four-year follow-up study agree with the original study. Statistically significant improvements were observed in all groups for all outcomes (i.e., cure rate, number of voids/24-hour and frequency of UI), but no-significant differences were shown between groups. Similar results were found in the study by Firinci et al. (94) in women with UUI. Improvements were observed in all groups for all outcomes (e.g. frequency of voiding, frequency of incontinence episodes and pad test) but no significant differences were found between PFMT plus biofeedback and BT groups. The study by Schmidt et al. (95) in women with SUI and MUI, showed improvements in the frequency of UI in the BT plus PFMT and biofeedback alone groups but between-group statistical differences were not reported.*
iv. **PFMT plus drug therapy versus drug therapy alone***: Hagovska et al. (96) conducted a large study comparing PFMT plus duloxetine to duloxetine alone in women with SUI. Significant differences were found between the two groups for ICIQ-IU, number of pads per day, and frequency of UI. These results were in favour of the group receiving the combined treatment.*
v. **PFMT plus surgery versus surgery:** *Two large multicentre RCTs examined the addition of perioperative PFMT to mid-urethral sling surgery in women with MUI (97) and SUI (98). Sung et al. (97) reported greater improvements in UDI scores in the PFTM plus surgery group compared to the surgery alone group at 12-month follow-up. However, the authors explained that the between-group difference did not reach MCID threshold. They also found greater improvements in the Incontinence Impact Questionnaire-6 (IIQ-6) scores, the frequency of urinary leakage, and the number of pads used in the combined treatment group. In contrast, no statistically significant between group differences were found for the PGII and Overactive Bladder Questionnaire. In the study by McLean et al. (98), mixed findings were also reported. PFMT combined with surgery yielded superior effects compared to surgery alone in terms of cure rates and Female Lower Urinary Tract Symptoms (FLUTS-UI) questionnaire total scores.*
vi. **PFMT plus continence pessary versus continence pessary:** *No further evidence.*

Summary

There is no evidence of any benefit from adding PFMT to VC in women with SUI. **(Level of evidence: 2)**

There is limited evidence of any benefit from adding PFMT to EStim in women with SUI. **(Level of evidence: 2)**

Previous pooled data suggest that it may be beneficial to add PFMT to BT. **(Level of evidence: 2)**

Previous pooled data suggest that PFMT may be more effective to reduce SUI over intravaginal oestrogen alone when treating women with vaginal atrophy. **(Level of evidence: 2)**

Based on previous pooled data and current evidence, the addition of PFMT to drug therapy (i.e., tolterodine and duloxetine) showed superior effects compared to drug therapy alone. **(Level of evidence: 2)**

Some benefits of adding PFMT to mid-urethral sling surgery were found in women with MUI and SUI. There is however uncertainty about the clinical significance of these improvements. **(Level of evidence: 2)**

Evidence suggests that there is some benefit to adding PFMT when using a continence pessary. **(Level of evidence: 2)**

Recommendations

Based on limited evidence, combining PFMT with either VC or EStim could not be recommended routinely as it does not appear to add any benefits. **(Grade of recommendation: C)**

For the treatment of SUI, UUI, or MUI in women, the addition of PFMT to BT provides additional benefits compared to BT alone and therefore could be recommended. **(Grade of recommendation: C)**

When treating women with SUI and vaginal atrophy, combining PFMT and intravaginal oestrogen over oestrogen alone could be considered. **(Grade of recommendation: C)**

For treatment of UUI (tolterodine) and SUI (duloxetine), adding PFMT to drug therapy can be considered. **(Grade of recommendation: B New)**

Adding PFMT to the insertion of a mid-urethral tape can benefit women with MUI and SUI. **(Grade of recommendation: B New)**

When treating stress-predominant incontinence, adding PFMT to a continence pessary can be considered. **(Grade of recommendation: B)**

Table 13. Summary of data on PFMT + another treatment vs this other treatment

Study	Comparator	N	Study Population	Intervention	Outcomes/Results	Follow-up	Notes
Firinci, Yildiz (2020) (94)	BT (18) vs. BT + BF (17) vs. BT+EStim (18) vs. BF+BT+EStim (17)	70	Women with idiopathic OAB	BT consisting of 4 stages (1teaching of PFM contraction for urgency suppression; 2-urgency suppression technique (PFM contraction, breathing, relaxation, distraction); 3- timed voiding programme, 4- encouragement to pursue BT. Duration of each stage not specified. BF: 20-min of intravaginal pressure BF (40 cycles of 10 s of contraction followed by 20 s of relaxation) EStim: 20 min of intravaginal EStim at 10 Hz, a 5–10 s work□ rest cycle, and 100 ms pulse width (symmetric biphasic). BF and EStim were performed 3 days per week, for a total of 24 sessions over 8 weeks	The four groups sign. improved from baseline to post-tx regarding the incontinence severity (24-h pad test), frequency of voiding and incontinence episodes (3-day voiding diary) ($p < .05$). As for btw-group differences, changes in incontinence severity (24-h pad test), frequency of voiding and incontinence episodes (3-day voiding diary) were superior in the BT+EStim and BF+BT+EStim groups compared to the other 2 groups. Cure/improvement rate (according to the 24-h pad test) was sign. higher in BT+EStim and BF+BT+EStim groups compared to the other groups.	Post-tx (after 8 weeks of tx)	Randomisation adequate Concealment not reported Assessors blinded (evaluation performed by a physician blinded to group assignation) Dropouts: BT 1/18 BT + BF 1/17 BT+EStim 1/18 BF+BT+EStim 1/17 Adverse events: None except temporary discomfort due to vaginal irritation in three women in the EStim groups Dose: same tx regimen (BT, BF and EStim) across groups. The groups differed only in the combination.

Study	Comparator	N	Study Population	Intervention	Outcomes/Results	Follow-up	Notes
Hagovska (2021) (96)	Duloxetine + PFMT (79) vs. Duloxetine (79)	158	Women with SUI	Duloxetine: 40 mg BID PFMT: exercises were performed 5x per week for 30 min per day (various positions, progression in number of repetitions, strength and endurance exercises, PFMT in conjunction with lumbo-pelvic stabilization exercises). Education was provided by a physiotherapist in cooperation with a nurse over 5 sessions.	Duloxetine+PFMT resulted in higher changes from baseline to post-tx compared to duloxetine alone: - ICIQ-UI SF (average reduction 8.3 ± 3.8 vs. 9.7 ± 4.2; p=0.04); - Number of pads/day (percentage of reduction 50.0% vs 22.5%; p < 0.001); - PGI-I: 70.8% vs. 65.6% (p=.0001); - IEF/week (voiding diary percentage of reduction 66.7% vs. 50.0%; p<.001)	After 12 weeks of tx	Randomisation adequate Concealment not reported Assessor not blinded (self-reported questionnaire). Diaries were checked by an outpatient nurse at baseline and post-tx (no more info) Dropouts: Duloxetine+PFTM 14/79 (8 related to adverse events and 6 to low adherence) Duloxetine 15/79 (related to adverse events) Adverse events: Duloxetine+PFMT 8/79 Duloxetine 15/79 Duloxetine (nausea, fatigue, insomnia, dry mouth, constipation, dizziness, headache, and diarrhea) PFMT (no adverse events reported)

Study	Comparator	N	Study Population	Intervention	Outcomes/Results	Follow-up	Notes
McLean (2021) (98)	PFMT+Sx (52) vs. Sx+usual care (51)	103	Women with predominant SUI (30-min pad test >2g and a positive cough stress test)	All participants received a handout including usual care and PFMT instructions. Sx: Mid-urethral sling PFMT: supervised PFMT, 6 sessions over 12 weeks: manual assessment, education, BF, manual therapy and home PFMT programme that was progressed. After 12 weeks, assessments (V2) were repeated and then women proceeded to sx. After sx: physiotherapy sessions at weeks 1, 3 and 5 post-Sx. Usual care: no instructions beyond handout, asked to keep log of exercise performance. After 12 weeks, assessments (V2) were repeated and then women proceeded to sx. No further instructions were given after sx.	FLUTS-UI total scores sign. improved from V1 to V3 in both groups (p<.001). PFMT+Sx group demonstrated sign. lower scores at V2 compared with V1, and at V3 compared with V2, whereas the Sx+usual care only demonstrated sign. lower scores at V3 compared with both V1 and V2. Sign. group*time effects were found (p<0.01). For both groups, the lower scores at V3 were maintained at V4 and V5. At V3, FLUTS-UI subscale scores were sign. lower for the PFMT+Sx group than for the Sx+usual care group. For both groups, the lower scores at V3 were maintained at V4 and V5. No sign. group differences in the 3-day-bladder diary and 30-min pad test at V3 (p>0.05), yet all were sign. improved at V3 relative to V1 (p<.001). Cure rate (based on FLUTS-UI subscale<4) at V3 was higher in PFMT+Sx (73%) than in Sx+usual care (47%) (p=0.012). The cure rate was also higher in the PFMT+Sx at V4 and V5 (p<.01) No sign. group difference in cure-rate at V3, V4 and V5 based on the pad test, bladder diary and FLUTS-UI total score.	Baseline (V1) Assessment prior to Sx (V2) (12 weeks after PFMT or usual care) 12-weeks post-Sx (V3) 12-months post-Sx (V4)* 24-months post-Sx (V5)* *only for FLUTS-UI	Randomisation and concealment adequate Blinding of surgeons Dropouts at V3: PFMT+Sx 10/52 Sx+usual care 9/51 Dropouts at V5: PFMT+Sx 29/52 Sx+usual care 38/51
Schmidt (2020) (95) Short communication	BT (14) Vs BT + BF (14)	28	Women with SUI or MUI with a predominance of stress symptoms	BT: Instruction sheets on behavioural measures and lifestyle changes. BF: Standardized series of mixed exercises for rapid and slow response fibers No further details presented.	Both groups showed sign. improvement in the number of daily leakages from baseline to post-tx (p<.001). Btw-group differences not reported.	Post-tx (after 12 weeks of tx)	Randomisation adequate Concealment not reported Assessor non-blinded Dropouts: none reported Adverse events: none observed

Study	Comparator	N	Study Population	Intervention	Outcomes/Results	Follow-up	Notes
Sung (2019) (97)	Sx + PT (242) vs. Sx (238)	480	Women with moderate to severe bothersome SUI and UUI symptoms ≥3 months with at least 1 SUI and 1 UUI on a 3-day bladder diary	Sx: Retropubic and transobturator midurethral sling techniques PT: Education (pelvic floor anatomy, bladder function and voiding habits) + PFMT + BT (strategies to control stress and urgency symptoms). 1 preoperative visit and 5 post operative visits over 6 months.	UDI total score: Greater improvement in the Sx+PT compared to Sx was found from baseline to 12-month follow-up (mean difference -13.4 95%CI -25.9 to -1.0; p=.04). However, the authors argued that it did not reach MCID threshold. Btw group difference non sign. at 3- and 6-month follow-up. 3-day bladder diary: Greater reduction in total number of incontinence episodes from baseline to 12-month follow-up in the Sx+PT group compared to Sx group (mean difference −1.0 95%CI −1.7 to −0.2; p=.009) Non sign. differences btw groups (baseline-12 months): Number of voids (nighttime), Overactive bladder symptom severity questionnaire (OAB-q-SS), OAB Treatment Satisfaction Questionnaire, Patient Global Impression of Improvement (PGI-I) and Patient Global Impression of Severity were not sign. different btw groups at 12 months. Sign. differences btw groups (baseline-12 months): Number of pads per day, Number of voids (daytime), void frequency (normalization), void frequency (high voiding), Incontinence Impact Questionnaire and additional treatment were sign. different btw groups at 12 months in favor of the Sx+PT group (p≤.009)	12-month follow-up* (after surgery) *Also measured at 3- and 6-month follow-up but 12-month was the primary endpoint	Randomisation and concealment adequate Assessor blinded Dropouts: Sx+PT 14/242 Sx 3/238 Adverse events (over 12 months): Worsening urgency: Sx+PT 11 vs. Sx 5 Abdominal or genital pain: Sx+PT 28 vs. Sx 36 Dyspareunia : Sx+PT 29 vs. Sx 35 Sensation of difficulty emptying bladder: Sx+PT 32 vs. Sx 31 Vaginal mesh exposure: Sx+PT 4 vs. Sx 1 Emergency department for complication: Sx+PT 5 (urinary retention 3, acute pyelonephritis 1 and lower abdominal pain 1) vs. Sx 0 Reoperation Sx+ PT 3 vs. Sx 4 (reasons for reoperation: sling release 3, mesh excision 2 and cystotomy 2)

Abbreviations: BF: biofeedback; BT: bladder training, btw: between; DT: drug therapy; EStim: electrical stimulation; FLUTS-UI: Female Lower Urinary Tract Symptoms – Urinary Incontinence questionnaire; I-QOL: Incontinence Quality of Life questionnaire; MCID: minimal clinically important difference; MUI: mixed urinary incontinence; OAB: overactive bladder; PFM: pelvic floor muscles; PFMT: pelvic floor muscle training; PT: physiotherapy; sign.: significant(ly); SUI: stress urinary incontinence; Sx: surgery; Tx: treatment; UDI: urogenital distress inventory; UUI: urge urinary incontinence

3. WEIGHTED VAGINAL CONES

Weighted vaginal cones (VC) were developed as a method for testing PFM function as well as to provide progressive muscular overload during PFM strengthening exercises (99). In theory, when a cone is inserted into the vagina, the sensation of 'losing the cone' provides sensory feedback that prompts the PFMs to contract to prevent the cone from slipping out. Women typically start in a standing position with a weighted VC held inside the vagina for at least one minute. The amount of time for which the VC is held, and the cone weight is increased incrementally while standing. For instance, the goal could be to stand or walk around without losing the cone; the gradual increase in cone weight maintains muscle overload over the course of the exercise programme.

There are various VC weights and sizes (Figure 1) and the effects of VC may vary depending on different factors. For instance, as the orientation of the vagina is not completely vertical, some women can retain the VC without contracting the PFMs. For example, radiographic studies have shown that VC can rest in a transverse position (100). Depending on the axis of the vagina, women need to produce different force intensities to retain the VC. Thus, using VC as a measure of PFM function may be invalid. Finally, some women may find it impossible to insert the VC due to a narrowed vaginal opening or, conversely, to retain it due to an enlarged vaginal opening, prolapse, or an insufficient PFM contraction that is incapable of holding even the lightest VC.

Figure 1. Weighted vaginal cones

This section examines the evidence for VC in the prevention and treatment of UI in women. Questions addressed:

- Are VC better than no treatment, placebo, or control for the prevention of UI?
- Are VC better than no treatment, placebo, or control for the treatment of UI?
- Are VC as effective as other treatments for the treatment of UI?
- Are VC combined with PFMT better than PFMT alone for the treatment of UI?

3.1. Prevention

Consistent with previous ICI, no studies were found investigating VC for primary or secondary prevention in women.

3.2. Treatment

Three new RCTs investigating the efficacy of VC were identified. Of these, one study was not retained due to the absence of incontinence outcomes (101). Table 14 illustrates the studies included in previous consultations (N=32) as well as the two new studies. Characteristics of each new RCT are presented in Table 15.

Table 14 Studies using VCs included in previous ICI reviews and the current update (7th ICI)

	Studies included in previous ICI reviews	New studies identified in this update (7th ICI)
PFMT vs VC (section II.2.3.3i)	14	0
PFMT/VC vs VC (section II.2.3.4i)	2	0
VC vs no treatment, placebo or control treatments	5	0
VC vs other treatment	6	2
PFMT/VC vs PFMT	5	0

Abbreviations: PFMT: Pelvic floor muscle training, VC: vaginal cone

3.2.1. Are VC better than no treatment, placebo, or control treatments for UI?

The previous ICI included five RCTs comparing the effects of VC to the absence of treatment or a placebo. No new studies have been published.

Summary

VC with supervised training sessions by a trained health professional are better than control treatments for subjective reporting of *cure* or *cure/improvement* and the QOL impact of the treatment on SUI. **(Level of evidence: 1)** However, VC treatment may be inappropriate in some cases due to potential side effects (102).

Recommendations

For women with SUI, VC with supervised training sessions by a trained health professional can be offered as a first-line conservative therapy to those who can and are prepared to use them. **(Grade of recommendation: B)**

VC may be inappropriate in some cases due to an inability to insert or retain the cone, or because of side effects and discomfort and therefore assessment by a trained health professional is recommended. **(Grade of recommendation: D)**

3.2.2. Are VC as effective as other treatments for UI?

i. VC versus PFMT

As reported in Section II.2.3.3, our literature search revealed no further trials.

ii. VC versus EStim
No new studies were added to the seven RCTs included in the previous ICI editions.

iii. VC versus surgery
A single new RCT examined the efficacy of VC in comparison with trans obturator tape (103).

iv. VC versus drug therapy
Our search revealed one new study investigating the efficacy of VC compared to drug therapy (tolterodine extended) (104).

Quality of data
In the two studies (103, 104), participants were randomly assigned to treatments while the allocation concealment and blinding of assessors were not clearly reported. The study by Dur *et al.* (103) included 21 women in the VC arm and 20 women in the surgery arm respectively. Only one dropout was reported in the VC group. In the study by Yuce *et al.* (104), three women out of 19 included in the VC group dropped out of the study and one woman among the 20 included in the drug therapy group dropped out.

Results

i. **VC versus PFMT:** *No further evidence available.*
ii. **VC versus EStim:** *No further evidence available.*
iii. **VC versus surgery:** *No statistically significant differences were found in subjective self-reported cure between the VC group and the trans obturator tape group (103). However, women in the surgery group had a higher objective cure rate (cough stress test) and greater improvement in the pad test than the VC group at six-week and six-month follow-ups (103).*
iv. **VC versus drug therapy:** *No statistically significant differences between VC and tolterodine were found regarding the severity and impact of symptoms (measured with various validated questionnaires, bladder diary, and pad test) (104). Authors reported that the study may have been underpowered to detect differences between the two interventions.*

Summary

There are no significant differences between VC and EStim in terms of *self-reported cure, cure/improvement*, and improvement in pad test or the number of leakage episodes. However, both the VC and EStim groups reported adverse events. **(Level of evidence: 1)**

Trans obturator tape insertion showed superior effects compared to VC for objective cure rate and improvement in the pad test. **(Level of evidence: 2)**

There is limited evidence regarding the efficacy of VC compared to drug therapy.

Recommendations

VC and EStim can be equally recommended in the treatment of SUI and MUI**. (Grade of recommendation: B)** However, side effects and discomfort limit the utility of these modalities in clinical practice. **(Grade of recommendation: D).**

No recommendation is possible regarding VC compared to trans obturator tape insertion and drug therapy.

3.2.4. Are VC combined with PFMT better than PFMT alone?

The previous ICI included five RCTs comparing the effects of VC combined with PFMT to PFMT alone. However, our search revealed no additional studies.

Summary

Limited evidence suggests that there is no benefit from adding VC to PFMT for women with SUI. **(Level of evidence: 2)**

Recommendations

No recommendation is possible for this combined intervention. Adequately powered RCTs are needed to confirm or refute the advantages of adding VC to PFMT.

Table 15. Summary of data on VC

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/Results	Follow-up	Notes
Dur (2019) (103)	VC (21) vs. Sx (20)	41	Women with SUI (confirmed with urodynamic assessment, positive cough stress test, and standardized pad test (>3 g))	VC: VC weight 20-70 g for 15 min twice a day for 3 months (instructions provided by a gynecologist) Sx: transobturator tape	Improvement in pad test in both groups from baseline to follow ups (p<.05). Lower pad weight is observed in the Sx group compared to VC group at both 6-week and 6-month follow ups (p<.015). Subjective cure rates (self-reported) were similar in both groups at the 6-week and 6-month follow up (VC 65% vs Sx 75%; VC 75% vs Sx 80%; both p>.05). Objective cure rates (cough stress test) were sign. higher in the Sx group than in the VC group (10% vs 80%; 30% vs 75%) (p<.05).	6-week follow up 6-month follow up	Randomisation adequate Concealment not reported Blinding of assessor unknown Dropouts: VC 1/21 Sx 0/20 Adverse events: none observed
Yuce (2016) (104)	VC (19) vs. DT (20)	39	Women with OAB (urinary frequency ≥8/day / nocturia ≥2/night / urgency and OAB-V8 score ≥ 8)	VC: 4 VC (same volume and size) of different weights (20g, 34g, 50g and 68g). They had to hold the VC during various activities (e.g., stand up, walk, housework) twice a day for 10 min each time. The weight was increased if/when they were able to retain the current weight >10 min). For 8 weeks DT: tolterodine extended release 4 mg per day, for 8 weeks	3-day bladder diary: Daytime frequency, nocturia, and number of UUI episodes sign. improved from baseline to post- Tx in both groups (p<.034). No sign. differences btw groups at post- Tx were found. 24-h pad test: Sign. reduction in pad weight was found in both groups from baseline to post- Tx (p<.003). No difference btw groups at post-Tx. Similarly, the number of patients with a dry pad test was similar btw the two groups at post-Tx (VC 68.7% vs DT 84.2%; p=.613). UDI-6, IIQ-SF7, OAB-V8: Sign. reductions were found in both groups (p<.019). No sign. difference btw groups at post- Tx. Wagner questionnaire: Sign. reduction from baseline to post- Tx in the VC group (40.50±23 to 27.63±21.9; p=.002) but not in DT group (28.95±17 to 28.53±18.5; p=.591). No sign. difference btw groups at post-tx (p=.896) Urodynamic examination: Detrusor overactivity was reduced from baseline to post-tx in the VC group (10/16 to 7/16; p=.003) and DT group (5/19 to 3/19; p=.426). Btw-group differences not reported. No sign. changes were seen in either group regarding normal or strong desire to void, post-void residual, max detrusor pressure, max abdominal pressure, max cystometric capacity. Sign. differences from baseline to post-Tx were found in VC group but not in DT group for: Max vesical pressure and first sensation of bladder filing (p<.036), but no sign. difference btw groups post- Tx (p≥.068).	Post-tx (after 8 weeks of tx)	Randomisation adequate Concealment not specified Blinding of assessor: Not mentioned Dropouts: VC 3/19 DT 1/20 Adverse events: no side effects requiring discontinuation of tx occurred in either group

Abbreviations: btw: between; DT: drug therapy; IIQ-SF7: Incontinence Impact Questionnaire Short Form 7; OAB: overactive bladder; OAB-V8: Overactive Bladder-Validated 8-question Screener; sign.: significant(ly); SUI: stress urinary incontinence; Sx: surgery; Tx: treatment; UDI-6: Urogenital Distress Inventory Short Form-6; UUI: urge urinary incontinence; VC: vaginal cone

4. ELECTRICAL STIMULATION (ESTIM)

The literature concerning electrical stimulation (EStim) in the management of UI is difficult to understand due to the lack of a well-substantiated biological rationale underpinning its use. However, the theoretical basis of neuromuscular EStim is emerging with increasing understanding of the neuroanatomy and physiology of the central and peripheral nervous systems. The mechanisms of action may vary depending on the cause(s) of UI and the structure(s) being targeted by EStim, e.g., PFM or detrusor muscle, peripheral or central nervous system. In general, the aim of EStim for women with SUI is to increase proprioception and/or improve the muscle function of an atrophied or weak PFM, while for UUI the objective is to inhibit detrusor overactivity (DO) (105).

EStim is provided by clinic-based mains powered machines or portable battery powered stimulators (Figure 2) with a seemingly infinite combination of current types, waveforms, frequencies, intensities, electrode types and placements (Figure 3). Without a clear biological rationale, it is difficult to make choices about different ways of delivering EStim. Additional confusion is created by the relatively rapid market developments and a wide variety of stimulation devices and protocols that have been developed, even for the same condition. Finally, the terminology used to describe EStim remains inconsistent. EStim has not only been described based on the type of current being used (e.g., faradic, interferential), but also on the structures targeted (e.g., neuromuscular), the current intensity (e.g., Low-intensity, or maximal stimulation), and the proposed mechanism of action (e.g., neuromodulation).

This section presents the evidence for the use of EStim in the prevention and treatment of UI in women.

Questions addressed are:
- Is EStim effective in the prevention of UI?
- Is EStim better than no active treatment (placebo, sham, control, or no treatment) for the treatment of UI?
- Is one type of EStim better than another in the treatment of UI?
- Is EStim better than other treatments in the treatment of UI?
- Does the addition of EStim to other treatments add any benefit in the treatment of UI?

Eligible interventions were non-invasive EStim without implanted electrodes. (MStim and TNS are described in sections II.5 and II.6).

Other criteria for inclusion were: (1) randomised or quasi-randomised (alternate allocation) trial design, (2) adult women with UI or other LUTS, and (3) no participants with incontinence due to neurological or cognitive impairment (EStim for this population is presented in section VI.3), and (4) no pregnant or postpartum women (within 12 months of childbirth). Trial data reported in conference abstracts as well as full-text papers were included. EStim compared with PFMT and vaginal cones are covered in sections II.2 and II.3. This section focuses on EStim compared with no active treatment or other conservative treatments.

The primary outcomes were cure rates (the number of women with no UI episodes at the time of assessment) and improvement rates (the number of women improved, including cure). There was considerable variability in the way these outcomes were measured. Data on health related QoL and adverse effects were also extracted. Data from further follow-up were also recorded.

Due to the small number of available studies per intervention, data were sub-grouped by dominant type or pattern of incontinence: (1) studies with all or at least 50% of participants having SUI alone or a predominant symptom of SUI (as defined by trial investigators), (2) studies with all or >50% of participants having UUI alone or a predominant symptom of UUI (as defined by trial investigators), (3) other studies of participants with UI in which neither stress nor urgency UI represented a predominant symptom in the study population ('UI all types' hereafter), and (4) studies on overactive bladder (OAB) or DO, in which it was unclear whether all participants had UI.

In included studies, ROB was assessed for random allocation, allocation concealment (selection bias) and completeness of outcome data (attrition bias). ROB regarding blinding to the allocated intervention was high in most included studies: blinding of participants and care providers was not always feasible (other than the use of sham EStim) and blinding of outcome assessors was equally difficult for self-reported outcomes such as cure, improvement and QoL.

Overview

Fifty trials were included in the sixth ICI, of which none were on prevention. For treatment, trials from the sixth ICI were broadly similar to those from the fifth ICI. Included studies were generally at high ROB.

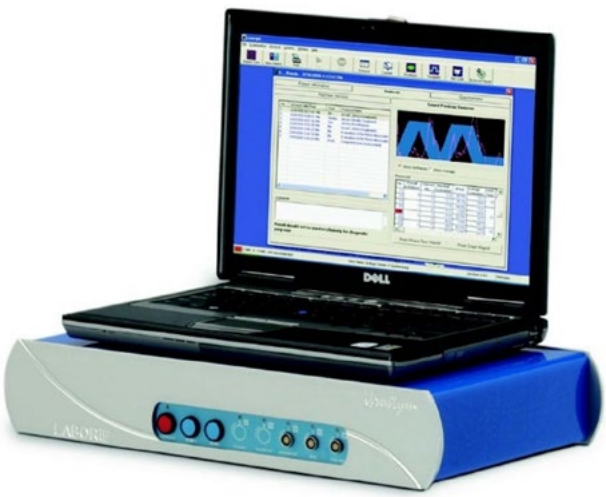

Figure 2. Neuromuscular electrical stimulation equipment

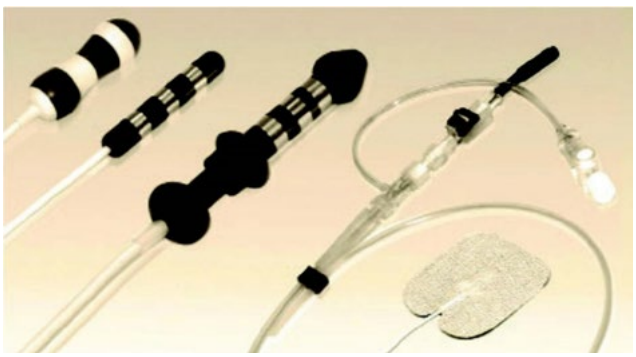

Figure 3. Neuromuscular electrical stimulation electrodes

Eleven new trials were identified for this update, making a total of 61 trials included. Three new trials targeted women with SUI or predominant SUI (106-108), and eight studies focused on predominant UUI, detrusor overactivity (DO) or OAB (incontinent or not) (94, 109-112). Further analysis of three trials can be found in section II.6. (113-115). The number of included studies by dominant type or pattern of incontinence is summarized in Table 16.

The EStim parameters and protocols in this section are summarised in Table 17. Once more, there was considerable variation in the intervention protocol. Although the biological rationale and purpose of EStim might be different depending on diagnosis, there was no consistency in the EStim protocols used for women with SUI, UUI, UI all types, or DO.

Table 16. Studies on EStim included in the previous review (6th ICI) and current update (7th ICI)

	Studies included in the previous review (6th ICI)	**New studies identified in this update (7th ICI)**	**Total**
Prevention	0	0	0
EStim vs No active treatment			
SUI or predominant SUI	13	1	14
UUI or predominant UUI	3	0	3
UI all types	2	0	2
DO/OAB (dry or wet)	3	1	4
One type of EStim vs another			
SUI or predominant SUI	6	2	8
UUI or predominant UUI	0	1	1
DO/OAB (dry or wet)	2	3	5
EStim vs other treatment			
SUI or predominant SUI	1	0	1
UUI or predominant UUI	1	1	2
DO/OAB (wet or dry)	4	0	4
Addition of Estim to other treatment			
EStim+PFMT vs PFMT			
SUI or predominant SUI	10 (no BF)	0	10
	3 (with BF)	0	3
UUI or predominant UUI	0	1	1
UI all types	2 (no BF)	0	2
Estim+TTNS vs TTNS			
UUI	0	1	1

Abbreviations: PFMT: pelvic floor muscle training; EStim: electrical stimulation; SUI: stress urinary incontinence; UUI: urge urinary incontinence; UI: urinary incontinence; DO: detrusor overactivity OAB: overactive bladder; BF = biofeedback; TTNS: transcutaneous tibial nerve stimulation

Table 17. Summary of EStim protocols

Author, year	Current	Current intensity	Pulse shapes & duration	Frequency	Duty cycle	Electrodes	Treatment duration	Target UI
Sharma 2016 (109)	biphasic	NR	NR	75-100 Hz	NR	TENS S2-S4 dermatome	30 min 5 session/W X 2W	OAB (±UI)
Hwang 2020 (106)	biphasic	17.63±7.47 (2.5-30) mA	11s	25 Hz	11s:11s	Surface Bottom and sacral	15 min	SUI
Wang 2016 (107)	EPNS biphasic Vaginal	45-55mA (Max tolerable intensity) >60mA (Max tolerable intensity)	2ms	2.5 Hz 15 Hz and 85 Hz, alternate 3 min periods	NR	Pudendal Vaginal	60 min, 3times/w x 4 w 40 min, 3 times/w x 4 w	SUI
Wang 2017 (110)	biphasic	25-35 mA (moderate intensity) >60 mA (max tolerable intensity)	2 ms	2 Hz 12.5-30 Hz	NR	Pudendal Vaginal	60 min, 3 times/w x 3 w 45 min, 3 times/w x 4 w	UUI
Vecchioli-Scaldazza 2017 (111)	Biphasic PTNS	NR NR	NR NR	20Hz (5sec)+5Hz (30 sec) NR	NR NR	Vaginal PTNS	30 min x 10 sessions followed by PFMT 6 months 30 min 2 times/w x 6 weeks	OAB
Domochowski (2019) (108)	NMES	<0.05 mA/cm2 NR	620 µs 300 µs	50 Hz 50 Hz	0.5 sec up – 0.5 sec down 1 sec up-5 sec plateau-10 sec rest	NMES vaginal	30 min. 5 times/w x 12 w 20 min. once/day x 12 w	Predominant SUI
Abdelbary (2015) (112)	TES	30-60 mA Max tolerable intensity	32 ms	20 Hz	NR	Vaginal	30 min, 2 times/w x 6 w	UUI only
Firinci (2020) (94)	biphasic	0-10mA max tolerable intensity	100 ms	10 Hz	5-10s	Vaginal	20 min, 3 times/w x 8 w	OAB

Abbreviations: NR: Not reported; EPNS: electrical pudendal nerve stimulation; BF: biofeedback; NMES: neuromuscular external; Estim: electrical stimulation, UI: urinary incontinence; SUI; stress urinary incontinence; UUI: urge urinary incontinence; MUI: mixed urinary incontinence; OAB: overactive bladder; POP: pelvic organ prolapse

4.1. Prevention

No trials were found.

4.2. Treatment

4.2.1. Is EStim better than no treatment, placebo, sham, or control for treatment of UI?

In the sixth ICI, 21 studies assessed the effect of EStim compared to no active treatment, including 13 in women with SUI or predominant SUI, three studies on UUI or predominant UUI, two studies on all types of UI, and three studies on DO/OAB (incontinent or not).

Two new studies were found on EStim compared to no active treatment or sham treatment. One study included 40 women with OAB and compared the effectiveness of transcutaneous electrical nerve stimulation (TENS) to a placebo TENS for reducing OAB symptoms (109). Another study included 34 women with SUI and compared surface EStim through transvaginal and sacral region stimulation with a control intervention (walking 20 min daily) (106). Characteristics of the new studies are presented in Table 18.

Results

In the study by Sharma *et al.* (109), there was a significant improvement in the Overactive Bladder Symptom Score (OABSS) in the TENS group with two patients 'completely dry' following TENS therapy. No significant improvement was found in the control group. A statistically significant difference in total OABSS was found in the TENS group compared to control group, which favoured TENS. In a study by Hwang *et al.* (106), significant differences in the UDI-6 score and pad weight were observed both between groups (EStim versus control group) and within groups (pre-EStim versus post-EStim), again favouring EStim.

Summary

EStim may be more effective than no treatment or a control treatment in improving symptoms and QoL in women with SUI. **(Level of evidence: 2)**

EStim may improve symptoms in women with UUI or OAB, but it may not cure their condition. **(Level of evidence: 2)**

Information on QoL was sparsely reported, particularly for UUI or OAB/DO, and the limited data available were inconsistent. Adverse effects appear uncommon but some women experienced discomfort with the treatment device. Scant data were available on long-term performance.

Recommendations

EStim can be recommended as being better than no treatment to improve symptoms and QoL in women with SUI. **(Grade of recommendation: B)**

EStim can be considered for treatment to improve symptoms for UUI. **(Grade of recommendation: B)**

However, this recommendation should be viewed with caution until the findings are supported or refuted in longer-term follow up.

Table 18. Summary of data on EStim vs no active treatment

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow-up	Notes (side effects, loss of follow up…)
Sharma 2016 (109)	TENS vs sham	40	OAB	OABSS Cure (dry)	TENS: 2 participants dry Significant difference between-groups favoring EStim	NR	Adverse effects: none reported
Hwang (2020) (106)	TENS vs control	34	SUI	Pad test UDS-6	TENS > control (p<0.01) TENS> control(p<0.001)	8 weeks	AEs: none Loss to follow-up: 2 patients (1 each)

Abbreviations: TENS: transcutaneous electrical nerve stimulation; OAB: overactive bladder; OABSS: overactive bladder symptom score; UDS-6: distress inventory-6

4.2.2. Is one type of EStim better than another in the treatment of UI?

Until now, a total of eight studies have assessed the effects of one approach of EStim compared with another. Of these, six studies involved women with SUI and predominant SUI, and two involved women with DO. No study focusing on UUI or predominant UUI was identified.

Six new studies including 502 women with SUI (two studies, n=222) or with OAB with/without UUI (four studies, n=280) were found. Three studies compared EStim and percutaneous TNS or transcutaneous TNS (111, 114, 115); and can also be found in Section II.6. and in Table 28. The three other studies compared Estim to other modalities. The characteristics of the new studies comparing one type of EStim to another are presented in Table 19. Different variants of EStim were assessed, either alone (108, 110, 114, 115) or as an adjunct to PFMT and biofeedback (107, 111).

Quality of data

Randomisation was reported in all six trials and was done by random draw in two studies (107, 110), online randomisation in two others (111, 114), or by using permuted block-format in one study (108) and computer sequence generated in the other (115).

Reporting of data: In two studies by the same authors, cure and improvement were reported (107, 110). QoL was assessed using I-QOL in one study (108). Adverse events were not reported in two studies (107, 110). One study reported adverse events in 19.1% of participants using an external EStim approach (device in underwear) and 13.1% of those using transvaginal EStim (108). Adverse events were mild/moderate. Urinary tract/vaginal infections occurred in 7.7% of participants using transvaginal EStim but were none reported in those who had undergone external EStim (108).

Results

For SUI or predominant SUI, one small new study found that pudendal EStim was better than biofeedback plus PFMT transvaginal EStim for cure rates and improvement rates (107). See Table 19.

One single-blind randomised controlled non-inferiority study comparing external EStim and transvaginal EStim reported that most subjects in both groups achieved more than a 50% reduction in the pad test weight respectively (56.3%, 63.0%), but non-inferiority was not established. Significant improvements in pad tests, number of incontinence episodes, pads used /day, and incontinence QoL score (I-QoL) were seen in both groups immediately after treatment with no clinically relevant between-group differences (108). See Table 19.

For UUI, one new study found that pudendal EStim was better than biofeedback-PFMT plus transvaginal EStim for cure and improvement rates (110). See Table 19.

Vecchioli-Scaldazza *et al.* (111), reported no significant differences in number of daytime voids (primary endpoint) between percutaneous TNS and transvaginal EStim + PFMT, but greater improvements were noted in number of night-time voids, UUI and voided volume as well as patient global impression of improvement (PGI-I) in favour of percutaneous TNS versus transvaginal EStim group. A significant improvement in QoL (OAB-q) was noted in the percutaneous TNS group compared with transvaginal ES+PFMT group. However, the treatment duration was different in the two groups (111). See Table 28.

Jacomo *et al.* (114), reported a reduction of UUI using transcutaneous TNS ($p<0.01$), but no change in parasacral EStim. However, no between-group differences were found. Both transcutaneous TNS and parasacral EStim showed improvement in ICIQ-OAB and ICIQ-SF (114). See Table 28.

Mallmann *et al.* reported that both transcutaneous TNS and parasacral EStim were effective, with no between-group differences in terms of KHQ domains, average KHQ and proportions of categories of ISI. However, OAB-V8 showed a significant improvement in the transcutaneous TNS group compared with the parasacral EStim group ($p = 0.019$) (115). See Table 28.

Summary

A total of 14 studies, including six new studies, assessed the effect of one approach of EStim compared to another. There were four small new trials (107, 109, 114, 115) and two relatively large-scale trials (108, 110).

Findings from updated reports on SUI only suggest that pudendal Estim could be more effective than biofeedback plus PFMT-assisted transvaginal EStim, but the data lost to follow up may have affeccted the results (107). External EStim and transvaginal EStim significantly improved predominant SUI, but non-inferiority was not established (108).

For UUI or OAB, pudendal EStim may be more effective than transvaginal EStim, but the duration of stimulation differed (110). Parasacral EStim may be as effective as transcutaneous TNS (114, 115). Included studies generally had a high ROB. **(Level of evidence: 2)** Further comparisons of EStim protocols are needed.

Recommendations

For women with SUI and UUI, pudendal EStim could be recommended as it may be more effective than transvaginal EStim in improving symptoms. **(Grade of recommendation: C)**

External EStim and transvaginal EStim could be recommended to improve SUI in short term. **(Grade of recommendation: B New)**

Transcutaneous TNS may be slightly better than parasacral EStim and therefore could be recommended. **(Grade of recommendation: C)**

There is a need for studies to elucidate the purpose and biological rationale for EStim in different diagnostic groups. More RCTs are needed.

Table 19. Summary of data on different types of EStim comparisons

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Wang (2016) (107)	Pudendal EStim vs BF-PFMT+ transvaginal EStim	42	SUI alone	Cure Improvement (determined by stress test + 24-h pad test + QoL score)	52.4% vs 14.3% (P<0.01) 85.7% vs 28.6% (P<0.1)	Post-treatment group (n=196, 52 Mo): complete resolution 47.1%	AE: NR
Wang (2017) (110)	Pudendal EStim (n=80) vs transvaginal EStim (n=40)	120	UUI alone	Cure Improvement	42.5% vs 2.5% 70.1% vs 45% Pudendal EStim > transvaginal EStim (P<0.05)	Post-treatment UUI score: Pudendal EStim > transvaginal EStim (P<0.01)	AE: NR
Dmochowski (2019) (108)	External EStim vs transvaginal EStim	180	Predominant SUI	Provocative pad test 24-h pad test I-QOL PGI-I	Non-inferiority was not established (difference -6.7%, 95% CI, -21 to 8.4%). Improved in both groups (no between-group differences) External EStim (56.3%), transvaginal EStim (63%)	NR	Missing: NMES (1.1%), transvaginal EStim (2.2%) AE: NMES (19.1%) transvaginal EStim (13.1%) UTI and vaginal infection: External EStim (0%), TES (7.7%) Device discomfort/pain : External EStim (13.5%), transvaginal EStim (2.2%)

Abbreviations: NR: not reported; EStim: electrical stimulation; EPNS: Electrical Pudendal nerve stimulation; TENS: transcutaneous electric nerve stimulation; NMES: neuromuscular external electrical stimulation device; PTNS: percutaneous tibial nerve stimulation; TTNS: transcutaneous tibial nerve stimulation; PGI-I: patient global impression of improvement; AE: adverse device effects; OAB: overactive bladder; OAB-V8: OAB-8 question awareness tool; ISI: incontinence severity index; SUI: stress urinary incontinence; UUI: urge urinary incontinence; MUI: mixed urinary incontinence; I-QOL: Incontinence Quality of Life Questionnaire; QoL: quality of life; BF: biofeedback; KHQ: King's Health Questionnaire; ICIQ-OAB: International Consultation on Incontinence Questionnaire – Overactive bladder; ICIQ-SF: International Consultation on Incontinence Questionnaire – Short-form; NS: non-significant.

4.2.3. Is EStim better than other treatments for UI?

The fifth ICI edition included six studies: one study in women with SUI, one in women with predominant UUI, and four in women with OAB/DO (wet or dry). No new studies were found for the sixth ICI. Overall, there was insufficient evidence to determine if EStim is better than vaginal oestrogens in women with SUI, propantheline bromide in women with UUI, or oxybutynin and tolterodine for DO (Level of Evidence: 2). Pharmacotherapy (drugs) appeared to be no more effective than EStim (Grade of Recommendation: B).

For this ICI, one new three-armed study was found that included EStim, oestrogen cream and the combination of both (Table 20) (112).

Quality of data

In the new study, random allocation was conducted using a computer-generated random numeric table, but with no indication of third-party involvement in the allocation procedure. Participants and evaluators were not blinded. Data were reported and analysed only for those who completed the trial. Fifteen patients were lost to follow-up. Finally, adverse effects were not reported (112).

Results

There was more improvement in the combination group than in the EStim group for all UI outcomes except for daytime voids, UI episodes and QoL. There was more improvement in the EStim group than in the oestrogen group for all parameters except for DO. No cure

rates were reported. After the six-month follow-up, deterioration was noted in all groups except for UI episodes in the combination group.

Summary

A total of seven studies, including one new moderate-quality RCT including a large number of participants assessed the effect of EStim plus another treatment versus the other treatment. One study included women with SUI, predominant UUI in two studies, and OAB/DO (UI or continent) in four studies.

The new study showed that the effects of the combination of EStim plus oestrogen was better than vaginal oestrogens alone for the treatment of UUI in women at 6 months. **(Level of evidence: 2)**

Other studies were generally assessed as having a high ROB. There is insufficient evidence to determine if EStim alone is better than vaginal oestrogens alone in women with SUI, propantheline bromide in women with UUI, or oxybutynin and tolterodine for DO. **(Level of evidence: 2)**

Recommendation

Medical treatments appear to be less effective than EStim or a combination of PFMT and EStim for SUI and therefore cannot be routinely recommended. **(Grade of recommendation: B)**

Propantheline bromide in women with UUI or oxybutynin and tolterodine for DO cannot be routinely recommended for UUI as they are less effective than EStim. **(Grade of recommendation: B)**

These findings need to be investigated further with high-quality trials, as this is a clinical question of interest to women.

Table 20. Summary of data on EStim vs another treatment

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Abdelbary (2015) (112)	Vaginal EStim (n=100) vs Vaginal estrogen (n-98) vs Combination (n=102)	315	UUI only	Cure UUI QoL	NR Improved in all groups Combination > each monotherapy (p=0.000, 0.009 ES and combination > estrogen (p=0.005, 0.004) NS Improvement decreased in all groups (Except UUI in combination groups	Post-treatment 1 week, 3 weeks and 6 months	Loss to follow-up: 15 patients (vaginal EStim n=5, vaginal estrogen cream n=7, combination n=3) Side Effects: NR

Abbreviations: EStim: electrical stimulation; UUI: urge urinary incontinence; QoL: quality of life; NR: not reported; NS: non-significant

4.2.4. Does the addition of EStim to other treatments add any benefit in the treatment of UI?

In the sixth ICI edition, 15 studies assessed the effect of EStim as an adjunct to another treatment, compared with the other treatment alone. All but two studies included women with SUI or predominant SUI. No study focusing on UUI or predominant UUI was identified.

Two new studies were available for this ICI (Table 21). Firinci *et al.* (94) was an assessor-blinded RCT, studying 70 women with UUI, and assigned them to four groups, including BT alone, BT plus biofeedback training, BT plus EStim, and BT plus biofeedback plus EStim (94). The follow-up assessment took place eight weeks after the intervention. BT included one 30-minute education session with a physician and a written brochure. Women were taught how to contract their PFMs via vaginal palpation, were encouraged to use urgency suppression strategies (PFM contraction, relaxation and distraction) and to follow a timed voiding programme based on their bladder diary. No further details were provided on the BT protocol. Biofeedback treatment included three 20-minute sessions per week. In each session, the participants completed 40 cycles of 10-second contractions followed by 20-second of relaxation performed in supine position with the aid of an intravaginal pressure probe. EStim also included three 20-minute sessions per week. The stimulation parameters were a frequency of 10 Hz, a 5–10-second work-rest cycle, and a 100ms pulse width. The symmetric biphasic pulse wave was delivered over a range of 0–100mA, according to the patient's feedback on their level of discomfort. Further analysis of this trial is found in section II.2.3.4, and II.7.2.

Giarreta *et al.* randomly assigned 106 women with OAB or MUI to a vaginal EStim plus TTNS group (n=54) and a TTNS group (n=54) (113). Further analysis of this trial is found in section II.6.2.4.

Quality of data

A power calculation and adequate random allocation were reported for Firinci *et al.* The assessor was blinded to the participant's allocation. ITT analysis was not used. Loss to follow-up was low and balanced between groups but reasons were unclear (6% giving up treatment). Side effects were minor and specific to the EStim groups (temporary discomfort due to vaginal irritation [n=3]). Overall ROB was moderate (94).

The second study by Giarreta *et al.* 2021 was published in Spanish with an English abstract only, and an assessment of the quality of the data was infeasible (113).

Results

In the study by Firinci *et al.* (94), patient-reported outcomes (number of leakages and number of pads used according to a 3-day bladder diary, UI-specific QoL or impact questionnaires) and clinician-reported outcomes (cure and improvement and UI severity, based on a 24-hour pad-test) for the four treatment groups improved compared to baseline. At post-treatment, results favoured the two combined treatment groups including EStim compared to BT alone or BT added to biofeedback. Moreover, the improvement in nocturia was significantly higher in the triple combination group (BT plus biofeedback plus EStim) compared with the other three groups.

In the study by Giarreta *et al.,* a significantly higher reduction in urinary frequency was reported (1.5 micturitions) in the EStim plus transcutaneous TNS versus transcutaneous TNS alone, but no data on cure rates or improvement rates were reported (113).

Summary

A total of 17 studies assessed the effect of EStim as an adjunct to another treatment, compared with the other treatment alone.

For comparisons of EStim with PFMT versus PFMT alone, there was no clear evidence of a difference between the groups in women with SUI or predominant SUI in terms of cure and improvement. Evidence for QoL outcomes was not consistent across studies. **(Level of Evidence: 2)**

There is no evidence to suggest that the addition of EStim to biofeedback-assisted PFMT was more effective than biofeedback-assisted PFMT in women with SUI. **(Level of evidence: 2).**

For UUI, there is no evidence from which to draw conclusions about the effect of adding EStim to PFMT or transcutaneous TNS for women with UUI. (**Level of evidence: 2, Level of evidence: 3 respectively)**

A combination of BT plus EStim or BT plus biofeedback plus EStim may be more effective than BT alone or BT plus biofeedback. **(Level of evidence: 2)**

Recommendations

For SUI, the addition of EStim to PFMT or biofeedback-assisted PFMT programmes cannot be routinely recommended **(Grade of recommendation: B)**

For OAB or MUI, the addition of EStim to BT or BT plus biofeedback can be considered as this could add benefit for the treatment. **(Grade of recommendation: B)**

Combinations of treatment approaches need to be investigated further with high-quality trials as this is a clinical/research question of interest to women.

Table 21. Summary of data on EStim + another treatment vs the other treatment

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Firinci (2020) (94)	BT (G1) vs BT+BF (G2) vs BT+EStim (G3) vs BT+BF+EStim (G4)	G1(30) G2(17) G3(18) G4(17)	UUI	Incontinence severity (pad test) PFM strength Voiding diary Treatment success (positive response rate) Cure/improvement rate Treatment satisfaction QoL(IIQ)	G3, G4>G1 and G2 G4>G2 and G3. G1	NR	Discomfort level (VAS): NS No severe adverse events in all groups.
Giarreta (2021) (113)	EStim+TTNS vs TTNS	106 (52 vs 54)	OAB or Mixed UI	Bladder diary KHQ OABq	No cure or improvement rates reported	NR	NR

Abbreviations: BT: bladder training; BF: biofeedback; EStim: Electrical stimulation; TTNS: transcutaneous tibial nerve stimulation; OAB: overactive bladder; PFM: pelvic floor muscles; QoL: quality of life; UUI: urge urinary incontinence; NR: not reported; KHQ: King's Health Questionnaire; IIQ: Incontinence Impact Questionnaire; OABq: OABq: Overactive Bladder Questionnaire

5. MAGNETIC STIMULATION (MSTIM)

MStim was developed to stimulate the central and peripheral nervous systems (116). Since its introduction in 1985, the technique has been used to manage a variety of neurological and psychiatric conditions. Following the US Food and Drug Administration approval of MStim as a conservative treatment for UI in 1998, Galloway reported the use of MStim for female SUI in 1999 (117). Conventional magnetic stimulators generate repetitive pulses at frequencies of 10 to 50 Hz with a pulse width between 55 and 300 us (117-121). In general, lower frequencies (5-10 Hz) are more likely to be used to treat UUI, while higher frequencies (15-50 Hz) are suitable for treatment of SUI (122, 123)

The main advantages of MStim include patients' comfort and convenience. Compared to EStim, MStim is more comfortable because it does not require an intra-cavity probe. Moreover, patients do not need to undress or undergo skin preparation for treatment.

The exact mechanism of action of MStim has so far not been fully understood. In terms of SUI, the potential mechanism could be that the direct magnetic stimulation on PFM fibres and pudendal nerves enhances the contraction strength of PFM, and consequently increases maximum urethral closure pressure (8). For UUI, it is hypothesised that MStim could activate pudendal nerve afferents, inhibiting the spinal reflex, and/or inhibitory hypogastric sympathetic neurons, which might suppress DO (9). Moreover, MStim could improve internal urethral sphincter tone by stimulating sympathetic fibres and external sphincter tone by activating the pudendal nerve, and thereby promoting bladder relaxation (119). Additionally, MStim has been thought to significantly relieve patients' depression, which may be secondary to the improvement of UI symptoms (124, 125).

This section presents the evidence for the use of MStim in the prevention and treatment of UI in women. Questions addressed are:

- Is MStim effective in the prevention of UI?
- Is MStim better than no treatment, placebo, control, or sham for the treatment of UI?
- Is one MStim approach better than another in the treatment of UI?

- Is MStim better than other treatments in the treatment of UI?
- Does the addition of MStim to other treatments add any benefit in the treatment of UI?

Eligible interventions were non-invasive MStim. Other criteria for inclusion were: (1) randomised trial design, (2) women with UI or other LUTS, (3) no participants with incontinence due to neurological or cognitive impairment and, (4) no pregnant or postpartum women (within 12 months of childbirth). Trial data reported in conference abstracts as well as full-text papers published or accepted for publication in peer-reviewed journals were included.

The primary outcomes were cure rates (the number of women without UI episodes at the time of assessment) and improvement rates (the number of women with improvement in UI, including cure). There was considerable variability in the way these outcomes were measured. Women's self-reports were prioritised. However, for studies where this was not reported, the improvement/cure rates based on diaries were used as a proxy. When diary data were also not reported, the rates were based on pad tests, or any other definitions chosen by the trial investigators (93). Data on health related QoL and adverse effects were also extracted. Data at the end of the prescribed treatment phase or at the first outcome measurement (if later) were used in the analysis. Any treatment effects shown are likely to reflect maximum effects of each intervention. Data from further follow-up were also recorded.

Due to the small number of available studies per intervention, data were sub-grouped by dominant type or pattern of incontinence: (1) studies with all or at least 50% of participants having SUI alone or a pre-dominant symptom of SUI (as defined by trial investigators), (2) studies with all or >50% of participants having UUI alone or a predominant symptom of UUI (as defined by trial investigators), (3) other studies of participants with UI in which neither stress nor urgency UI represented a predominant symptom in the study population ('UI all types'), and (4) studies on overactive bladder (OAB) or DO in which it was unclear whether all participants had UI.

Single estimates with 95% confidence intervals (CI) were derived for each study comparison using odds ratios (OR) for dichotomous variables or mean difference (MD) for continuous variables. Summary estimates were calculated using random effects models if there was more than one study reporting the same outcome (meta-analysis).

ROB in the included studies was assessed for allocation concealment (selection bias) and completeness of outcome data (attrition bias), using relevant items in a standard tool developed by the Cochrane UI Group. ROB regarding blinding to the allocated intervention was high in most included studies: blinding of participants and care providers is not always feasible (other than the use of sham MStim) and blinding of outcome assessors is equally difficult for self-reported outcomes such as cure, improvement and QoL.

Description of intervention

In addition to 13 studies included in the sixth ICI, four new trials were identified for this update. The number of included studies by dominant type or pattern of incontinence is summarised in Table 22 and Table 23 illustrates the intervention characteristics of the four new trials.

Table 22. Studies on MStim included in the previous review (6th ICI) and current update (7th ICI)

	Studies included in the previous review (6th ICI)	New studies identified in this update (7th ICI)	Total
MStim vs No active treatment			
SUI or predominant SUI	4	4*	8*
UUI or predominant UUI	1	0	1
MUI	1	0	1
UI all types	2	0	2
DO/OAB (wet or dry)	3	0	3
One type of MStim vs another		No study found	
SUI or predominant SUI	0		0
UUI or predominant UUI	0		0
UI all types	1		1
MStim vs other treatment	No study found		
SUI or predominant SUI		1*	1*
UUI or predominant UUI		0	
MStim+PFMT vs PFMT		No study found	
SUI or predominant SUI	1		1
UUI or predominant UUI	0		0

**One of the studies provides multiple comparisons.*
Abbreviations: MStim: mechanical stimulation; SUI: stress urinary incontinence; UUI: urge urinary incontinence; MUI: mixed urinary incontinence; UI: urinary incontinence; DO: detrusor overactivity; OAB: overactive bladder; PFMT: pelvic floor muscle training

Table 23. Summary of data on MStim

Study	Intervention description
Lim (2017) (126)	Therapy was performed using the QRS-1010 PelviCenter chair (QRS-International, Liechtenstein) with a homogeneous magnetic field emitted via a magnetic coil embedded beneath the surface of the seat. [cD1] Patients were treated in a sitting position. The stimulation was generated at a frequency of 50Hz with an 8-second "on" and a 4-second "off" pulsing pattern. The treatment regimen involved 2 sessions per week for 2 months (16 sessions, 20 minutes each). The intensity was not described in detail.
Weber-Rajek (2018) (125)	Therapy was performed using the NeoControl chair (Neotonus Inc., Marietta, GA, USA) with a 2.0 Tesla magnetic field. Patients were treated in a sitting position. The stimulation was generated at a frequency of 50Hz with an 8-second "on" and a 4-second "off" pulsing pattern. The treatment regimen involved 3 sessions per week for 4 weeks (12 sessions, 15 minutes each). The intensity increased from 20% to 100% during consecutive treatment sessions. Also, the strength of electromagnetic stimulation matched the highest patient-tolerated level.
Yamanishi (2019) (127)	Therapy was performed using an armchair type of magnetic stimulator (Nihon Kohden, Tokyo, Japan) with a magnetic coil positioned beneath the seat of the chair. The patients were treated in a sitting position. Stimulation was generated at a frequency of 50 Hz with a 5-second "on" and a 5-second "off" pulsing pattern. The treatment regimen involved one session per week for 10 weeks (10 sessions, 20 minutes each). The intensity was set at a maximum output of ≤42% of the active stimulation during consecutive treatment sessions.
Weber-Rajek (2020) (51)	Therapy was performed using the NeoControl chair (Neotonus Inc., Marietta, GA, USA) with a 2.0 Tesla magnetic field. The patients were treated in a sitting position. The stimulation was generated at a frequency of 50Hz with an 8-seconds "on" 4-second and a 4-second "off" pulsing manner. The treatment regimen involved 3 sessions per week for 4 weeks (12 sessions, 15 minutes each). The intensity increased from 20% to 100% during consecutive treatment sessions. Also, the strength of electromagnetic stimulation corresponded to the highest patient-tolerated level.

5.1. Prevention

There remain no trials on the prevention of UI or LUTS.

5.2. Treatment

5.2.1. Is MStim better than no treatment, placebo, control, or sham for treatment of UI?

Four new studies including 298 women were identified; all participants had SUI (51, 125-127). Only two arms of one study with multiple arms were included in the comparison (51). One study included patients with SUI that were refractory to PFMT (127).

Characteristics of the four new studies comparing MStim to no active treatment are presented in Table 24. Of these, two studies used sham treatment (126, 127) and two used no intervention as the control (51, 125). As the study designs, sample populations and outcomes were heterogenous, only limited study findings could be combined.

Quality of data

Randomisation was considered appropriate in four studies (51, 125-127). Allocation concealment was considered unclear in three studies as important details were not described although two reported the use of envelopes (51, 125) and the other reported the use of a magnetic card (127) in the randomisation process. The fourth study did not describe methods used for allocation concealment (126). In terms of blinding, two studies were double-blind (125, 127) and two other studies were single-blind (51, 126). One study reported the complete data and performed data analysis based on the ITT principle (126). In three other studies, data were reported only for participants who completed the study (51, 125, 127). In the study by Yamanishi (2019), 30.8% (8/26) of participants from the MStim group and 7.7% (1/13) in the sham MStim group withdrew from the study and were not included in the analysis (127).

Results

1. SUI

When adding new studies to previously reported research, pooled data suggest that cure rates were on average significantly higher for MStim compared with no active treatment (N = 234, 23.5% versus 3.5%, OR 8.85, 95% CI 3.39 to 23.09, P<0.00001, I^2=0%) (125, 126, 128). Improvement rates were significantly higher for MStim compared to no active treatment (N = 182, 74.7% versus 25.3%, OR 8.72, 95% CI 4.46 to 17.03, P<0.00001, I^2=0%) (126, 128).

QoL was assessed in five studies, including two new studies (51, 127), but the results were inconsistent. Similar to a previous study (129), one new study found no significant differences between groups (127). In contrast, three studies, including one new study, reported that MStim was associated with significant improvement in QoL compared with no active treatment (51, 128, 130). Specifically, in the new study, four items of the KHQ were statistically significantly different and favoured MStim over control, post treatment (51). A total of three studies, including one new study, reported no adverse effects (121, 127, 129).

2. UUI

No new study was found for this update. The level of evidence and recommendations remain unchanged from the sixth ICI edition.

3. MUI

No new study was found for this update. The level of evidence and recommendations remain unchanged from the sixth ICI edition.

4. All types of UI

No new study was found for this update. The level of evidence and recommendations remain unchanged from the sixth ICI edition.

Summary

A total of 15 studies assessed the effect of MStim compared with no active treatment, including eight focusing on SUI or predominant SUI, one on UUI, one on MUI, two on all types of UI, and three on OAB/DO (where only some but not all had UI). Using

the additional data from newly identified studies, findings were broadly similar to those in the sixth ICI edition.

Evidence from a moderate- to good-quality trial of small to moderate size suggests that MStim is more effective than sham treatment for cure and improvement of symptoms in women with SUI. **(Level of evidence: 2)**

Data from five small trials on MStim examining the effect on QoL provided inconsistent results. **(Level of evidence: 2)**

For women with UUI, evidence from a small trial (120) suggests that active MStim might result in better QoL than the sham treatment, although there is some uncertainty as data were limited and no statistical test was performed. (**Level of evidence: 4)**

Active MStim was associated with higher cure rates than the sham treatment in a small trial (131) with women with MUI. **(Level of Evidence: 2)**

MStim also produced higher cure and improvement rates (118) in women with all types of UI **(Level of evidence: 2)** but this difference was not observed in women with DO (wet or dry). **(Level of evidence: 2)**

In general, adverse effects appear uncommon.

Recommendations

For women, MStim can be considered as it appears to control MUI and SUI symptoms when compared to no active treatment. **(Grade of recommendation: B New) However, this recommendation should be viewed with caution until these findings are supported or refuted in further trials with large sample sizes and clear and consistent reporting of core outcome data.**

Table 24. Summary of data on MStim vs no active treatment

Author, year	Comparator	N (randomised)	Study population	Modality details or parameters	Oucomes/results	Follow up	Notes (side effects, loss of follow-up…)
Lim (2017) (126)	MStim (60) vs Sham MStim (60)	120	SUI alone	MStim: see also table 23. Sham MStim: The magnetic coil was tilted 22 degrees down.	Subjective Cure ('never' response to question 3 of ICIQ-UI SF): 19/60 vs 3/60 Objective Cure (leakage of <1g on 1-h pad test): 25/60 vs 4/60 Improvement (based on ICIQ-UI-SF): 45/60 vs 13/60 QoL: NR Adverse effects: NR	2 months	Loss of follow-up: NR Note: The study included 2 stages. Stage 1 was designed as a double-blind randomised controlled trial with a follow-up at 2 months. Stage 2 was an open-labelled study with a one-year follow-up. In stage 2, participants can choose whether or not to receive additional therapy..
Weber-Rajek (2018) (125)	MStim (30) vs No treatment (25)	55	SUI alone	MStim: see also table 23. Control: no treatment.	Cure (based on RUIS): 5/28 vs 0/24 no significant diff. between groups Improvement: NR QoL: NR Adverse effects: NR	4-week	Loss of follow-up: 2 patients in MStim group and 1 patient in control group.
Yamanishi (2019) (127)	MStim (26) vs Sham MStim (13)	39	SUI refractory to PFMT	MStim: see also table 23. Sham MStim: 1 Hz in 5-s on/5-s off cycles, with a maximum output of ≤42% of the active stimulation.	Cure: NR Improvement: NR QoL via ICIQ-QOL: N= 30 at 10-week, mean change in score, standard deviation -1.66 (3.23) vs 0.25 (1.36), P=0.377. Adverse effects: no events observed	10-week	Loss of follow-up: 8 patients in active group and 1 patient in the sham group.
Weber-Rajek (2020)* (51)	MStim (44) vs PFMT (44) vs No treatment (40)	128 (84 were involved in the comparison)	SUI alone	MStim: see also table 23. PFMT: 3 sessions per week for 4 weeks (12 sessions, 45 minutes each). Control: no treatment.	Cure: NR RUIS score (Mstim vs Control: median (IQR) at final assessments): MStim (n=37) 7 (4) P=0.001 vs Control (n=34) 9 (5) P=0.19. Improvement: NR QoL via KHQ (Mstim vs Control: median, IQR at final assessments): General health/incontinence impact, N = 71, 33.3 (33.3) vs 33.3 (50), P=0.47; Role limitations, 33.3 (50) vs 33.3 (41), P=0.52; Physical limitations, N = 71, 0 (22.2) vs 22.2 (48.6), P=0.016; Social limitations, 22.2 (22.2) vs 22.2 (31.9), P=0.027; Personal relationships, 33.3 (50) vs 44.4 (45.8), P=0.033; Emotions, 33.3 (50) vs 50 (31.2), P=0.008; Sleep/energy, 41.7 (41.7) vs 38.2 (41.7), P=0.51; Severity measures, 25 (16.6) vs 31.3 (33.3), P=0.07; Bladder-related symptoms, 6 (2) vs 7.5 (4.5), P=0.14. Adverse effects: NR	4-week	Loss of follow-up: 7 patients in MStim group and 6 patients in the control group.

** Two arms of the study were involved in the comparison.*
Abbreviations: MStim: manual stimulation; SUI: stress urinary incontinence; NR: none reported; QoL: quality of life; KHQ: King's Health Questionnaire

5.2.2. Is one approach of MStim better than another in the treatment of UI?

No new study comparing one approach of MStim with another was found for this update. The level of evidence and recommendations remains unchanged from the sixth ICI edition.

Summary and Recommendation

No new trials contributed evidence in this area. A small trial (reviewed in the previous edition) comparing the two different MStim chairs in management of UI found no significant differences between the two MStim approaches (132). There is insufficient evidence to determine if one type of MStim is better than another. **(Level of evidence: 2)**

No recommendation is possible.

5.2.3. Is Mstim better than other treatments for the treatment of UI?

There were no trials for this comparison in the sixth ICI. A single new study was identified (51). Only two arms of the new study with multiple arms were included in the comparison. In the two-arms of the study, MStim was compared to PFMT in 88 women with SUI (51). The characteristics of the new study are presented in Table 7. Further analysis of this trial is found in section II.2.3.1. Randomisation was considered appropriate (51). Allocation concealment was considered unclear as important details were not described, although the use of envelopes was reported. The study only reported data from the participants who completed the study and found no significant differences between MStim and PFMT for UI symptoms, although it should be noted that the PFMT intervention was suboptimal with only four weeks of training.

Summary and Recommendation

A new trial assessed the effect of MStim compared to PFMT. Data from two arms of the small trial suggest no significant differences between MStim and a PFMT intervention of suboptimal intensity and duration (51). There is insufficient evidence to determine if MStim is superior to another treatment. **(Level of evidence: 2)**

It is not possible to make a recommendation regarding MStim vs PFMT.

5.2.4. Does the addition of MStim to other treatments add any benefit in the treatment of UI?

No new study was found investigating the effect of adding MStim to other treatments compared with the other treatments alone. The level of evidence and recommendations remain unchanged.

Summary and Recommendation

No new trials contributed evidence in this area. A small trial found no additional benefits to adding MStim to PFMT in women with SUI (132). **(Level of evidence: 2)**

Adding MStim to PFMT could not be recommended as this does not appear to add benefits. **(Grade of recommendation: C)**

6. TIBIAL NERVE STIMULATION (TNS)

Tibial nerve stimulation (TNS) is targeted towards symptom relief of OAB and UUI (133). Indirect access to the sacral plexus is achieved by intermittent, electrical stimulation of the tibial nerve, which lies behind the medial malleolus. TNS may be minimally invasive, involving insertion of a fine needle close to the nerve (Percutaneous TNS), or non-invasive, using skin surface electrodes applied to the medial malleolar area (Transcutaneous TNS) (133).

TNS aims to stimulate the sacral nerve plexus through the afferent fibres of the tibial nerve, a mixed nerve containing L5-S3 fibres (134). The S3 nerve root contains sensory fibres from the pelvic floor and parasympathetic motor efferent fibres to the detrusor muscle as well as the pelvic sphincters and the PFMs. Afferent nerve stimulation can therefore lead to activation of inhibitory sympathetic neurons and suppression of detrusor contraction through a direct sacral route. Urodynamic studies have shown that electrical stimulation of the tibial nerve increases cystometric capacity and suppresses detrusor contraction (135-137). The full mechanism of action of treatment effect for TNS is not yet fully understood, however it is thought that the observed effects may be related to a neuroplastic reorganisation of sacral spinal reflexes and regulation of cortical excitability (138, 139).

Percutaneous TNS is performed as an outpatient procedure. It involves inserting a 34-gauge needle 3–5 cm cephalad to the medial malleolus. The needle is connected to a low-voltage stimulator device, and a grounding pad is placed on the bottom of the foot just below the smallest toe. Transcutaneous TNS may be delivered either in clinic or self-administered at home. Self-adhesive electrodes are placed behind the medial malleolus and 10cm proximal to this. The positive lead is connected to the proximal electrode and the negative to the distal electrode, and both are connected to a portable battery-powered stimulator. The intensity level of the stimulation current for percutaneous TNS and transcutaneous TNS is determined once correct positioning has been established by noting sensory and motor (hallux) reaction (Figure 4).

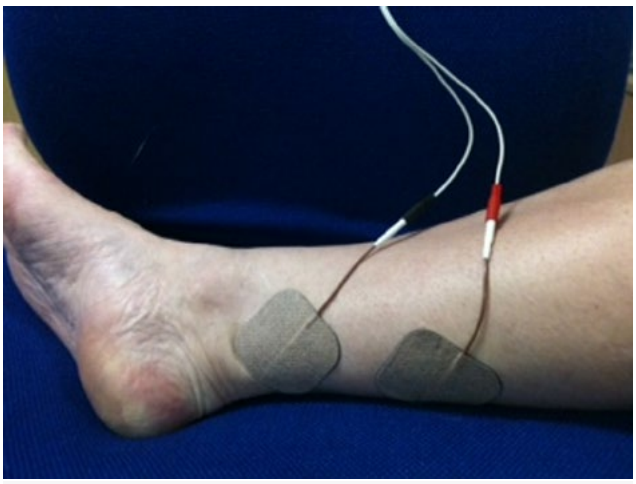

Figure 4. PTNS equipment

This section presents the updated evidence for the use of TNS in the prevention and treatment of UI in women. Date restrictions between Sep 2015 and December 2020 have been applied to the literature search and abstract-only reports have not been included.

Questions addressed are:
- Is TNS effective in the prevention of UI?
- Is TNS better than no active treatment (placebo, sham, control, or no treatment) for treatment of UI?
- Is one type of TNS better than another in the treatment of UI?
- Is TNS better than other treatments in the treatment of UI?
- Does the addition of TNS to other treatments add any benefit in the treatment of UI?
- What is the effect of TNS on other LUTS?
- What factors might affect the outcome of TNS in the treatment of UI?

Eligible interventions were TNS/neurostimulation/ neuromodulation, percutaneous or transcutaneous. Eligibility criteria for study participants and outcomes, as well as criteria used to assess 'ROB' in the included studies, were identical to those used in the previous section.

Evidence overview

A total of 17 new studies were eligible to add to the 11 studies in the 6th ICI, when TNS was first reported. Of these new studies 10 involved Transcutaneous TNS only (113-115, 140-146), 4 included Percutaneous TNS only (111, 147-149) and 3 compared Transcutaneous TNS and Percutaneous TNS. Two studies compared TNS with no active treatment (141, 146), both of which assessed transcutaneous TNS; four studies considered whether one type of TNS is better than another for UI and OAB treatment (141, 150-152); nine studies compared TNS with other treatments for UI (111, 114, 115, 142, 144, 147-150); five studies assessed the effects of adding TNS to another treatment for UI in women. No pooling of data was possible due to the heterogeneity in the interventions, comparators and outcome measures used.

The stimulation parameters for the new studies are summarised in Table 25. Treatment programmes for percutaneous TNS were similar across the studies, using the same stimulation frequency and intensity range for 30 minutes sessions, once weekly over a 12-week period. Transcutaneous TNS involved more varied treatment programmes with frequencies of 10-20Hz, stimulation intensity ranging from 10-50mA and a variety of delivery programmes ranging from 8 to 36 stimulation sessions delivered between 4- and 12-week periods.

Table 25. Summary of TNS protocols

Author, year	Type of TNS and current	Current Intensity	Pulse Shape & Duration	Frequency (Hz)	Duty Cycle	Electrodes	Treatment Duration	Number stimulation sessions (total)	Target UI
Abdulseoud (2018) (140)	TTNS NR	amplitude adjusted below patient's discomfort threshold.	250 micro-seconds	10	NR	Above and behind medial malleolus and other 10 cm cephalad	30 minutes, 8 weeks	24	OAB
Ahmed (2020) (150)	PTNS TTNS NR	PTNS: 0.5 – 9mA; adjusted in accordance to patient's tolerance TTNS: 10 – 50mA; according to sensitivity and hallux mobilisation	200 micro-seconds both	PTNS 20 TTNS 10	NR	PTNS: One 34gauge needle electrode, 4-5cm cephalad to medial malleolus. One surface electrode on the medial aspect of the calcaneus TTNS: Negative surface electrode placed behind medial malleolus and positive electrode placed 10cm above it	30 minutes, 3 times weekly, 12 weeks	36	OAB
Alve (2020) (141)	TTNS NR	Group 1: current maintained at sensory threshold (tingling sensation, but without any toe flexion /hallux) Group 2: current maintained at motor threshold (visualization of hallux flexion).	200 micro-seconds both -	10	NR	An electrode was fixed and positioned 10 cm above the medial malleolus, medial to the tibia, and the other electrode was movable and positioned posterior to the medial malleolus, and could follow the path of the tibial nerve.	30 minutes, 2 times weekly, 4 weeks	8	OAB older women
Aya-la-Quispe (2020) (151)	TTNS PTNS NR	TTNS: according to sensation in foot and hallux mobilisation PTNS: 0.5 – 8mA; adjusted in accordance to patient's tolerance	200 micro-seconds both	10	NR	TTNS: calcaneus (ground electrode) and other electrode to 5 cm above medial malleolus 1.5 cm posterior to tibia. Connected to stimulus BioTENS voltage meter. PTNS: surface electrode on calcaneus (ground electrode), needle inserted percutaneous 34 gauge to 5 cm above medial malleolus 1.5 cm posterior to tibia. Needle connected to BioTENS voltage meter.	20 minutes, once weekly, 12 weeks	12	Non-neurogenic, idiopathic OAB
Giarreta (2021) (113)	TTNS Continuous	highest intensity tolerated without reaching the motor threshold	200 micro-seconds	10	NR	One electrode placed inferior edge of medial malleolus, second electrode placed along tibial nerve path, 10 cm above the first.	30 minutes Once weekly 12 weeks	12	UUI SUI
Boaretto (2019) (142)	TTNS NR	According to patient threshold, below the motor threshold: range 10 - 25mA	200 micro-seconds	10	NR	Electrode placed between the medial malleolus and the Achilles tendon. Other placed 10cm above	30 minutes 2 times weekly 6 weeks	12	OAB UUI

Author, year	Type of TNS and current	Current Intensity	Pulse Shape & Duration	Frequency (Hz)	Duty Cycle	Electrodes	Treatment Duration	Number stimulation sessions (total)	Target UI
Bykoviene (2018) (143)	TTNS NR	Adjusted to highest level tolerated (10 – 50 mA) without pain/discomfort	300 micro-seconds	10	10sec work 15 sec rest ramp up 3 sec ramp down 2 sec	Both legs. Electrodes (5 x 5 cm) placed behind medial malleolus (negative) and 10 cm above the first one (positive).	30 minutes3 times weekly 6 weeks	18	UI OAB
Jacomo (2020) (114)	TTNS Biphasic	Adjusted below the motor response	200 micro-seconds	10	NR	One surface electrode placed below the left medial malleolus, second electrode placed 5 cm above the first.	30 minutes 2 times weekly 4 weeks	8	OAB
Kızılyel (2015) (147)	PTNS NR	Adjusted according to flexion of the big toe (0-10 mA).	200 micro-seconds	20	NR	34-gauge needle insert 5 cm above to either the right or left malleolus, the surface electrode was placed medial surface of the ipsilateral calcaneus.	30 minutes, Once weekly	12	OAB
Mallmann (2020) (115)	TTNS NR	Adjusted to maximum tolerable threshold	300 micro-seconds	20	NR	Neoprene anklet with embedded electrodes applied to tibial nerve path. Conducting gel used.	20 minutes 3 times weekly 6 weeks	18	OAB UUI MUI
Manríquez (2016) (144)	TTNS NR	Adjusted by patients each time they achieved motor response (plantar flexion of the big toe and/or toe fanning)	NR	20	NR	NR	30 minutes 2 times weekly 12 weeks	24	OAB
Martin-Garcia (2019) (152)	PTNS TTNS Continuous	TTNS: Adjusted avoiding flexion of the big toe or fanning or other toes PTNS: Adjusted according to flexion of the big toe or fanning of all toes, or tingling sensation in the sole of the foot, maximum tolerable level (0.1 – 20 mA)	200 micro-seconds	20	NR	TTNS: Bilaterally. Surface round electrodes, one placed 3 finger-breaths above the medial malleolus and the other medial surface of the ipsilateral calcaneus. PTNS: Bilaterally, 34-gauge needle insert 3 finger-breaths above the medial malleolus and posterior to the medial border of the tibia, the surface self-adhesive electrode was placed medial surface of the ipsilateral calcaneus.	TTNS 30 minutes, 3 times weekly 6 months. PTNS 30 minutes 4 weekly 6 months	TTNS > 78 PTNS: 6	OAB
Schreiner (2021) (145)	TTNS Continuous	According to the sensitivity and mobilization of the patient's hallux (10-50 mA)	200 micro-seconds	10	NR	Unilateral. Negative electrode was placed on the medial malleolus of the right ankle, and the positive electrode 10 cm proximal to the other	30 minutes Once weekly 12 weeks	12	UI
Ugurlucan (2013) (148)	PTNS NR	According to flexion of the great toe or fanning of the toes and a tingling sensation and adjusted to pain threshold	200 micro-seconds	20	NR	34-gauge needle insert 3-4 cm above the medial malleolus between the posterior margin of the tibia and soleus muscle.	30 minutes, Once weekly 12 weeks	12	OAB

Author, year	Type of TNS and current	Current Intensity	Pulse Shape & Duration	Frequency (Hz)	Duty Cycle	Electrodes	Treatment Duration	Number stimulation sessions (total)	Target UI
Vecchiolo-Scaldazza (2017) (111)	PTNS NR	NR	NR	NR	NR	NR	30 minutes, 2 times weekly 6 weeks	12	OAB
Vecchi-olo-Scaldaz-za (2018) (149)	PTNS NR	According to patient's sensory and motor response 0.5 – 9 mA	NR	20	NR	34-gauge needle insert 6-8 cm above to the medial malleolus and slightly posterior to the tibia	30 minutes once weekly 8-12 weeks	12	OAB
Welk (2020) (146)	TTNS NR	Patient was instructed to titrate the amplitude of the current to their maximum non-painful tolerance or toe twitch	200 micro-seconds	10	NR	Skin surface electrodes posterior and 5-10 cm above the medial malleolus of the same leg behind the medial tibial edge	30 minutes, 3 times weekly 12 weeks	36	OAB

Abbreviations: NR: not reported; TTNS: Transcutaneous tibial nerve stimulation; PTNS: Percutaneous tibial nerve stimulation; OAB: Overactive bladder; UUI: urge urinary incontinence; SUI: stress urinary incontinence; UI: urinary incontinence; MUI: mixed urinary incontinence

6.1. Prevention

No studies that investigated either primary or secondary prevention of UI or LUTS were identified.

6.2. Treatment

6.2.1. Is TNS better than no active treatment (placebo, sham, control, or no treatment) for treatment of UI?

Two new studies compared transcutaneous TNS with no active treatment (Table 26) (141, 146). Both studies included women with OAB where some but not all participants had UI. In one study (141) the participants were older women aged 60 years and over.

In one study, outcomes from participants in a sensory-threshold group and those in a motor-threshold group were compared with no stimulation (141). A sham procedure was employed as a comparator in the other study (146). The sham procedure was described as having electrodes placed on the lateral side of the lower leg and using a frequency of 10Hz and a pulse width of 200microseconds, increased in intensity until they could feel a tingling sensation.

Quality of data

Both studies described using computer generated randomisation and allocation concealment but neither study reported the method of allocation concealment. Blinding of assessors was confirmed in both studies. Results were reported for everyone who entered the trial in one study (146), and the other study (141) reported attrition of 6/39 from the sensory-threshold group, 3/33 from the motor-threshold group and 4/29 from the no intervention control group. The reasons for drop out from each group were unrelated to the treatment. Sample size calculations were provided in both studies. Analysis was by ITT in one (146) and per protocol in the other (141). Adverse events were 'almost nil' in one study (141) and no adverse effects were reported in the other (146). Overall, ROB was assessed as high for both studies.

Results

(a) UUI. Neither included study reported information on cure rates. In one study (141) UUI episodes and ICIQ-OAB improved statistically significantly in both the sensory-threshold and the motor-threshold groups compared with no active treatment. No difference in 24-hour pad weights was found between the transcutaneous TNS group and sham group in the other study (146). Reported degree of discomfort associated with UUI was statistically significantly reduced in both groups in one study (141). No serious adverse effects were reported in either group.

(b) DO/OAB. There was no information on cure rates. In one study (141) urinary frequency, urgency, nocturia were statistically significantly improved in both the sensory-threshold and the motor-threshold groups compared with no active treatment. No difference in Patient Perception of Bladder Condition or frequency was found between the transcutaneous TNS

group and sham group in the other study (146). Reported degree of discomfort associated with UUI was statistically significantly reduced in both groups in one study (141).

Summary

A total of five studies assessed the effects of TNS compared with no active treatment. One study investigated percutaneous TNS, and four studies investigated transcutaneous TNS. Four studies were small (20-43 participants), and one had 101 participants. Four were generally assessed as having a high ROB and one had a low ROB but was small and underpowered. Data pooling was not possible.

Data available from three studies on women with UUI or OAB suggests TNS may be more effective than no active treatment in improving symptoms and quality of life, although no data were available on cure. **(Level of evidence: 2)**

The included studies reported no serious adverse effects associated with either active or sham treatment. **(Level of evidence: 2)**

No evidence was available for women with SUI or predominant SUI.

Recommendations

For women with UUI or OAB, TNS could be considered as its use may be more effective than no active treatment in symptom control. **(Grade of recommendation: C)**

More studies with larger sample sizes and consistent and clear reporting of core outcomes would be beneficial in reaching a conclusion on the effectiveness of TNS over no active treatment.

Table 26. Summary of data on TNS compared with No Active Treatment (Placebo, Sham, Control or No Treatment)

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
UUI					
Alve (2020) (141)	Group 1: current maintained at sensory threshold (tingling sensation, but without any toe flexion /hallux) Group 2: current maintained at motor threshold (visualization of hallux flexion). Group 3: control. No intervention	101 Group 1: 39 Group 2: 33 Group 3: 29	Women > 60	1 30 minutes sessions, 2 times weekly, 4 weeks	Cure: NR Sensory TTNS vs control UUI episodes: AMD (95% CI) -1.562 (-2.282 to -0.843), p=0.000 Urge-Incontinence Discomfort: AMD (95% CI) −5.513 (-7.454 to -3.572) p=0.000 ICIQ-OAB: AMD (95% CI) -5.115 (-6.601 to -3.630), p=0.000 Motor TTNS vs control UUI episodes: AMD (95% CI) -1.047 (-1.782 to -0.312), p=0.006 Urge-Incontinence Discomfort: AMD (95% CI) −4.273 (-6.256 to -2.291) p=0.000 ICIQ-OAB: AMD (95% CI) -4.700 (-6.217 to -3.183), p=0.000 Adverse events: almost nil (both groups presented minimal discomfort)
Welk (2020) (146)	Group 1: Transcutaneous TNS Group 2: sham	20 Group 1: 10 Group 2: 10	OAB	3	Cure: NR 24 h pad weights TTNS: Means (95%) 204 (77-333) Sham Means (95%) 135 (0-270). Between-group: p=0.44 Adverse events: none
OAB					
Alve (2020) (141)	Group 1: current maintained at sensory threshold (tingling sensation, but without any toe flexion /hallux) Group 2: current maintained at motor threshold (visualization of hallux flexion). Group 3: control. No intervention	101 Group 1: 39 Group 2: 33 Group 3: 29	Women > 60	1 30 minute sessions, 2 times week-ly, 4 weeks	Cure: NR Sensory TTNS vs control Urinary frequency: AMD (95% CI) −3.950 (-5.519 to -2.380), p=0.000 Nocturne: AMD (95% CI) −1.392 (-2.174 to -0.610), p=0.001 Urgent episodes: AMD (95% CI) −1.697 (-2.470 to -0.925), p=0.000 Motor TTNS vs control Urinary frequency: AMD (95% CI) −3.910 (-5.513 to -2.307), p=0.000 Nocturne: AMD (95% CI) −1.086 (-1.884 to -0.287), p=0.008 Urgent episodes: AMD (95% CI) −1.368 (-2.157 to -0.579), p=0.001 Adverse events: almost nil (both groups presented minimal discomfort).
Welk (2020) (146)	Group 1: Transcutaneous TNS Group 2: sham	20 Group 1: 10 Group 2: 10	OAB	3	Cure: NR Patient Perception of Bladder Condition TTNS: Means (95%) 3 (2-4) Sham Means (95%) 4 (3-5). Between-group: p=0.26 Daily frequency TTNS: Means (95%) 12 (11-13) Sham Means (95%) 12 (11-14). Between-group: p=0.89 Adverse events: none

Abbreviations: UUI: urge urinary incontinence; OAB: overactive bladder; NR: not reported; TTNS: transcutaneous tibial nerve stimulation; UUI: urge urinary incontinence; ICIQ-OAB: International Consultation on Incontinence Questionnaire – Overactive bladder: TNS: tibial nerve stimulation: AMD: Adiusted Mean Difference.

6.2.2. Is one type of TNS better than another in the treatment of UI?

Four studies compared types of TNS. Transcutaneous TNS and percutaneous TNS were compared in three studies (150-152) and one study compared transcutaneous TNS delivered at two different stimulation intensities – sensory threshold and motor threshold (141) (Table 27). Two studies investigated TNS as a primary intervention for UUI (141, 151) and one investigated effectiveness of transcutaneous TNS compared to percutaneous TNS for maintenance of symptom improvement in responders to percutaneous TNS (152)lectronic-resource-num></record></Cite></EndNote>A. A further study compared transcutaneous TNS and percutaneous TNS added to drug therapy for reducing severity of overactive bladder symptoms in post-menopausal women (150).

Quality of data

Computerised randomisation was used in two studies (141, 151) and sealed envelopes in two (141, 152). Adequate allocation concealment was reported in one study (152) and was unclear in the other three (141, 150, 151). Two studies (150, 151) did not report blinding of assessors however assessor blinding was reported by two (141, 152). One study reported ITT analysis (152), one a per protocol analysis (141); the type of analysis was not reported in two (150, 151). There was no attrition in two trials (150, 152) and no apparent inequality in loss to follow-up across the groups in one study (141), where attrition of 15% in the transcutaneous TNS sensory-threshold group, 9% in the motor-threshold group and 14% in the control group were reported, but reasons were not given. Ayala-Quispe (2020) (151) did not report on follow-up. Adverse events were 'almost nil' in both sensory and motor thresholds in one study of transcutaneous TNS (141). No adverse effects associated with transcutaneous TNS were reported for three studies (150-152) but two studies reported minor discomfort with percutaneous TNS (151, 152) and bleeding at the needle site was reported by one (152). Power calculations were reported for two studies (141, 152). Overall ROB was low in two trials (141, 152) and high in two studies (150, 151).

Results

a) UUI: No included studies reported information on cure rates. Two studies (141, 151) reported statistically significant reductions in UUI episodes. One with transcutaneous TNS at both sensory-threshold and motor-threshold compared to no treatment (p=0.0001) (141) and one with transcutaneous TNS and percutaneous TNS compared to baseline (p=0.0001) (151). Two studies found no statistically significant difference between effectiveness of transcutaneous TNS and percutaneous TNS for treating UUI at 12 weeks (p=0.968) (151) or for maintaining outcomes over a 6-month period (p=0.755) (152). One study found no statistical difference between two stimulation intensities of transcutaneous TNS at 5 weeks (p= 0.139) (141).

b) OAB: No included studies reported information on cure rates. Two studies (150, 151) reported statistically significant reductions in OAB symptoms with both transcutaneous TNS and percutaneous TNS compared to baseline (p<0.0001, (150); p=0,0001, (151)). One study reported statistically significant reductions in OAB symptoms with transcutaneous TNS delivered at both sensory and motor thresholds compared to no treatment (p=0.0001) (141). Two studies found no statistically significant difference between effectiveness of transcutaneous TNS and percutaneous TNS for treating OAB symptoms at 12 weeks (p=0.947, (150); p=0.968; p=0.436, (151)) or for maintaining outcomes over a 6-month period (p=0.160) (152). One study found no difference between effectiveness of sensory and motor thresholds of transcutaneous TNS for treating OAB symptoms at 5 weeks (frequency p=0.186, urgency p=0.375, nocturia p=0.415, (141)). No difference in quality of life improvement was found between the two types of TNS in two studies (p=0.577, (150); p=0.088, (151)).

Summary

Four small studies (24-72 participants) assessed different types of TNS and three had a high ROB. Three assessed the effects of transcutaneous TNS compared to percutaneous TNS and reported no difference between percutaneous TNS and transcutaneous TNS in effectiveness for treatment of urgency UI or OAB symptoms. **(Level of evidence: 2)**

Two studies reported no differences in QoL improvements between transcutaneous TNS and percutaneous TNS.

Overall data available from three studies on women with UUI or OAB suggests transcutaneous TNS and percutaneous TNS are equally effective in improving symptoms and quality of life, although no data were available on cure. **(Level of evidence: 2)**

One study compared two different intensities of transcutaneous TNS and found both were effective in treating urgency UI and OAB symptoms in women.

Two studies reported minor adverse effects associated with percutaneous TNS. No adverse effects associated with transcutaneous TNS were reported by three studies. (**Level of evidence: 2)**

Recommendation

For women with urgency UI or OAB, transcutaneous and percutaneous TNS could be recommended as each is equally effective treatments. Transcutaneous TNS is associated with fewer adverse effects. **(Grade of recommendation: C)**

More studies with larger sample sizes and consistent and clear reporting of core outcomes would be beneficial in reaching a conclusion on the effectiveness of transcutaneous TNS compared with percutaneous TNS.

Table 27: Summary of data comparing types of TNS

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
UUI					
Alve (2020) (141)	Transcutaneous TNS: Group 1: current maintained at sensory threshold (tingling sensation, but without any toe flexion /hallux) Group 2: current maintained at motor threshold (visualization of hallux flexion).	72 Group 1: 39 Group 2: 33	Women > 60	30 minutes sessions, 2 times week-ly, 4 weeks	Cure: NR UUI episodes: AMD (95% CI) −0.515 (-1.199 to 0.170), p=0.139 Urge-Incontinence Discomfort: AMD (95% CI) −1.239 (-3.086 to 0.607) p=0.186 ICIQ- OAB: AMD (95% CI) -0.415 (-1.829 to 0.998), p=0.561 Adverse events: almost nil (both groups presented minimal discomfort).
Ayala-Quispe (2020) (151)	Group 1: Transcutaneous TNS Group 2: Percutaneous TNS	61 Group 1: 33 Group 2: 28	Idiopathic OAB	3	Cure: NR Number of UUI episodes: TTNS: UUI episodes decreased significantly – 6 weeks: Mean difference 2.18 (95% CI 1.74-2.63) P< 0.0001* 12 weeks: Mean difference 1.82 (95% CI 1.44-2.20) P < 0.0001 PTNS: UUI episodes decreased significantly 6 weeks: Mean difference 2.68 (95% CI 2.11-3.35), P< 0.0001 12 weeks: Mean difference 1.52 (95% CI 1.02-2.03) P < 0.0001 Between-group comparison showed no statistical difference at 6 weeks (P = 0.99) and 12 weeks (P = 0.968). No serious adverse events.
Martin-Garcia (2019) (152)	Group Transcutaneous TNS vs Percutaneous TNS	24 TTNS: 12 PTNS: 12	Idiopath-ic OAB who had responded to PTNS	6	Cure: NR Improvement based on diary: TTNS: Number of UUI episodes per 24h. NS. Median (IQR) pre- 0.5 (1) post- 0.2 (1.7), P = 0.9 PTNS: Number of UUI episodes per 24h. NS. Median (IQR) pre- 0 (1.5) post- 0 (0.7), P = 0.655 Between-group p=0.755 Adverse effects: TTNS no adverse events reported. PTNS 3 participants reported minor episodes – 2 reported bleeding at the needle site and 1 episode of discomfort/pain over the needle area
OAB					

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
Ahmed (2020) (150)	Group 1: Transcutaneous TNS + daily oxybutynin Group 2: Percutaneous TNS +daily oxybutynin	60 Group 1: 20 Group 2: 20	OAB in post-menopausal women	3	Cure: NR Improvement in OABq: TTNS decreased significantly 65.96± 14.45 to 41.3±12.12 (P<0.0001) and PTNS decreased significantly 65.61 ± 14.06 to 42.45±12.36 (P<0.0001). Between-group comparison showed no statistical difference (P = 0.947) HRQoL improvement: TTNS increased significantly 47.18± 8.68 to 73.61±8.14 (P<0.0001) and PTNS increased significantly 65.61 ± 14.06 to 42.45±12.36 (P<0.0001). Between-group comparison showed no statistical difference (P = 0.577) Maximum bladder capacity: TTNS increased significantly 262.65± 13.44 to 355±20.28 (P<0.0001) and PTNS increased significantly 263.45 ± 13.2 to 353.8±17.53 (P<0.0001). Between-group comparison showed no statistical difference (P = 0.945) Adverse effects: NR
Alve (2020) (141)	Transcutaneous TNS: Group 1: current maintained at sensory threshold (tingling sensation, but without any toe flexion /hallux) Group 2: current maintained at motor threshold (visualization of hallux flexion).	72 Group 1: 39 Group 2: 33	Women > 60	30 minutes sessions, 2 times weekly, 4 weeks	Cure: NR Urinary frequency: AMD (95% CI) −1.239 (-3.086 to 0.607), p=0.186 Nocturne: AMD (95% CI) −0.306 (-1.050 to 0.438), p=0.415 Urgent episodes: AMD (95% CI) −0.329 (-1.064 to 0.405), p=0.375 Adverse events: almost nil (both groups presented minimal discomfort).

Abbreviations: TNS: tibial nerve stimulation; TTNS: transcutaneous tibial nerve stimulation; PTNS: percutaneous tibial nerve stimulation; OAB: Overactive bladder; NR: not reported; ICIQ-OAB: International Consultation on Incontinence Questionnaire – Overactive bladder; UUI: urge urinary incontinence; NS: non-significant; OABq: Overactive Bladder Questionnaire; IQR: interquartile range; AMD: Adjusted Mean Difference; CI: confidence interval; HRQoL: Health-Related Quality of Life.

6.2.3. Is TNS better than other treatments for treatment of UI?

Nine new studies compared TNS with another treatment (111, 114, 115, 142, 144, 147-150) (Table 28). Four studies assessed transcutaneous TNS (114, 115, 142, 144), four assessed percutaneous TNS (111, 147-149) and one compared both transcutaneous TNS and percutaneous TNS with another treatment (150). In five studies the other treatment was an antimuscarinic drug: oxybutynin (142, 144, 150), solifenacin (149), tolterodine (147). In three studies TNS was compared with another type of EStim: transvaginal Estim (148); parasacral transcutaneous electrical stimulation (114, 115) and in one study percutaneous TNS was compared with transvaginal EStim and PFMT (111). The target population had OAB (with UI in some but not all of the participants) except for one study (142) where the participants all had UUI. One study was focused on OAB symptoms (150). No study on SUI or predominant SUI was found. Six studies were two arm randomised trial designs and three were three-arm trials comparing percutaneous TNS vs tolterodine vs percutaneous TNS and tolterodine (147); percutaneous TNS vs solifenacin vs percutaneous TNS and solifenacin (149); or transcutaneous TNS vs oxybutynin vs PFMT (142). The findings for TNS versus a single other treatment are reported here.

Quality of data

Computerised randomisation was used in five studies (111, 114, 115, 148, 149), sealed envelopes in one (150) and method of randomisation was not reported in three studies (142, 144, 147). Adequate allocation concealment was reported in four studies (111, 114, 149, 150) and was unclear in the other five (115, 142, 144, 147, 148). Blinding of participants and/or intervention providers was not reported by any study as this is not possible for the type of physical interventions under investigation. However, assessor blinding was only reported in three studies, by two investigators (111, 114, 149). One study reported a per protocol analysis (114) and in all others type of analysis undertaken was not reported. Attrition rates were provided in five studies (114, 115, 144, 148, 149). Attrition in three studies comparing TNS with another form of EStim (114, 115, 148) showed similar losses of 14% in one

(114) due to participant travel difficulties; greater loss to follow up in the parasacral transcutaneous electrical stimulation group of 16% compared with no loss in the TNS group (115) and twice the attrition in the TNS group compared to the transvaginal EStim group in one study (148) but no reasons were provided for loss in either study. No loss to follow-up was reported in three studies (111, 147, 150) and no information was provided on attrition by one study (142). Two studies comparing TNS with antimuscarinic drug treatment provided information on attrition, both showing higher attrition in the groups receiving the drugs. Attrition of 23% was found in the group taking solifenacin compared to 3% in those receiving percutaneous TNS in one study (149) due to side effects of dry mouth and constipation. Similar side effects were the reasons provided for attrition in another study where 12% of the drug group were lost to follow up compared to 6% of the transcutaneous TNS group (144). No other adverse effects were noted in the seven studies that reported them (111, 114, 115, 142, 144, 147, 149). Power calculations were reported for three studies (114, 115, 144). Overall, ROB was high in eight trials (111, 115, 142, 144, 147-150) and low in one study (114).

Results

(a) UUI. One study reported information on cure rates. Significantly more women receiving transvaginal EStim reported they were cured compared to those receiving percutaneous TNS (148) (p=0.08) however the study was underpowered with a high ROB and disproportionate attrition of 23% in those receiving percutaneous TNS compared to 8% in the transvaginal EStim group, with no reasons provided. The interventions differed in terms of number of stimulation sessions: 18-24 transvaginal EStim group compared with 12 in the percutaneous TNS group.

Improvements in UUI episodes were reported in seven trials (111, 114, 115, 142, 144, 147-149). Four studies compared TNS with a drug treatment (136, 142, 144, 149) and reported outcomes for UUI. In three studies outcomes were based on bladder diaries (142, 144, 147) and in one the OABSS (149). In all four studies (144, 147, 149) UUI episodes were statistically significantly decreased in the TNS group and three studies also reported statistically significant reductions in the antimuscarinic drug groups (144, 147, 149). One study reported statistically significantly better reduction in UUI episodes using percutaneous TNS compared to tolterodine (147) and one 3-arm study (142) reported statistically significantly better reductions in UUI episodes with transcutaneous TNS compared to oxybutynin and also with transcutaneous TNS compared to PFMT. For the four studies comparing TNS and other forms of EStim (111, 114, 115, 148) three reported UUI based on bladder diaries (111, 114, 148). Two reported statistically significant reductions in UUI episodes with both types of EStim (114, 148) and no between group differences in effectiveness. One study (111) showed statistically significant reductions in the number of UUI episodes following a course of percutaneous TNS but not with transvaginal EStim combined with PFMT. In one study (115) there was no difference between transcutaneous TNS and parasacral transcutaneous electrical stimulation in improvements in the proportions of categories in the Incontinence Severity Index (p=0.307).

Quality of life outcomes were reported by five trials (115, 142, 147-149) and in all, QoL was statistically significantly improved with TNS. Three studies reported no statistically significant difference between the groups, based on KHQ in two studies (115, 148) and the PGI-I at 3 months (post-treatment) in one study (149). However, in one study (147) a statistically significant difference in the IIQ-7 at three months was reported between the groups in favour of percutaneous TNS and in another (149) at 10 months' follow-up, where the PGI-I was statistically significantly better in the percutaneous TNS group than the solifenacin group. One study (142) reported statistically significantly improved quality of life in the TNS, PFMT and oxybutynin groups based on the Overactive Bladder-V8 (OAB-V8) but did not compare them.

(b) OAB: In one study (142) 32% participants reported their urgency to be cured following 12 sessions of transcutaneous TNS. An equal number reported cure with a 12 sessions programme of PFMT. Improvements in OAB symptoms after TNS interventions were reported by five studies based on bladder diary information: five studies reported statistically significant improvements in urinary frequency (111, 142, 144, 147, 149); four studies reported statistically significant improvements in urgency (111, 114, 144, 149), five studies reported statistically significant improvements in nocturia (111, 114, 142, 147, 149).

Quality of life outcomes were reported in four studies based on the Overactive Bladder Questionnaire (OABq). Statistically significant improvements with both percutaneous and transcutaneous TNS added to oxybutynin compared to oxybutynin alone were reported (150); and with percutaneous TNS compared with transvaginal EStim and PFMT (111) and transcutaneous TNS compared with extended release oxybutynin (144). No difference between the groups was found in two studies (149, 150). Statistically significantly improved scores on the OAB-V8 with transcutaneous TNS compared to parasacral stimulation were found in one study (115).

Summary

Nine new studies were included bringing the total to fourteen comparing TNS with another treatment. These were small (20-70 participants) and generally assessed as having a high ROB. There were limited and widely heterogeneous data reporting mainly short-term outcomes with minimal long-term follow up. Data pooling was not possible.

Comparing TNS with drug treatment, three studies reported TNS to be as effective as drug treatment and one study reported transcutaneous TNS to be better than drug treatment for treating urgency UI in the short-term. **(Level of evidence: 2)**

Two studies reported that quality of life improved at three months with both TNS and drug treatment, with no significant difference between them, but in one of the studies only the percutaneous TNS group maintained improved quality of life at 10 months follow up. One study reported that quality of life improved more in the percutaneous TNS group. **(Level of evidence: 2)**

When comparing TNS with other non-drug treatments for urgency UI, two studies reported TNS to be statistically significantly better than the other treatment (parasacral EStim; transvaginal EStim plus PFMT) and two studies reported TNS to be as effective as other forms of ES. **(Level of evidence: 2)**

For reducing severity of OAB symptoms TNS was statistically significantly better than drug treatment in two studies and it was as effective as drug treatment for reducing symptoms of frequency (three studies), urgency (two studies) and nocturia (one study)**. (Level of evidence: 2)**

TNS was better at reducing overall OAB symptom severity compared with other-non-drug treatment (parasacral EStim; transvaginal EStim plus PFMT) in two studies. Urgency, nocturia and frequency improved significantly with TNS in two studies compared to another non-drug treatment. **(Level of evidence: 2)**

Table 28. Summary of data on TNS vs other treatments

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
UUI					
Boaretto (2019) (142)	Group 1 : Transcutaneous TNS Group 2 : PFMT Group 3 : oxybutynin	65 TTNS n=22 PFMTn=22 Oxybutynin n=13	UUI	3	Cure: NR Improvement based on diary: TTNS: UUI episodes decreased. Significant Mean (SD) pre-1.7±2.1, post-0.5±0.9, P=0.015 PFMT: UUI episodes decreased. NS Mean (SD) pre-0.8±1.7, post-0.4±0.7, P=0.130 Oxybutynin: UUI episodes decreased. NS Mean (SD) pre-1.7±2.1, post-1±1.3, P=0.262 QoL via OAB-V8: TTNS: Improved significantly Mean (SD) pre- 23.55±7.13, post- 13.18±9.85, P= 0.035 PFMT: Improved significantly Mean (SD) pre- 22.68±8.51, post- 10.27±6.2, P=0.000 Oxybutynin: Improved significantly Mean (SD) pre- 23.92±8.84, post- 12.77±11.35, P=0.000 Adverse effects: No events noted
Jacomo (2020) (114)	Group 1 : Transcutaneous TNS Group 2: parasacral TENS	58 Group 1: 29 Group 2: 29	OAB	2	Cure: NR Improvement based on diary: TTNS: UUI episodes decreased. Significant. MD 1.19 (0.13 to 2.25), P < 0.001 PS: UUI episodes NS. MD -0.23 (-1.59 to 1.12), P = 0.84 ICIQ-SF: TTNS: Improved significantly MD 6.3 (3.46 to 9.14), P < 0.001 PS: Improved significantly MD 5.33 (1.8 to 8.87), P < 0.001 No Between-group differences in ICIQ-SF scores and number of UUI episodes Adverse effects: No events noted
Kizilyel (2015) (147)	Group 1: Percutaneous TNS Group 2: Tolterodine	20 Group 1: 10 Group 2: 10	Refractory OAB	3	Cure: NR Improvement based on diary: PTNS (n=4): UUI episodes decreased. Significant. Mean (SD) pre- 1.2 ± 1.6 post- 0.13 ± 0.23, P = 0.003 Tolterodine (n=9): UUI episodes decreased. Significant. Mean (SD) pre- 2.43 ± 1.05 post- 1.93 ± 0.86, P = 0.02 Between-group: PTNS vs Tolterodine MD: -1.8 (-2.41 to -1.19) P < 0.00001 UDI-6: PTNS: Significant decrease. Mean (SD) pre- 8 ± 1.5 post- 2.9 ± 1.59, P = 0.001 Tolterodine: UUI episodes decreased. Significant. Mean (SD) pre- 9.7 ± 2.58 post- 7.6 ± 2.95, P = 0.002 Between-group: PTNS vs Tolterodine MD: -4.7 (-6.78 to -2.62) P < 0.00001 IIQ-7: PTNS: Significant decrease. Mean (SD) pre- 17.5 ± 1.73 post- 5.75 ± 0.95, P = 0.039 Tolterodine: UUI episodes decreased. Significant. Mean (SD) pre- 14.6 ± 5.19 post- 13 ± 4.74, P = 0.016 Between-group: PTNS vs Tolterodine MD: -7.25 (-10.25 to -4.25) P < 0.00001 Adverse effects: NR

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
Mallmann (2020) (115)	Group 1: Transcutaneous TNS Group 2: parasacral transcutaneous electrical stimulation	50 Group 1: 50 Group 2: 50	OAB wet	1.5	Cure: NR Improvement in proportion of categories of Incontinence Severity Index post-intervention in both groups; no differences between groups P=0.307 QoL No between-group differences in KHQ domains or symptom scale post-intervention Adverse effects: No events noted
Manriquez (2016) (144)	Group 1: Transcutaneous TNS Group 2: extended release oxybutynin	70 Group 1: 36 Group 2: 34	OAB	3	Cure: NR Improvement based on diary: TTNS: UUI episodes. Significant. Median and range pre- 5 (0-24), post- 0 (0-30), P= 0.001 Oxybutynin : UUI episodes. Significant. Median and range pre- 4 (0-22), post- 0 (0-27), P= 0.0005 Between-group comparison: NS p=0.232 TTNS: Daily pads. Significant. Median and range pre- 7 (0-19), post- 2 (0-13), P= 0.0022 Oxybutynin : Daily pads. Significant. Median and range pre- 9 (0-36), post- 0 (0-30), P= 0.001 Between-group comparison: NS p=0.767 Adverse effects: No events noted in the TTNS group. 3 participants in the oxybutynin group reported adverse events (dry mouth)
Ugurlucan (2013) (148)	Group 1: Percutaneous TNS Group 2: transvaginal EStim	52 Group 1: 17 Group 2: 35	OAB	PTNS 3 ES 2	Cure: PTNS: 1/17 EStim: 12/35 RR: 0.17 (0.02 to 1.21) p = 0.08 1-hour Pad-test PTNS: Decrease NS. Mean (SD) pre- 30.4 ± 47.9 post- 19.8 ± 26.2, P = 0.721 EStim: Significant decrease. Mean (SD) pre- 14.9 ± 26.9 post- 0.7 ± 3.7, P = 0.000 Between-group p = 0.242 Improvement based on diary: PTNS: Mean number of incontinence episodes. Significant decrease. Mean (SD) pre- 2.4 ± 2.3 post- 1.4 ± 1.5, P = 0.018 EStim: Mean number of incontinence episodes. Significant decrease. Mean (SD) pre- 2.3 ± 2.6 post- 0.9 ± 1.4, P = 0.034 Between-group p = 0.45 KHQ Total score PTNS: NS. Mean (SD) pre- 467.9 ± 189.1 post- 394.9 ± 214.7, P = 0.19 EStim: Significant decrease. Mean (SD) pre- 469.7 ± 222.4 post- 328.1 ± 195.1, P = 0.02 Between-group p = 0.32 Adverse effects: NR

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
Vecchiolo-Scaldazza (2017) (111)	Group 1: Percutaneous TNS Group 2: EStim with PFMT	60 Group 1: 30 Group 2: 30	OAB	PTNS 3 months ES plus PFMT 6 months	Cure: NR Improvement based on diary: PTNS: Mean number of urge incontinence. Significant decrease. Mean (SD) pre- 3.05 ± 0.97 post- 1.45 ± 1, P = 0.0009 EStim: Mean number of urge incontinence. NS. Mean (SD) pre- 2.54 ± 0.63 post- 2.0 ± 0.68, P = 0.1293 Between-group p = 0.0251 Adverse effects: No events noted
Vecchiolo-Scaldazza (2018) (149)	Group 1: Percutaneous TNS Group 2: solifenacin succinate	70 Group 1: 35 Group 2: 35	OAB	PTNS 3 months SS 3 months	Cure: NR Improvement OABSS after treatment: PTNS: UUI episodes decreased. Significant. Mean (SD) pre- 4 ± 0.69 post- 2.24 ± 1.35, P = 0.0001 SS: UUI episodes decreased. Significant. Mean (SD) pre- 3.71 ± 1.12 post- 2.67 ± 1.49, P = 0.0005 Between-group: PTNS vs SS P = 0.3742 PGI-I after treatment: PTNS: UUI episodes decreased. Significant. Mean (SD) 2.41 ± 0.84 SS: UUI episodes decreased. Significant. Mean (SD) 2.81 ± 0.96 Between-group: PTNS vs SS P = 0.1997 PGI-I 10 months follow-up: PTNS: UUI episodes decreased. Significant. Mean (SD) 2.1 ± 1.92 SS: UUI episodes decreased. Significant. Mean (SD) 0.71 ± 1.13 Between-group: PTNS vs SS P = 0.0017 Adverse effects: PTNS group none reported, SS group n=8 (dry mouth and constipation, PTNS + SS n=1.
OAB					
Ahmed (2020) (150)	Group 1: Transcutaneous TNS + daily oxybutynin (10 mg) Group 2: Percutaneous TNS +daily oxybutynin (10 mg) Group 3: daily oxybutynin (10 mg)	60 Group 1: 20 Group 2: 20 Group 3: 20	OAB	3	Cure: NR Improvement in OABq: Control group (daily oxybutynin) decreased significantly 64.13± 13.81 to 53.19± 9.89 (P<0.0001). Between-group comparison (Control group vs TTNS and Control group vs PTNS) showed significant statistical difference (P<0.0001) HRQoL improvement: Control group (daily oxybutynin) decreased significantly 48.63± 9.26 to 62.92± 5.87 (P<0.0001). Between-group comparison (Control group vs TTNS and Control group vs PTNS) showed significant statistical difference (P<0.0001) Adverse effects: NR

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
Boaretto (2019) (142)	Group 1: Transcutaneous TNS Group 2: PFMT Group 3: Oxybutynin	65 TTNS n=22 PFMT n=22 Oxybutynin n=13	UUI	3	Urinary frequency Cure: NR Improvement based on diary: TTNS: Frequency decreased. Significant Mean (SD) pre-7.8±2.7, post-7.1±2.0, P=0.015 PFMT: Frequency decreased. NS Mean (SD) pre-6.9±1.9, post-6.2±1.8, P=0.150 Oxybutynin: Frequency decreased. Significant Mean (SD) pre-7.4±2.4, post-5.6±2.2, P=0.014 Nocturia Cure:NR Improvement based on diary: TTNS: Nocturia decreased. Significant Mean (SD) pre- 2.5±1.7, post- 1.8±1.5, P=0.012 PFMT: Nocturia decreased. Significant Mean (SD) pre- 1.7±1.3, post- 1.1±1.1, P=0.005 Oxybutynin: Nocturia decreased. NS Mean (SD) pre- 3.3±1.8, post- 3.0±2.1, P=0.646 Urgency Cure: TTNS: 7 of 22 (32%) PFMT: 7 of 22 (32%) Oxybutynin 3 of 13 (23%) RR: TTNS vs PFMT: 1 (0.42 to 2.38) p=1 TTNS vs Oxybutynin: 1.38 (0.43 to 4.42) p=0.59
Jacomo (2020) (114)	Group 1: Transcutaneous TNS Group 2: parasacral TENS	58 Group 1: 29 Group 2: 29	OAB	2	Cure: NR Improvement based on diary: TTNS: Daytime micturition frequency NS MD -0.06 (-2.16 to 2.03), P = 0.87 PS: Daytime micturition frequency NS. MD 0.68 (-0.12 to 1.49), P = 0.07 TTNS: Number of urgency episodes decrease significantly MD 0.71 (0.16 to 1.27), P < 0.001 PS: Number of urgency episodes NS. MD 0.10 (-0.8 to 0.99), P = 0.373 TTNS: Nocturia decrease significantly MD 0.46 (0.10 to 0.97), P < 0.001 PS: Nocturia decrease significantly MD 0.93 (0.31 to 1.55), P < 0.001 ICIQ-OAB: TTNS: Improved significantly MD 4.43 (2.37 to 6.48), P < 0.001 PS: Improved significantly MD 2.57 (0.63 to 4.51), P < 0.001 Adverse effects: No events noted

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
Kizilyel (2015) (147)	Group 1: Percutaneous TNS Group 2: Tolterodine	20 Group 1: 10 Group 2: 10	Refractory OAB	3	Cure: NR Improvement based on diary: PTNS: Void frequency decreased. Significant. Mean (SD) pre- 10.1 ± 0.88 post- 8.9 ± 0.88, P = 0.011 Tolterodine: Void frequency decreased. Significant. Mean (SD) pre- 11.27 ± 0.44 post- 10.57 ± 0.5, P = 0.024 Between group: PTNS vs Tolterodine MD: -1.67 (-2.3 to -1.04) P < 0.00001 PTNS: Nocturia decrease. Significant. Mean (SD) pre- 5.3 ± 0.9 post- 2.03 ± 0.5, P = 0.007 Tolterodine: Nocturia decrease. Significant. Mean (SD) pre- 5.9 ± 0.47 post- 4.93 ± 0.49, P = 0.008 Between-group: PTNS vs Tolterodine MD: -2.9 (-3.33 to -2.47) P < 0.00001 OABSS: PTNS: Significant decrease. Mean (SD) pre- 20.5 ± 4.6 post- 6.5 ± 2.83, P = 0.001 Tolterodine : Significant decrease. Mean (SD) pre- 21.2 ± 2.61 post- 17.4 ± 3.47, P = 0.005 Between-group: PTNS vs Tolterodine MD: -10.9 (-13.68 to -8.12) P < 0.00001
Mallmann (2020) (115)	Group 1: Transcutaneous TNS Group 2: parasacral transcutaneous EStim	50 Group 1: 50 Group 2: 50	OAB wet	1.5	Cure: NR OAB discomfort via OAB-V8: TTNS: Median (95% CI) pre-28.00 (24.03-29.73); post- 14.00 (10.93-18.51), P= 0.035 PS: Median (95% CI) pre- 31.00 (26.93-33.07); Post 21.00 (16.88-23.22), Improved significantly in TTNS group compared with PS, P=0.0019

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
Manríquez (2016) (144)	Group 1: Transcutaneous TNS Group 2: extended release oxybutynin	70 Group 1: 36 Group 2: 34	OAB	3	Cure: NR Improvement based on diary: TTNS: Urinary frequency. Significant. Median and range pre- 24 (12-48), post- 18 (11-54), P= 0.0035 Oxybutynin: Urinary frequency. Significant. Median and range pre- 28 (11-55), post- 20.5 (9-44), P= 0.0011 Between-group comparison: NS p=0.400 TTNS: Urinary urgency. Significant. Median and range pre- 14 (0-49), post- 5 (0-15), P < 0.001 Oxybutynin: Urinary urgency. Significant. Median and range pre- 16 (4-47), post- 4.5 (0-27), P = 0.0004 Between-group comparison: NS p=0.490 OAB-q Domain 1 TTNS: Significant. Median and range pre- 33 (30-35), post- 16 (10-46), P < 0.001 Oxybutynin: Significant. Median and range pre- 33 (31-36), post- 18 (8-45), P= 0.0004 Between-group comparison: NS p=0.886 Domain 2 TTNS: Significant. Median and range pre- 55 (49-60), post- 30 (15-83), P < 0.001 Oxybutynin: Significant. Median and range pre- 60 (54-66), post- 37 (17-79), P= 0.0002 Between-group comparison: Significant. p=0.036 Domain 3 TTNS: Significant. Median and range pre- 35 (31-39), post- 20 (10-51), P < 0.001 Oxybutynin: Significant. Median and range pre- 36 (32-40), post- 23 (11-57), P= 0.0281 Between-group comparison: NS. p=0.136 Adverse effects: No events noted in the TTNS group. 3 participants in the oxybutynin group reported adverse events (dry mouth)
Urgurlucan (2013) (148)	Percutaneous TNS vs transvaginal EStim	52	OAB	PTNS 3 ES 2	Improvement based on diary: PTNS: Mean number of urgency episodes. NS. Mean (SD) pre- 2.0 ± 3.1 post- 1.3 ± 0.5, P = 0.093 EStim: Mean number of urgency episodes. NS. Mean (SD) pre- 2.9 ± 4.1 post- 1.6 ± 0.5, P = 0.35 Between-group p = 0.54 PTNS: Mean number of daytime micturition. NS. Mean (SD) pre- 7.6 ± 2.6 post- 7.4 ± 2.9, P = 0.683 EStim: Mean number of daytime micturition. Significant. Mean (SD) pre- 7.8 ± 2.7 post- 5.8 ± 1.9, P = 0.006 Between-group p = 0.03 PTNS: Mean number of nocturia. NS. Mean (SD) pre- 0.9 ± 1.4 post- 0.7 ± 0.9, P = 0.160 EStim: Mean number of nocturia. NS. Mean (SD) pre- 1.4 ± 1.1 post- 1 ± 0.8, P = 0.119 Between-group p = 0.92

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
Vecchioli-Scaldazza (2017) (111)	Group 1: Percutaneous TNS Group 2: EStim with PFMT	60 Group 1: 30 Group 2: 30	OAB	PTNS 3 months ES plus PFMT 6 months	Cure: NR Improvement based on diary: PTNS: Number of daily micturition. Significant decrease. Mean (SD) pre- 11.25 ± 1.13 post- 9 ± 2.02, P = 0.0307 EStim: Number of daily micturition. NS. Mean (SD) pre- 11.15 ± 2.07 post- 9.03 ± 1.68, P = 0.0620 Between-group p = 0.3758 PTNS: Nocturia. Significant decrease. Mean (SD) pre- 2.5 ± 1.02 post- 1.45 ± 1.02, P = 0.0201 EStim: Nocturia. NS. Mean (SD) pre- 2.62 ± 1 post- 1.54 ± 0.93, P = 0.1683 Between-group p = 0.049 PTNS: Voided volume. Significant increase. Mean (SD) pre- 140.21 ± 13.5 post- 171.42 ± 12.68, P = 0.0003 EStim: Voided volume. Significant increase. Mean (SD) pre- 136.75 ± 11.92 post- 157.92 ± 10.30, P = 0.0048 Between-group p = 0.0222 Patient Perception of Intensity of Urgency Scale (PPIU-S) PTNS: Significant improvement. Mean (SD) pre- 3 ± 0.63 post- 1.75 ± 0.7, P < 0.0001 EStim: NS. Mean (SD) pre- 2.77 ± 0.80 post- 2.00 ± 0.68, P = 0.1014 Between-group p = 0.0459 Patient Global Impression of Improvement (PGI-I) PTNS: Significant improvement. Mean (SD) 2.3 ± 0.78 EStim: NS. Mean (SD) 2.85 ± 0.36 Between-group p = 0.0415 OAB-qSF QoL PTNS: Significant improvement. Mean (SD) pre- 21.35 ± 2.57 post- 12.90 ± 2.93, P < 0.0001 EStim: Significant improvement. Mean (SD) pre- 19.46 ± 3.13 post- 15.77 ± 5.48, P = 0.0420 Between-group p = 0.0172 OAB-qSF PTNS: Significant improvement. Mean (SD) pre- 44.4 ± 8.51 post- 24.85 ± 5.96, P < 0.0001 EStim: Significant improvement. Mean (SD) pre- 36.85 ± 13.02 post- 29.38 ± 9.32, P = 0.0420 Between-group p = 0.0295 Adverse effects: No events noted

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome**
Vecchioli-Scaldazza (2018) (149)	Percutaneous TNS vs solifenacin succinate	105	OAB	PTNS 3 months SS 3 months	Cure: NR Improvement OABSS after treatment: PTNS: Daytime frequency. Significant. Mean (SD) pre- 1.24 ± 0.42 post- 0.47 ± 0.50, P < 0.0001 SS: Daytime frequency. Significant. Mean (SD) pre- 1.19 ± 0.39 post- 0.71 ± 0.45, P = 0.002 Between-group: PTNS vs SS P = 0.1334 PTNS: Night time frequency. Significant. Mean (SD) pre- 2.71 ± 0.67 post- 1.41 ± 1.19, P = 0.001 SS: Night time frequency. Significant. Mean (SD) pre- 2.62 ± 0.79 post- 1.76 ± 1.31, P = 0.0078 Between-group: PTNS vs SS P = 0.411 PTNS: Urgency. Significant. Mean (SD) pre- 4.35 ± 0.59 post- 3 ± 1.14, P < 0.0001 SS: Urgency. Significant. Mean (SD) pre- 4.29 ± 0.63 post- 3.43 ± 1.09, P = 0.0002 Between-group: PTNS vs SS P = 0.2586 OABq-SF6 QoL after treatment PTNS: Significant. Mean (SD) pre- 4.08 ± 0.32 post- 2.98 ± 0.79, P < 0.0001 SS: Significant. Mean (SD) pre- 3.85 ± 0.59 post- 3.08 ± 0.95, P = 0.0001 Between-group: PTNS vs SS P = 0.7525 OABq-SF13 QoL after treatment PTNS: Significant. Mean (SD) pre- 4.22 ± 0.32 post- 2.96 ± 0.97, P < 0.0001 SS: Significant. Mean (SD) pre- 3.92 ± 0.62 post- 3.16 ± 0.95, P = 0.0001 Between-group: PTNS vs SS P = 0.5318 Adverse effects: PTNS group none reported, SS group n=8 (dry mouth and constipation, PTNS + SS n=1.

Note: For modality details or parameters, see Table 25.
Abbreviations: NR: not reported; EStim: electrical stimulation; ICIQ-SF: International Consultation on Incontinence-Short Form (higher scores indicate increased severity); ICIQ-OAB: International Consultation on Incontinence-OAB (higher scores indicate increased severity); OABq-SF: Overactive Bladder Questionnaire (higher scores indicating worse condition) Short-form; PGI-I: Patient Global Impression of Improvement Questionnaire (lower scores indicate greater improvement); VAS: Global response assessment on visual analogue scale (higher scores indicate greater impact on QoL); PTNS: percutaneous tibial nerve stimulation; TTNS: transcutaneous tibial nerve stimulation; KHQ: King's Health Questionnaire; PFMT: pelvic floor muscle training; RR: Risk ratio; UDI-6: Urinary Distress Inventory; IIQ-7: short form of Incontinence Impact Questionnaire (lower scores indicate better QoL); SD: standard deviation; SS: solifenacin succinate; ES: electrical stimulation; NS : non-significant
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6.2.4. Does the addition of TNS to other treatments add any benefit in the treatment of UI?

Six new studies assessed the effect of TNS as an adjunct to another treatment, compared with the other treatment alone or with percutaneous TNS alone (113, 140, 143, 145, 147, 149) (Table 29). Four studies involved transcutaneous TNS (113, 140, 143, 145) and two percutaneous TNS (147, 149). For the transcutaneous TNS studies one compared the effects in women with OAB (where some but not all participants had UI) of combining transcutaneous TNS with transvaginal EStim versus transcutaneous TNS alone (113); one compared transcutaneous TNS combined with daily trospium versus transcutaneous TNS alone in women with OAB (140); one compared transcutaneous TNS combined with lifestyle changes and PFMT versus lifestyle changes and PFMT alone in women with OAB (143) and one compared transcutaneous TNS combined with BT and PFMT versus BT and PFMT alone in older women with UUI (145). Both percutaneous TNS studies were three-arm trials comparing percutaneous TNS combined with an antimuscarinic drug (tolterodine, solifenacin) versus percutaneous TNS or drug alone in women with OAB (147, 149). The results for percutaneous TNS plus drug versus percutaneous TNS alone or drug alone are reported here. No study focusing on SUI or predominant SUI was found.

Quality of data

Computerised randomisation was used in four studies (113, 143, 145, 149) and sealed envelopes in one (140). Adequate allocation concealment was reported in three studies (113, 140, 149) and was unclear in the other three (143, 145, 147). Two studies (143, 147) did not report blinding of assessors however assessor blinding was reported by four (113, 140, 145, 149). Two studies reported ITT analysis (113, 145), one reported a per protocol analysis (143); the type of analysis was not reported in three (140, 147, 149). There was no attrition reported in three trials (140, 145, 147). Attrition of 23% due to adverse effects of the antimuscarinic drug solifenacin was reported in one trial (149) compared to 6% in the combined solifenacin and percutaneous TNS group. In one trial (113) 9% of transcutaneous TNS group participants were lost to follow-up for 'personal reasons' compared to 26% of the transvaginal EStim plus transcutaneous TNS group participants, where reasons for drop out given were: 4 women did not agree with the use of the vaginal electrode, 7 women found the transvaginal EStim uncomfortable and 4 left for personal reasons. In one study (143) attrition of 17% in the PFMT group and 10% in the PFMT plus transcutaneous TNS group occurred due to time needed to attend appointments (2 in each group) and exacerbation of comorbidities (2 in PFMT group). No adverse effects associated with transcutaneous TNS were reported for five studies (113, 140, 143, 147, 149) but one study (145) reported minor discomfort at electrode placement site in three participants. Power calculations were reported for four studies (113, 140, 143, 145). Overall ROB was assessed as low in one study (113) and high in five studies (140, 143, 145, 147, 149).

Results

a) UUI. No information was available on cure rates.

Significant improvements in UUI episodes were reported in four trials (113, 145, 147, 149) by bladder diary (113, 145, 147) or patient reported symptom score (OABSS) (149). Both of the studies comparing percutaneous TNS combined with an antimuscarinic drug (147, 149) found statistically significant improvements in UUI over percutaneous TNS alone (147, 149) or the drug alone (149). One study (113) reported statistically significant reductions in UUI episodes with transcutaneous TNS alone and when combined with vaginal EStim no additional benefits were conferred. One study (145) reported that improvement rates were statistically significantly higher for the group combining transcutaneous TNS with PFMT and BT, compared with PFMT and BT alone at 16 weeks. ICIQ-SF scores improved for both groups of older women, but the combination treatment group had a statistically significantly greater improvement and their satisfaction with transcutaneous TNS treatment was maintained for 12 months in 80.5%.

Quality of life outcomes were reported by four trials (113, 145, 147, 149) using the KHQ (113, 145, 147) and PGII (149). In all studies quality of life was statistically significantly improved by treatments assessed. In two studies (113, 147) there was no difference reported in quality of life with the addition of vaginal EStim (113) or tolterodine (147) but in one study (145) the combination treatment group of transcutaneous TNS added to PFMT and BT showed a statistically significantly greater improvement. In one study (149) the Global Impression of Improvement was statistically significantly greater in the combined drug and percutaneous TNS group at three months and sustained over the 10 month follow up period.

b) OAB. No information was available on cure.

Statistically significant improvements in urinary frequency with both TNS alone and TNS added to other treatments were reported by all six studies (113, 140, 143, 145, 147, 149). Differences between the groups were reported in four studies (113, 140, 147, 149) in favour of TNS alone (113, 147) or when combined with another treatment: PFMT and BT (145) or antimuscarinic drug (149). Improvements in urgency were reported by three studies (113, 143, 149) with two studies reporting no difference between the treatments (113, 143) and one study (149) reporting statistically significant differences in favour of the combined treatment for both the drug versus the percutaneous TNS and drug combined and also percutaneous TNS versus percutaneous TNS and drug combined. Four studies reported statistically significant improvement in nocturia. Three studies (113, 147, 149) reported no difference between the groups and one study (145) reported statistically significantly reduced nocturia frequency in the transcutaneous TNS added to PFMT and BT group.

Quality of life was reported by two studies using the IIQ (140) and the Overactive Bladder Questionnaire-Short Form (149). Both reported statistically significant improvements in quality of life with TNS treatment alone and TNS combined with drug treatment (trospium – (140), or solifenacin – (149)) but the improvements were statistically significantly better with the combination treatment.

Summary

Six small studies were included (20-106 participants) bringing the total to nine assessing the addition of TNS to another treatment. All except one study was assessed as having a high ROB. There were limited and widely heterogeneous data reporting mainly short-term outcomes with minimal long-term follow up. Data pooling was not possible.

Three studies reported that TNS successfully improved OAB symptoms/urgency UI and quality of life in women with OAB, but outcomes were better if TNS was added to an antimuscarinic drug treatment. This effect was sustained for a longer term (10 months) for the treatment with TNS than the treatment without TNS. **(Level of evidence: 2)**

Data from one study suggested that the addition of transcutaneous TNS to PFMT and BT was more effective in improving OAB symptoms/urgency UI and quality of life than PFMT and BT alone, in older women with UUI. The improvements were

sustained for 12 months in those older women who responded to the initial combined treatment. **(Level of evidence: 2)**

One study showed the success of transcutaneous TNS as a single therapy and no additional benefit from adding transvaginal ES for OAB symptoms/urgency UI and quality of life. **(Level of evidence: 2)**

Adverse events from TNS are uncommon.

Recommendations

Transcutaneous TNS or percutaneous TNS can be considered for symptom control in combination with other effective treatments by women with urgency UI or OAB. **(Grade of recommendation: B New)**

This recommendation should be viewed with caution until the findings are supported or refuted in further trials with large sample sizes and clear and consistent reporting of core outcome data.

Table 29. Summary of data on TNS + another treatment vs the other treatment

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome
UUI					
Giarreta (2021) (113)	Group 1: Transcutaneous TNS Group 2: Transcutaneous TNS plus vaginal stimulation (VS)	106 Group 1: 52 Group 2: 54	OAB	3	Cure: NR UUI: TTNS mean difference -1.0 episode (95% CI −1.8 to −0.3) P= 0.007; TTNS plus VS mean difference −0.9 episode (95% CI −1.7 to −0.1) P= 0.026; Between groups mean difference 0.1 (-0.9 to 1.2) p=0.810, NS SUI: TTNS mean difference −0.6 episode (95% CI -1.1 to −0.1) P= 0.030; TTNS plus VS mean difference −0.3 episode (95% CI −0.9 to 0.3) P= 0.315. Between groups mean difference 0.3 (-0.5 to 1.1) p=0.445, NS QoL(KHQ): TTNS mean difference -38.4 (95% CI -50.0 to -26.7) P<0.001; TTNS plus VS mean difference -40.6 (95% CI -52.8 to -28.3) P<0.001. Between groups mean difference-2.2 (-19.1 to 14.7), P=0.802, NS Adverse effects: no events noted
Bykoviene (2018) (143)	Group 1: Lifestyle recommendations Group 2 : PFMT plus lifestyle recommendations Group 3: Transcutaneous TNS plus PFMT plus lifestyle recommendations	67 Group 1: 22 Group 2: 24 Group 3: 21	UI	1.5	Cure: NR Improvement based on diary: TTNS: Incontinence episodes decreased. NS Mean (SD) pre- 1.78 ± 2.16, post- 1.58 ± 2.14, p=0.608 PFMT: Incontinence episodes decreased. Significant Mean (SD) pre- 3.84 ± 4.62, post- 2.89 ± 4.83, p=0.045 Control: Incontinence episodes decreased. NS Mean (SD) pre- 2.06 ± 2.46, post- 2.27 ± 3.07, p=0.616 MD: TTNS vs PFMT -1.31 (-3.64 to 1.02) p=0.27 TTNS vs Control -0.69 (-2.29 to 0.91) p=0.4 QoL (KHQ) TTNS: Incontinence impact NS. Mean (SD) pre- 73.77 ± 23.75, post- 63.18 ± 24.66, p=0.082 PFMT: Incontinence impact NS. Mean (SD) pre- 68.33 ± 25.38, post- 66.67 ± 26.56, p=0.716 Control: Incontinence impact NS. Mean (SD) pre- 65.59 ± 30.82, post- 69.77 ± 25.04, p=0.394 MD: TTNS vs PFMT -3.49 (-19.57 to 12.59) p=0.67 TTNS vs Control -6.59 (-21.84 to 8.66) p=0.4

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome
Kizilyel (2015) (147)	Group 1: Percutaneous TNS Group 2: Percutaneous TNS plus tolterodine	20 Group 1: 10 Group 2: 10	Refractory OAB	3	Cure: NR Improvement based on diary: PTNS (n=4): UUI episodes decreased. Significant. Mean (SD) pre- 1.2 ± 1.6 post- 0.13 ± 0.23, P = 0.003 PTNS + Tolterodine (n=4): UUI episodes decreased. Significant. Mean (SD) pre- 1.33 ± 1.77 post- 0.33 ± 0.57, P = 0.001 Between-group: PTNS vs PTNS + Tolterodine MD: -0.2 (-0.8 to 0.4) P = 0.52 UDI-6: PTNS: Significant decrease. Mean (SD) pre- 8 ± 1.5 post- 2.9 ± 1.59, P = 0.001 PTNS + Tolterodine: Significant decrease. Mean (SD) pre- 8.2 ± 2.74 post- 3.8 ± 2.57, P = 0.001 Between-group: PTNS vs PTNS + Tolterodine MD: -0.9 (-2.77 to 0.97) P = 0.35 IIQ-7: PTNS: Significant decrease. Mean (SD) pre- 17.5 ± 1.73 post- 5.75 ± 0.95, P = 0.039 PTNS + Tolterodine: Significant decrease. Mean (SD) pre- 14 ± 2.58 post- 4.75 ± 1.7, P = 0.047 Between-group: PTNS vs PTNS + Tolterodine MD: 1.00 (-0.21 to 2.21) P = 0.1
Schreiner (2021) (145)	Group 1: Transcutaneous TNS plus PFMT and BT Group 2: PFMT and BT	106 Group 1: 54 Group 2: 52	UUI	3	Cure: NR Episodes of UUI TTNS: Significant decrease. Mean (SD) pre- 7.2 ± 4.5 post- 1.8 ± 2.7, P = 0.004 Control: Significant decrease. Mean (SD) pre- 6.2 ± 2.9 post- 4.9 ± 3.6, P < 0.001 Between-group: P < 0.001 ICIQ-SF scores TTNS: Significant decrease. Mean (SD) pre- 15.7 ± 3.3 post- 8.3 ± 4.6, P = 0.026 Control: Significant decrease. Mean (SD) pre- 15 ± 3 post- 11.9 ± 5, P < 0.001 Between-group: P < 0.001 King's Health Questionnaire score post-treatment the TTNS group showed significantly better improvement than control in all domains. Adverse events: 3 participants in the TTNS group reported discomfort at the point of placement of the electrode

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome
Vecchiolo-Scaldazza (2018) (149)	Group 1: Percutaneous TNS Group 2: Percutaneous TNS plus solifenacin succinate	70 Group 1: 35 Group 2: 35	OAB	PTNS 3 months PTNS plus SS 2 months	Cure: NR Improvement OABSS after treatment: PTNS: UUI episodes decreased. Significant. Mean (SD) pre- 4 ± 0.69 post- 2.24 ± 1.35, P = 0.0001 PTNS + SS: UUI episodes decreased. Significant. Mean (SD) pre- 3.44 ± 1.5 post- 0.56 ± 1.26, P < 0.0001 Between-group: PTNS vs PTNS + SS P = 0.0015 PGI-I after treatment: PTNS: UUI episodes decreased. Significant. Mean (SD) 2.41 ± 0.84 PTNS + SS: UUI episodes decreased. Significant. Mean (SD) 1.83 ± 0.76 Between-group: PTNS vs PTNS + SS P = 0.0468 PGI-I 10 months follow-up: PTNS: UUI episodes decreased. Significant. Mean (SD) 2.1 ± 1.92 PTNS + SS: UUI episodes decreased. Significant. Mean (SD) 5.63 ± 2 Between-group: PTNS vs PTNS + SS P = 0.0002 Adverse effects: PTNS group none reported, SS group n=8 (dry mouth and constipation, PTNS + SS n=1.
OAB					
Abdulseoud (2018) (140)	Group 1 : Transcutaneous TNS Group 2 : Transcutaneous TNS plus daily trospium	30 Group 1: 15 Group 2: 15	OAB	2	Cure: NR Improvement in OABSS: mean decreased significantly to 10.0 ± 2.0 TTNS (P = 0.001) and 8.53 ± 1.30 TTNS + trospium (P = 0.001). Between-group comparison showed statistical difference (P = 0.024). QoL, mean IIQ-7 score decreased significantly to 51.86 ± 17.26 TTNS (P = 0.002) and 31.99 ± 9.26 in TTNS + trospium (P = 0.001). Between-group comparison showed statistical difference (P = 0.001). Mean frequency decreased to 10.60 ± 2.32 TTNS (P = 0.003) and 8.60 ± 0.83 TTNS+ trospium (P = 0.001). Between-group comparison showed statistical difference (P = 0.006). Adverse effects: no events noted

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome
Giarreta (2021) (113)	Group 1: Transcutaneous TNS Group 2: Transcutaneous TNS plus vaginal stimulation (VS)	106 Group 1: 52 Group 2: 54	OAB	3	Urinary frequency TTNS mean difference−2.8 (95% CI −3.8 to −1.8) P<0.001 TTNS plus VS mean difference −4.3 (95% CI −5.3 to −3.2) P<0.001 Between groups mean difference -1.5 (95% CI -2.9 to -0.1) P=0.044, Sig Urgency TTNS mean difference−2.4 (95% CI −3.3 to −1.4) P<0.001 TTNS plus VS mean difference −2.2 (95% CI −3.2 to −1.2) P<0.001 Between groups mean difference 0.2 (95% CI -1.2 to 1.6) P=0.760, NS Nocturia TTNS mean difference−1.0 (95% CI −1.3 to −0.7) P<0.001 TTNS plus VS mean difference −1.3 (95% CI −1.6 to −0.9) P<0.001 Between groups mean difference -0.3 (95% CI -0.8 to 0.2) P=0.217, NS OABv8 TTNS mean difference−15.3 (95% CI −17.9 to −12.6) P<0.001 TTNS plus VS mean difference −16.8 (95% CI −19.6 to −14.0) P<0.001 Between groups mean difference -1.5 (95% CI -5.4 to 2.4) P=0.446, NS
Bykoviene (2018) (143)	Group 1: Transcutaneous TNS plus PFMT plus lifestyle recommendations Group 2: PFMT plus lifestyle recommendations Group 3: Lifestyle recommendations	67 Group 1: 22 Group 2: 24 Group 3: 21	UI	1.5	Improvement based on diary Frequency/day: TTNS: Significantly decreased. Mean (SD) pre- 8.81 ± 2.31, post- 7.36 ± 2.04, p=0.001 PFMT: Significantly decreased. Mean (SD) pre- 8.86 ± 3.24, post- 7.52 ± 2.30, p=0.025 Control: NS Mean (SD) pre- 9.83 ± 6.92, post- 8.58 ± 4.58, p=0.109 MD: TTNS vs PFMT -0.61 (-1.52 to 1.20) p=0.82 TTNS vs Control -1.22 (-3.34 to 0.90) p=0.26 Urgency episodes/day: TTNS: Significantly decreased. Mean (SD) pre- 6.76 ± 3.12, post- 4.43 ± 3.49, p=0.013 PFMT: Significantly decreased. Mean (SD) pre- 5.24 ± 3.64, post- 3.17 ± 2.87, p=0.006 Control: Significantly decreased. Mean (SD) pre- 5.14 ± 3.73, post- 3.79 ± 3.22, p=0.016 MD: TTNS vs PFMT 1.26 (-0.75 to 3.27) p=0.22 TTNS vs Control 0.64 (-1.43 to 2.71) p=0.54 Nocturia episodes/day: TTNS: NS. Mean (SD) pre- 1.93 ± 1.00, post- 1.56 ± 1.04, p=0.170 PFMT: NS. Mean (SD) pre- 1.55 ± 1.8, post- 1.60 ± 1.54, p=0.819 Control: NS. Mean (SD) pre- 2.17 ± 1.96, post- 1.82 ± 1.35, p=0.226 MD: TTNS vs PFMT -0.04 (-0.86 to 0.78) p=0.92 TTNS vs Control -0.26 (-0.99 to 0.47) p=0.49

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome
Kizilyel (2015) (147)	Group 1: Percutaneous TNS Group 2: Percutaneous TNS plus tolterodine	20 Group 1: 10 Group 2: 10	Refractory OAB	3	Cure: NR Improvement based on diary: PTNS (n=4): frequency decreased. Significant. Mean (SD) pre- 10.1 ± 0.88 post- 8.9 ± 0.88, P = 0.011 PTNS + Tolterodine (n=4): frequency decreased. Significant. Mean (SD) pre- 10.8 ± 0.9 post- 8.03 ± 1.07, P = 0.009 Between-group: PTNS vs PTNS + Tolterodine MD: 0.87 (0.01 to 1.73) P = 0.05 PTNS: Nocturia decrease. Significant. Mean (SD) pre- 5.3 ± 0.9 post- 2.03 ± 0.5, P = 0.007 PTNS + Tolterodine: Nocturia decrease. Significant. Mean (SD) pre- 5.3 ± 0.67 post- 2 ± 0.66, P = 0.001 Between-group: PTNS vs PTNS + Tolterodine MD: 0.03 (-0.48 to 0.54) P = 0.91 OABSS: PTNS: Significant decrease. Mean (SD) pre- 20.5 ± 4.6 post- 6.5 ± 2.83, P = 0.001 PTNS + Tolterodine: Significant decrease. Mean (SD) pre- 23.3 ± 3.4 post- 16.5 ± 5.33, P = 0.001 Between-group: PTNS vs PTNS + Tolterodine MD: -10 (-13.74 to -6.26) P < 0.00001
Schreiner (2021) (145)	Group 1: Transcutaneous TNS plus PFMT and BT Group 2:PFMT and BT	106 Group 1: 53 Group 2: 53	UUI	3	Cure: NR Micturitions per day TTNS: Significant decrease. Mean (SD) pre- 7.8 ± 3.1 post- 6 ± 1.4, P = 0.020 Control: Significant decrease. Mean (SD) pre- 7.9 ± 2.5 post- 7.5 ± 2.3, P < 0.001 Between-group: p = 0.003 Nocturia TTNS: Significant decrease. Mean (SD) pre- 3.5 ± 1.6 post- 1.6 ± 1.5, P < 0.001 Control: Significant decrease. Mean (SD) pre- 3.0 ± 1.1 post- 2.3 ± 1.3, P < 0.001 Between-group: P < 0.001 Adverse events: 3 participants in the TTNS group reported discomfort at the point of placement of the electrode

Author, year	Comparator	N randomised	Study population	Duration (months)	Outcome
Vecchiolo-Scaldazza (2018) (149)	Group 1: Percutaneous TNS Group 2: Percutaneous TNS plus solifenacin succinate	70 Group 1: 35 Group 2: 35	OAB	PTNS 3 months PTNS plus SS 2 months	Cure: NR Improvement OABSS after treatment: PTNS: Daytime frequency. Significant. Mean (SD) pre- 1.24 ± 0.42 post- 0.47 ± 0.50, P < 0.0001 PTNS + SS: Daytime frequency. Significant. Mean (SD) pre- 1.22 ± 0.42 post- 0.33 ± 0.47, P < 0.0001 Between-group: PTNS vs PTNS + SS P = 0.4224 PTNS: Night time frequency. Significant. Mean (SD) pre- 2.71 ± 0.67 post- 1.41 ± 1.19, P = 0.001 PTNS + SS: Night time frequency. Significant. Mean (SD) pre- 2.89 ± 0.31 post- 0.89 ± 0.87, P < 0.0001 Between-group: PTNS vs PTNS + SS P = 0.1585 PTNS: Urgency. Significant. Mean (SD) pre- 4.35 ± 0.59 post- 3 ± 1.14, P < 0.0001 PTNS + SS: Urgency. Significant. Mean (SD) pre- 4.44 ± 0.68 post- 2.11 ± 0.99, P < 0.0001 Between-group: PTNS vs PTNS + SS P = 0.0225 OABq-SF QoL after treatment PTNS: Urgency. Significant. Mean (SD) pre- 4.08 ± 0.32 post- 2.98 ± 0.79, P < 0.0001 PTNS + SS: Urgency. Significant. Mean (SD) pre- 4.21 ± 0.24 post- 2.32 ± 0.87, P < 0.0001 Between-group: PTNS vs PTNS + SS P = 0.0287 OABq-SF after treatment PTNS: Urgency. Significant. Mean (SD) pre- 4.22 ± 0.32 post- 2.96 ± 0.97, P < 0.0001 PTNS + SS: Urgency. Significant. Mean (SD) pre- 4.04 ± 0.24 post- 2.27 ± 0.84, P < 0.0001 Between-group: PTNS vs PTNS + SS P = 0.0361 OABSS 10 months follow-up: PTNS: UUI episodes decreased. Significant. Mean (SD) 2.5 ± 2.38 PTNS + SS: UUI episodes decreased. Significant. Mean (SD) 5.88 ± 2.2 Between-group: PTNS vs PTNS + SS P = 0.0009 Adverse effects: PTNS group none reported, SS group n=8 (dry mouth and constipation, PTNS + SS n=1.

Abbreviations: NR: not reported; ICIQ-SF: International Consultation on Incontinence-Short Form (higher scores indicate increased severity); ICIQ-OAB: International Consultation on Incontinence-OAB (higher scores indicate increased severity); IIQ-7: short form of Incontinence Impact Questionnaire (lower scores indicate better QoL); UDI-6: Urinary Distress Inventory; KHQ: King's Health Questionnaire (higher scores indicate greater impairment); OABq-SF: Overactive Bladder Questionnaire (higher scores indicating worse condition) Short-form; OABSS: Overactive Bladder Symptom Score; TENS: Transcutaneous Electrical Nerve Stimulation of the posterior tibial nerve; TTNS: Transcutaneous Tibial Nerve Stimulation; PTNS: percutaneous tibial nerve stimulation; PFMT: pelvic floor muscle training; SS: solifenacin succinate; NS : non-significant

Other LUTS
No trials were identified that analysed the effect of TNS in women with other LUTS alone, e.g., frequency of voiding, urgency and/or nocturia.

Factors Affecting Outcome
The included studies did not address factors that could potentially affect the response to treatment with TNS. A greater discussion of these factors is provided in the section on UI in men and women (see section V.1.4).

7. SCHEDULED VOIDING REGIMENS

This section examines the evidence on use of scheduled voiding regimens in cognitively intact, non-institutionalised women with UUI, SUI and MUI, and provides recommendations for their use in clinical practice. The chapters on frail older adults (Chapter 14) provides a detailed review of regimens that are used in people living with frailty or cognitive impairment. Trials involving women with OAB-wet or dry are included when UI-specific outcomes are reported. Outcomes that are not specific to UI (i.e., frequency, or OAB-specific symptoms or QoL validated questionnaires) are reported separately (section II.7.3. Other LUTS).

Scheduled voiding regimes have been categorized as: bladder training (BT), timed voiding, habit training, and prompted voiding (1). Habit training and prompted voiding are usually implemented by caregivers in institutional settings with cognitively and/or physically impaired adults, therefore this section focus on the use of BT and timed voiding, though most of the evidence available for the target population pertains to the effects of BT.

BT is also referred to as bladder drill, bladder discipline, bladder re-education, and bladder re-training. The intervention targets people with OAB or UUI, who do not suffer from significant cognitive or physical impairment. Its goal is to support lifestyle and behavioural changes to regain bladder control through education, progressively increasing voiding intervals using urgency suppression techniques and positive reinforcement (153). Specific goals of BT are to: 1) correct faulty habit patterns of frequent urination (if present), 3) improve control over bladder urgency, and 2) restore patient confidence in controlling bladder function. The underlying mechanism of how BT achieves its effect is poorly understood. Several hypotheses have been proposed including improved cortical inhibition over detrusor contractions; improved cortical facilitation over urethral closure during bladder filling; improved central modulation of afferent sensory impulses; altered behaviour resulting from improved individual awareness of the lower urinary tract function and circumstances that cause UI, and increasing the “reserve capacity” of the lower urinary tract system (154-156).

Timed voiding is a passive toileting assistance programme, initiated and maintained by caregivers for patients who cannot participate in independent toileting (1). It is a fixed voiding schedule that remains unchanged over the course of treatment (157). The goal is to prevent UI by providing regular opportunities for bladder emptying prior to exceeding bladder capacity.

Questions addressed in this section include:
- Can scheduled voiding regimens prevent UI?
- What is the most appropriate BT protocol for treating UI?
- Is BT better than no treatment, placebo, or control treatments for UI?
- Is BT better than other treatments for UI?
- Does the addition of another treatment to BT add any benefit for treating UI?
- Does the addition of BT to other treatments add any benefit for treating UI?
- Is timed voiding effective for treating UI?
- What is the effect of BT on other LUTS?
- What factors might affect the outcome of BT?

7.1. Prevention
No trials which examined scheduled voiding regimens as a sole intervention in the prevention of UI were found.

7.2. Treatment
Previous recommendations related to BT as a treatment for UI were based on reviews of individual published trials (92, 158-161) and three systematic reviews that provided descriptive syntheses with evidence grading (162-164). In this ICI, two new trials (94, 165) and one long-term follow-up of an existing trial (90) were identified and are described below. See Table 30.

7.2.1. What is the most appropriate bladder training (BT) protocol?
Previously, no trials that compared two or more methods of BT were identified. In this update, one trial comparing individual to group BT (165) was found.

Quality of data
In a non-blinded trial by Hulbæk *et al.* (165), 91 women were randomised to group or individual BT and followed-up for two months. A power calculation and adequate random allocation/concealment were reported. This was an open label trial, therefore both outcome assessor and participants were aware of treatment allocation. ITT analysis was used. Loss to follow-up was low and balanced between groups, with reasons unrelated to treatment. Side effects were minor and temporary (more frequent voiding treated by the general practitioner with antibiotics, n= 1). Overall, this trial was at low to moderate ROB.

Group treatment (three to four patients per group) followed the same protocol as individual treatment. In both settings, BT was performed daily for a two-month period supported by a diary, in addition to three training sessions at the hospital coached by a continence nurse.

Results

The number of UUI episodes was reduced after two months of individual or group BT, but there was no significant between group difference (mean difference, final-baseline: 1.8 [−5.2; 8.8], p=0.6 for group and −0.6 [−1.7; 0.6], p=0.3 for individual treatment). Furthermore, groups did not differ at the follow-up. Other outcomes were related to OAB symptoms and are reported bellow (section II.7.3. Other LUTS); they were also no different within or between groups.

Considering the lack of trials comparing two or more BT approaches, a content analysis was performed looking at the protocols used in all trials investigating effects of BT (not only those comparing different BT protocols). Twenty-four trials on BT involving a total of 3,355 women were identified, including two trials involving 161 women added since the last update (94, 165). Several of the trials previously reviewed (159, 160, 166-171) provided minimal or no details regarding the specific BT protocol used. Both newly included trials are more specific regarding the intervention description (94, 165). In this review of BT protocols, information from the two new studies is added to and integrated with previous information.

All protocols involved some type of patient education, namely:

- Brief verbal (167, 168) or written instructions (172, 173)
- Verbal, written and audio-visual instruction (94, 154, 156, 165, 174)
- Introduction to an individual who successfully completed BT (169)

If specified, education was provided by nurses (154, 156, 165, 166, 171, 175, 176), general practitioners (177), or physiotherapists (92, 158, 161).

Scheduling of voids varied in the following ways:

- Assignment of the initial voiding interval varied from 30 minutes to two hours, with one hour being the most common interval based upon the participant's voiding pattern or 30 minutes beyond the participant's average (172, 178) or longest (158) voiding interval.
- Adjustments to the voiding interval varied from 15 to 30 minutes, with 30 minutes the most common interval. Increases were made daily for inpatient regimens (169), after 48 hours of dryness (179), every four to five days (178) or weekly if schedule was well-tolerated (154, 156, 158, 165).
- Goals for optimal voiding intervals varied from three to four hours.
- Voiding was 'mandatory' with restriction of voiding in between assigned toileting times even if UI occurred (169), a scheduled voiding regimen that allowed interruptions in the schedule if urgency became unbearable (154, 156, 176), or self-scheduling of voiding with a target goal to reach (172).
- Voids were not scheduled (allowed) during sleeping hours (169); none of the other protocols identified how voids during sleeping hours were handled.

In some protocols, the scheduled voiding regimen was supplemented by specific strategies to control urgency and/or stress leakage, including distraction and relaxation (94, 154, 156, 158, 161, 165, 172, 176) and PFM contraction (94, 154, 158, 165, 166, 173). In other studies, there was encouragement to suppress urgency, but it was not clear what strategies were used (168, 177, 180). Feedback techniques included self-monitoring (94, 154, 156, 165, 167, 170, 176), goal setting with feedback of progress (175), and positive reinforcement (94, 154, 156, 165, 178).

Several protocols included use of adjunctive treatments:

- Fluid and caffeine adjustments (165, 174, 176, 180)
- Fluids allowed up to a certain level (1,500 ml) (179)
- No fluid modifications (154, 156, 158, 172, 177)
- Advice on constipation prevention (165, 176)
- Lifestyle modification (unspecified) (165)

Both inpatient and outpatient BT programmes have been used. Outpatient programmes are more commonly described, and the amount of health professional contact ranged from 20 weekly visits (161), to eight weekly visits (171), six weekly visits (154, 156), three visits every two weeks over six weeks (158, 178), and three visits over two months (165). A "simplified" BT treatment with minimal to no health professional contact (instructions given to patients on a one-page instruction sheet) has also been tested (94, 172, 173).

Considering the overall lack of consistency in BT reports across studies, key recommendations were synthesised to guide healthcare professionals on promoting consistent, cohesive, and achievable BT programmes. These were based on the evidence gathered to date, as well as the new International Continence Society Consensus statement on BT (153), and include:

- Supervision from a healthcare practitioner
- Duration of at least six weeks, varying according to the person's progress and goals
- Regular review and reinforcement (coaching) by the healthcare practitioners
- Follow-up support, in accordance with the person's goals and preferences
- Verbal and written information and education provided by the healthcare practitioner
- Voiding intervals agreed and implemented based on bladder diary and individual goals (usually during waking hours only) that can be standardised or individualised:

  a) If standardised, a fixed (or pre-determined) voiding schedule of half-hourly or hourly voids is implemented for an agreed time period. Once achieved, this schedule is increased by a pre-determined duration of 5, 10, 15 or 30 minutes at each progression point
  b) If tailored, individualised voiding intervals are implemented based on the person's average voiding interval calculated from their voiding diary. Progression time to prolong voiding intervals is negotiated on an individual basis, for example increased by 5, 10, 15, 30 minutes per week

- Urge & urgency suppression or deferment, including relaxation, PFM contraction, distraction techniques, self-motivation using self-affirming statements and application of perineal pressure. When urgency is controlled, the person is encouraged to walk to the toilet at a normal pace

- Active encouragement and support for:
  a) Self-monitoring
  b) Self-determining of progression
  c) Self-affirming strategies

Summary

Key recommendations on BT implementation and reporting were synthetised from the evidence available to date and the new Consensus statement on BT (153). **(Level of evidence: 2)**

Recommendations

Clinicians should provide the most intensive BT supervision possible within service constraints. **(Grade of recommendation: D)**

Clinicians and researchers are advised to follow the evidence based recommendations and the latest consensus statement on BT (153).

The ICS consensus statement and review papers on adherence and PFMT could be useful to clinicians and researchers (22-25).

Several areas could be investigated in future trials, including the instructional approach, supervisory intensity, strategies for controlling urgency, scheduling parameters, frequency of schedule adjustments, length of treatment, and use of adjunctive treatments.

7.2.3. Is BT better than no treatment, placebo, or control treatments?

As a sole therapy, BT has been used in the treatment of OAB, urodynamic SUI, MUI, UUI and UUI in the absence of DO.

No new trials were identified that addressed this question. Previously, five RCTs involving 515 women were identified that compared the effect of BT to no treatment or control (156, 170, 171, 176, 177). Out of four trials with relevant analysable data (156, 170, 171, 177), three reported improvements in the BT group compared to the control group (156, 170, 177). The trial quality and detailed results were presented in previous editions of this chapter.

Summary

The few available trials (reviewed previously) were small and of variable quality. No new trials were identified in this update.

There is limited **Level 1** evidence that BT may be an effective treatment for women with UUI, SUI and MUI. **(Level of evidence: 1)**

Recommendations

BT should be recommended as first line conservative therapy for UI in women. **(Grade of recommendation: A)**

Additional high-quality RCTs are needed that examine the effect of BT versus no treatment in treatment of women with UUI, SUI and MUI.

7.2.4. Is BT better than other treatments?

This section considered trials that compared BT alone versus another active therapy.

For the comparison of BT versus PFMT see section II.2.3.3.

The only other comparison for which trials were found was BT versus drug therapy (DT). In total, three small trials were identified that randomised 214 women with UUI to BT or DT (92, 169, 178). This update includes a new study, Azuri *et al.* (90), which presents a four-year follow-up of an RCT that was first published in 2013 (92) comparing BT, PFMT, DT (tolterodine, 4 mg) or combined behavioural therapy (BT and PFMT). Results from the BT and DT group comparison are included here, while results of the BT versus PFMT comparison are included in Section II.2.3.

Quality of data

Kafri *et al.* was a single-blind trial in which 83 women were randomised to DT or BT. Follow-ups took place- over 12 months (92) in the initial study and four years later in Azuri *et al.* (90). A power calculation and adequate random allocation/concealment were reported. The assessor was blinded to the participant's allocation. ITT analysis was used. Drop-out rates were unbalanced and likely related to treatment allocation (DT=36% 15/42 [13 unsatisfied with allocation; one acute back pain and one dizziness]; BT= 5% 2/41 [one medical complication and one no response to treatment]). Side effects were not tracked. After the four-year follow-up, dropout rates were still higher in the DT group (43% versus 15%), but reasons for dropping out or side effects were not reported (90). Overall, ROB was unclear.

Results

In Kafri *et al.* and Azuri *et al.* (90, 92), the number of self-reported UUI episodes per week significantly decreased at three months, 12 months and four years and were equal in the BT and DT groups. Differential dropout suggested DT was associated with more adverse effects, but this was not clearly reported. Similar results were reported in a previously reviewed trial (178), in which no differences in effect between DT and BT were observed in the short term (6 weeks), but DT was associated with higher drop-out rates. Conversely, in the same trial, DT results were not maintained in the long term (6 months) and the authors concluded that DT was not well tolerated and provided only short-term beneficial results while BT was well accepted and provided more persistent results (3 months).

Summary

Despite the additional follow-up of an existing low- to moderate-quality trial, it remains unclear whether BT or DT is more effective in women with OAB or UUI. This result is consistent with the findings of the 2004 Cochrane review (163), which concluded that there was insufficient evidence to determine whether first line therapy should be BT or anticholinergic drugs. Of interest, DT has been consistently associated with higher drop-out rates and adverse events in the long term. **(Level of evidence: 1)**

Recommendations

Either BT or anticholinergic drugs can be recommended to women with OAB or UUI. **(Grade of recommendation: B)**

BT may be the recommendation of choice and preferred by women and clinicians because of the absence of drug related adverse effects. **(Grade of recommendation: D)**

7.2.5. Can any other treatment be added to BT to add benefit?

Trials included here investigated the effects of BT versus BT plus therapy A to address the additive benefit of therapy. One new trial was identified, which tested the additional benefit of biofeedback, EStim or both when added to BT (94).

Quality of data

Firinci *et al.* (94) was an assessor-blinded randomised controlled trial, in which 70 women with OAB symptoms were randomised to either: (1) BT alone, (2) BT added to biofeedback, (3) BT added

to EStim, and (4) BT added to both biofeedback and EStim. The follow-up assessment took place at eight weeks. BT included one 30-minute education session with a physician and a written brochure. Women were taught how to contract their PFMs via vaginal palpation, were encouraged to use urgency suppression strategies (PFM contraction, relaxation and distraction) and follow a timed voiding programme based on their bladder diary. No further details were provided on the BT protocol. Biofeedback treatment included three 20-minute sessions per week. In each session, the participants completed 40 cycles of 10-second contractions followed by 20 seconds of relaxation performed in supine position with the aid of an intravaginal pressure probe. EStim also included three 20-minute sessions per week. The stimulation parameters were frequency at 10 Hz, a 5-10-second work-rest cycle, and a 100 ms pulse width. The symmetric biphasic pulse wave was delivered over a range of 0–100mA, according to the patient's feedback on their level of discomfort.

A power calculation and adequate random allocation were reported. The assessor was blinded to the participant's allocation. ITT analysis was not used. Loss to follow-up was low and balanced between groups, but reasons were unclear (6%, giving up treatment). Side effects were minor and specific to the EStim groups (temporary discomfort due to vaginal irritation [n=3]). Overall, ROB was moderate.

Results

Although inclusion criteria mentioned OAB symptoms only, different UI-specific outcomes were reported, including patient-reported outcomes (UI-specific QoL or impact questionnaires; number of leakages and number of pads used according to a 3-day bladder diary) and clinician reported outcomes (cure and improvement and UI severity, based on a 24-hour pad-test). For all outcomes, the four groups improved compared to baseline. At post-treatment, results favoured the two combined treatment groups including EStim compared to BT alone or BT added to biofeedback.

Summary

One new small moderate-quality trial contributed evidence in this area, suggesting that the effect of BT may be enhanced by EStim or EStim with biofeedback, but not biofeedback alone. **(Level of evidence: 2)**

Previous data from two small trials, comparing BT (or BT plus placebo) versus BT plus DT in participants with OAB, suggested that the effect of BT may be enhanced by the active drug. **(Level of evidence: 2)**

However, both trials were small, conducted in -mixed sex samples and outcomes were not common to both trials. Thus, there is insufficient evidence to derive a conclusion related to the effectiveness of augmenting BT with DT.

Recommendations

EStim or EStim plus biofeedback can be recommended as an adjunct treatment to BT, although further studies are needed. (**Grade of recommendation: B New**)

Direct comparisons are needed of BT versus BT plus DT for the treatment of UI to address the question of whether the effect of BT can be augmented by DT.

7.2.6. Does the addition of BT to another treatment add benefit?

Trials included needed to investigate the effects of Therapy A versus Therapy A plus BT to assess the added benefit of BT over Therapy A alone. A search of relevant trials that investigated the effects of PFMT alone versus PFMT plus BT, and DT alone versus DT plus BT was performed. No new trials focusing on this question were identified.

Summary

Previous evidence suggests that there is no evidence of additional benefits of combining brief written BT instructions with tolterodine (2mg twice daily) or solifenacin (5/10mg daily) compared to DT alone for UUI, although these trials were likely underpowered to study UI outcomes. **(Level of evidence: 2)**.

Recommendation

The addition of written information on BT to an antimuscarinic DT cannot be routinely recommended as it does not appear to further improve UI in women with OAB. **(Grade of recommendation: B)**

More research is needed using an appropriately supervised BT programme combined with DT versus DT alone.

7.2.7. Is timed voiding effective for treating UI?

No new trials were identified that tested timed voiding for UI in women without cognitive or physical disability.

Summary

There were no new RCT, or high-quality observational studies identified that provided evidence on the effects of timed voiding for UI in cognitively intact, community-dwelling women. Based upon the data from one previously reported small uncontrolled study, it appears that a two-hour timed voiding schedule may be beneficial in treating women with mild UI, infrequent voiding patterns, and stable bladder function. **(Level of evidence: 3)**

Recommendations

Timed voiding with a two-hour voiding interval could be considered as a sole intervention for women with mild UI or infrequent voiding patterns. **(Grade of recommendation: C)**

Timed voiding could also be considered as an adjunct to another treatment.

7.3. Other LUTS

Three new trials (94, 165, 181) and one long-term follow-up study of an existing trial (90) were identified, which reported on other LUTS. Outcomes included OAB-specific improvement, OAB-specific QoL or impact questionnaires, number of urgency episodes, frequency and nocturia. Firinci *et al.* (94) compared the added benefit of biofeedback and EStim when added to BT and reported on frequency and nocturia (other UI-specific outcomes presented in sections II.7.2.4 above and section II.4.2.4). Hulbæk *et al.* (165) compared two methods of BT (individual versus group treatment) and reported on OAB symptoms, number of urgency episodes and frequency using an OAB-specific questionnaire (other UI-specific outcomes

are presented in section II.7.2.1 above). Lee *et al.* (181) compared moxibustion (hot acupuncture) to BT and reported on OAB-specific QoL or impact questionnaires, frequency and nocturia. No UI-specific outcomes were reported in this trial. Finally, Azuri *et al.* (90) presented a four-year follow-up of a trial comparing DT to BT (92), and reported on the number of voids per 24 hours, in addition to UI-specific outcomes presented above (section II.7.2.3).

Quality of data

The quality of the data in Firinci *et al.* (94), Hulbæk *et al.* (165) and Azuri *et al.* (90) are presented earlier. Lee *et al.* (181) was a small assessor-blinded trial with a crossover design, in which 28 women were randomised to either behaviour treatment alone (including BT) or moxibustion. After four weeks, the treatment offered to the two groups was reversed. The follow-up took place at four weeks (before the crossover) and at eight weeks (after the crossover). Only results reported before the cross-over (at four weeks) were considered here. Behavioural training included instructions related to scheduled voiding (gradually increasing the time between bathroom visits) and lifestyle modifications (participants were asked to avoid coffee, tea, alcohol, soda, artificial sweeteners, chocolate and spicy foods). No further details were provided on the BT protocol.

This was a feasibility study and there was therefore no power calculation and a small sample size (28 participants, 14 per group). Adequate random allocation/concealment were reported, and the assessor was blinded to the participant's allocation. ITT analysis was used. The drop-out rate was unbalanced and high considering the sample size (all from the BT group: 29% [4/14]). Reasons for loss to follow-up were not clearly stated. Side effects were also unbalanced and exclusive to the moxibustion therapy, including superficial second-degree burns (n=2). Overall, ROB was moderate to high.

Results

Results from studies added to this update are integrated with information from previously reviewed studies below.

i. Urgency:

One new trial reported on urgency outcomes. No statistically significant differences were found within or between groups following individual and group BT treatment (165). In previously reviewed trials, urgency results were conflicting. An older trial suggested BT was superior to DT (169), but another reported greater improvement in urgency after DT or DT plus BT treatment compared to BT alone (166). Two larger trials found no additional improvement in urgency when a simplified BT treatment was added to DT in participants with OAB (172, 173).

ii. Daytime (diurnal frequency) and voids per 24 hours:

Two newly identified trials reported on frequency: one trial found no statistically significant differences within or between groups following individual and group BT treatment (165). In the other trial, improvements were reported across all groups, including BT alone or combined with biofeedback and/or EStim (94). Overall, frequency improved to a greater extent in BT groups that included EStim, compared to BT alone or BT combined with biofeedback. One other newly identified trial (181), and one long-term follow up of an existing trial (90), reported on voids per 24 hours. In the first study, no differences were found within or between groups following BT alone or added to moxibustion (181). In the second, both BT and DT were statistically significantly and equally effective to reduce voids in the short (three months) and long term (four years) (90, 92). On average, subjects reported two to four fewer voids per 24 hours immediately after treatment.

In previously reviewed trials, frequency improved to a greater extent in BT groups compared to no treatment (156, 170, 171). In trials testing BT compared to DT, frequency improved in both groups similarly (166, 178), or to a greater extent in the BT group (169). In one trial testing the additive effect of DT to BT, a greater reduction in frequency was reported in the BT plus DT group compared to BT plus placebo group (167). Lastly, two trials found that "simplified" BT significantly augmented the effect of DT alone. The BT plus tolterodine group showed more improvement in voiding frequency compared to DT alone (33% versus 25% improvement, respectively; $p<0.001$). Furthermore, BT plus solifenacin reduced the number of voids in 24 hours to a greater extent compared to DT alone (2.8 versus 2.1 fewer voids in 24 hours; $p<0.001$) (172, 173).

iii. Nocturia:

Three new trials were identified that reported on nocturia (94, 165, 181). Firinci *et al.* reported improvements in nocturia across all treated groups, including BT alone or combined with biofeedback and/or EStim (94). As for other outcomes of this trial, greater improvements were seen in BT groups that included EStim, compared to BT alone or BT plus biofeedback. Lee *et al.* reported on nocturnal volume and frequency, both favouring BT combined with moxibustion over BT alone (181). Hulbæk *et al.* (165) reported on nocturia bother, using a visual analogue scale, which slightly favoured individual over group BT treatment.

Three previously reviewed trials reported data comparing BT with no treatment and found reductions in nocturia after BT but not in the control group (156, 170, 171). Four previously reviewed trials compared BT with DT. Two smaller trials found that BT was superior to DT for treating nocturia (169, 178). Another trial compared BT plus placebo versus BT plus DT (167) and found no difference in nocturnal micturition frequency. Song (2006) reported that nocturia improved similarly in women with OAB treated with BT (56.1%), tolterodine (65.4%), and the combined treatment (66.3%) (166).

Summary

No trials which tested the effectiveness of BT compared to no treatment or a control for urgency were identified.

It remains unclear whether BT is more effective when provided individually or in groups, or if BT or DT is more effective in treating urgency. **(Level of Evidence: 2)**

Two large, high-quality trials show that the addition of "simplified" BT to DT improved frequency but did not provide additional benefits for treating urgency. **(Level of evidence: 1)**

Several trials, including one newer long-term follow-up study, suggest that BT is effective for improving frequency **(Level of evidence: 1)**, but it is unclear whether BT or DT is more effective. **(Level of Evidence: 2)**

In one new small moderate-quality trial, frequency improved more in BT groups that included EStim, compared to BT alone or BT combined with biofeedback. **(Level of evidence: 2)**

A few small, randomised trials of variable quality suggest that BT is effective at treating nocturia. **(Level of evidence: 2)**

One small new trial of moderate quality found that BT added to EStim is more effective to treat nocturia than BT alone or added to biofeedback. **(Level of evidence: 2)**

One small pilot study suggested that BT combined with moxibustion is more effective than BT alone to treat nocturia. **(Level of evidence: 3)**

The results were inconclusive for one large high-quality trial comparing individual and group BT to treat nocturia. **(Level of evidence: 2)**

Finally, small trials did not find that BT (or BT plus DT) is more effective than DT for the treatment of nocturia, but evidence is limited. **(Level of evidence: 2)**

Recommendations

The routine addition of a "simplified" BT to DT should be considered in the treatment of voiding frequency in women with UI and OAB. **(Grade of recommendation: A New)**

BT can be recommended to treat frequency in women with UUI. **(Grade of recommendation: B)**

Either BT and/or an anticholinergic drug can be recommended as they are effective to treat frequency in women. **(Grade of recommendation: B)** However, medication side effects always need to be considered.

Adding EStim, but not biofeedback, to BT may provide additional benefits for treating frequency and therefore can be recommended. **(Grade of recommendation: B New)**

BT can be offered as treatment for nocturia. **(Grade of recommendation: B)**

Combining EStim to BT can be recommended over BT alone, for treating nocturia. **(Grade of recommendation: B New)**

Moxibustion could be considered in addition to BT for treating nocturia. **(Grade of recommendation: C New)**

Either BT alone or BT plus anticholinergic drugs can be recommended for treating nocturia (with OAB) as they appear equally effective. **(Grade of recommendation: B)**

7.4. Factors affecting outcome

Few trials on BT have examined predictors of treatment response. New trials in this update did not contribute additional information related to predictors of timed voiding or BT treatment response.

Table 30. Summary of scheduled voiding regimens

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Firinci (2020) (94) Turkey	(1) BT added to biofeedback (BT+BF) (2) BT added to electrical stimulation (BT+ES) (3) BT added to biofeedback and electrical stimulation (BT+BF+ES)	N=70 BT: 18 BT+BF: 17 BT+ES: 18 BT+BF+ES:17	Women with OAB (>18 years, mean 56 years)	30 min education + written brochure, including: (1) PFM contraction assessment and education via digital palpation; (2) urgency suppression strategies (PFM contraction, relaxation and distraction); (2) relaxation; (3) timed voiding program based on BD; and (4) motivation.	UI-specific outcomes: UI-specific QoL or impact (IIQ-7); number of leakages (3-day BD); number of pads used (3-day BD); cure and improvement (24h pad-test); severity of incontinence (24h pad-test) Other patient-reported outcomes: frequency (3-day BD), nocturia (3-day BD), satisfaction (Likert scale) For all outcomes: all groups improved significantly compared to baseline. Overall results significantly favoured combined treatments including ES (BT+ES and BT+BF+ES) over BT alone or BT + BF	Post-treatment (8 weeks)	Side effects: temporary discomfort due to vaginal irritation (BT+ES=2, BT+BF+ES=1), no ITT analysis Loss to follow-up: 4 (one from each group)

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Hulbæk (2016) (165) Denmark	BT in groups (3-4 participants per group)	N=91 BT individual (BTi): 43 BT group (BTg): 48	Women with OAB (>18 years, mean 57 years)	Same for both arms: 2-month program including three training sessions supervised by a continence nurse. The BT programme included: (1) patient education; (2) scheduled voiding; and (3) motivation. The scheduled voiding was planned at each session based on the BD.	UI-specific outcomes: number of leakages (ICI-OAB-Q) Other patient-reported outcomes: improvement (PGI-I); number of urgency episodes (ICI-OAB-Q); frequency; OAB symptom-specific VAS (ICI-OAB-Q) For all outcomes: no significant difference between baseline and post-treatment or between groups post treatment.	Post Tx (2 months)	Side effects: more frequent voiding, treated with antibiotics (n=1). Treatment group unspecified Loss to follow-up: 12 (5 BTi, 7 BTg) did not fulfil the inclusion criteria, ITT analysis
Kafri (2013) (92) Azuri (2017) (90) Israel	(1) Drug therapy, tolterodine SR 4 mg (DT) (2) Pelvic floor muscle training (PFMT) (3) Combined Tx: BT, PFMT and behavioural advice (CPFR)	N=164 BT: 41 DT:42 PFMT:40 CPFR: 41	Women with ≥ 3 episodes of UUI per week (45-75 years; mean 57 years)	3-month BT program including 4 sessions with a physical therapist The BT program included: (1) patient education, (2) scheduled voiding using a prefixed or flexible timetable; and (3) psychological support and encouragement.	UI-specific outcomes: number of leakages (BD); UI-specific QoL or impact (I-QOL, VAS, ISI); pads/week Other patient-reported outcomes: frequency (BD); generic QoL questionnaire (LLFDI) Both BT and DT were significantly and equally effective for all outcomes at 1 and 4 years, except for number of leakages at 4 years, which favoured DT. 31% (11/35) and 25% (6/24) of the BT and DT were dry at 4 years, p=0.62	Post Tx (3 months), 1 year and 4 years	Side effects: dizziness (1 women in the DT group) Loss to follow-up: 27 post treatment (2 BT, 15 DT, 6 PFMT, 4 CPFR); 29 at 12 months (2 BT, 15 DT, 8 PFMT, 4 CPFR); 44 at 4 years (6 BT, 18 DT, 11 PFMT, 9 CPFR), ITT analysis Note: Adherence to DT was significantly lower than to BT, PFMT or CPFR (64% vs. 85-95%, p=0.01). Main reason for drop-out: unhappy with allocation (13/15).
Lee (2018) (181) Korea	Moxibustion (M) and bladder training (M+BT)	N=28 BT: 14 M+BT: 14	Women with OAB for over 3 months (between 20-75 years, mean 53 years)	4 weeks of BT including 8-12 sessions. The BT programme included: (1) gradually increasing the time between bathroom visits; (2) fluid intake advice (avoid potential bladder irritants).	UI-specific outcomes: none Other patient-reported outcomes: OAB-specific QoL or impact (OAB-V8, OABSS); LUTS (VAS); frequency; nocturia and volume (3-day BD). Only OABSS was different between groups at 4 weeks, favouring combined treatment (M+BT).	Post Tx (4 weeks), cross-over (8 weeks)	Side effects: superficial second-degree burns (n=2) Loss to follow-up: 4 (4 BT, 0 M+BT), ITT analysis Note: Pilot study, cross-over design, (only results reported before cross-over were considered here) No outcomes on UI, results reported in section 7.3. Other LUTS

Abbreviations: IIQ-7 scale: Incontinence Impact Questionnaire-7 scale; ICIQ-OABqol: International Consultation on Incontinence Questionnaire Overactive Bladder Quality of Life Module; PGI-I: Patient Global Impression: Improvement; I-QOL: Incontinence Quality of Life; VAS: visual analogue scale; ISI: Incontinence Severity Index; LLFDI: self-reported Late-Life Function and Disability Instrument; OAB-v8: 8-item overactive bladder questionnaire; OABSS: Overactive Bladder Symptom Score; M: Moxibustion (hot acupuncture); BT: bladder training; OAB: overactive Bladder; BD: bladder diary; UI: urinary incontinence; ITT: intention-to-treat; PFMT: pelvic floor muscle training; UUI: urgency urinary incontinence; QoL: quality of life; LUTS: lower urinary tract symptoms

8. COMPLEMENTARY AND ALTERNATIVES MEDICINES

Complementary and alternative medicine (CAM) refers to a series of medical and health care practices and products, which are not part of conventional medicine (182). According to the National Centre for Complementary and Alternative Medicine's (NCCAM) recommendation, CAM can be grouped into five domains: i) biologically-based therapies that use the substances found in nature, such as herbal therapy; ii) manipulative and body-based approaches that are based on the movement or realignment of parts of the body, such as massage and chiropractic; iii) mind-body interventions that focus on the influence of brain and mind on health, such as meditation, yoga, and Tai Chi; iv) energy therapies that involve use of energy field, such as Qi Gong; v) whole medical systems that cut cross more than one of the other groups, such as acupuncture, Ayurveda, and homeopathy (183).

This section reviews the current evidence for the effects of CAMs on UI. Eligible interventions were typical CAM interventions, including acupuncture, herbal therapy, massage, yoga, Tai Chi, Qi Gong, meditation, Ayurveda and homeopathy. In terms of types of acupuncture, scalp acupuncture, body acupuncture, electroacupuncture, warm acupuncture, elongated needle, auricular acupuncture and fire needle were included. In contrast, cupping, acupressure, laser acupuncture and dry needle acupuncture were excluded, because laser acupuncture and dry needle acupuncture are not routine or traditional acupuncture approaches, and cupping and acupressure are identified as different therapies to acupuncture. Eligibility criteria for study participants and outcomes, as well as criteria used to assess ROB in the included studies, were identical to those described in the previous section on MStim. (Section V).

In addition to the eight studies included in the sixth ICI, a new Cochrane review and 14 new trials were identified for this update (184). Of those, eight studies focused on the efficacy of acupuncture. The Cochrane review and three studies centred on the effectiveness of yoga. Additionally, three studies assessed the effect of herbal therapy. Included studies are summarised in Table 31 by pattern of incontinence or dominant UI type.

8.1. Prevention

No new trials were identified.

8.2. Treatment

8.2.1. Acupuncture versus no treatment, sham acupuncture or any other treatment

8.2.1.1. SUI

Five new studies were identified, including 930 women (185-189). The characteristics of the five new studies are presented in Table 32. Of those, two used sham treatment (186, 187) and two others used PFMT as the control (185, 189). Another study used midodrine as the control (188). As most of the new studies had different comparators and outcomes than the previous studies, only limited findings could be combined.

Quality of data

Randomisation was appropriate in three studies (186-188). By contrast, two studies did not provide sufficient information on the method of randomisation (185, 189). Allocation concealment was adequate in two studies (186, 189). Three other studies did not describe methods used for allocation concealment (185, 187, 188). In terms of blinding, two studies used a double-blind design (participants and outcome assessors) (186, 187), while three others were non-blinded (185, 188, 189). In addition, four studies reported the complete data (185, 186, 188, 189), whereas one only reported the data on participants who completed the study (187).

Results

Two previous low-quality RCTs reported that acupuncture may be associated with more improvement in women with SUI compared with no treatment or midrodrine (190, 191). Another previous trial reported that acupressure may enhance PFM strength and improve QoL compared to a sham treatment or usual care (192). Pooled data from the two new studies suggest that cure rates were on average statistically significantly higher for acupuncture compared to PFMT (N = 156, 32.1% versus 9%, OR 4.79, 95% CI 1.93 to 11.87, P<0.0007, I^2=19%), and improvement rate was on average significantly higher for acupuncture compared to PFMT (N = 156, 87.2% versus 73.1%, OR 2.88, 95% CI 0.16 to 50.74, P=0.003, I^2=88%)

Table 31. Studies of CAMs included in the previous review (6th ICI) and current update (7th ICI)

	Studies included in the previous review (6th ICI)	New studies identified in this update (7th ICI)	Total
Acupuncture vs other intervention SUI OAB/UUI MUI	3 3 2 (1 for UUI or MUI)	5 1 2	8 4 4
Yoga vs other intervention OAB/UUI UI all types	No study found	1 Cochrane Meta-analysis 1 2	1 Cochrane Meta-analysis 1 2
Herbal therapy vs other intervention OAB/UUI UI all types	No study found	1 2 (1 for SUI or MUI)	1 2

Abbreviations: SUI: stress urinary incontinence; OAB: overactive bladder; UUI: urge urinary incontinence; UI: urinary incontinence

(185, 189). However, these new trials had a high ROB and treatment intensity was unequal between intervention groups. In a new study comparing acupuncture to sham acupuncture, more women reported improvement in the acupuncture group at six weeks (N = 492, MD -15.0 95% CI -23.2 to -6.9, P<0.001), 18 weeks (N = 482, MD -25.6, 95% CI -34.3 to 16.9, P<0.001), and at the 30-week follow-up (N = 482, MD -25.6, 95% CI -34.2 to 16.9, P<0.001), respectively, compared to sham acupuncture (186). There was no difference in reported adverse events between the acupuncture and sham acupuncture groups (N = 496, 1.6% versus 2.0%, OR 0.8, 95% CI 0.21 to 3.03) (186). Another new study reported a significant improvement in QoL in the acupuncture group but not in the sham acupuncture group (187). Pooled data from one new study and previous research suggest that improvement rates were significantly higher for acupuncture compared to midodrine (N = 240, 86.7% versus 61.7%, OR 4.76, 95% CI 1.5 to 15.11, P<0.008, I^2=60%); however, there were no differences for cure rates (N = 240, 28.3% versus 18.3%, OR 1.8, 95% CI 0.97 to 3.34, P=0.06, I^2=0%) (188, 190).

Summary

A total of eight new trials assessed the effect of acupuncture on SUI compared with no active treatment and another treatment. Data from two small trials suggest that acupuncture may be more effective than PFMT for curing and improving SUI symptoms **(Level of evidence: 3)**, but results from these low-quality trials should be taken with caution. More research is needed before recommendation can be made.

Evidence from two trials one small (n=90) and one large (n= 492) good-quality trial suggests that acupuncture may have benefits for the improvement (186) of SUI symptoms and QoL (187) compared to a sham treatment. **(Level of evidence: 2)**

Additional findings from a newly identified study of moderate size (n=240) suggest that acupuncture may be associated with greater improvement of symptoms compared to midrodrine. **(Level of evidence: 2)**

Recommendations

Acupuncture could be recommended as an optional treatment for women with SUI. **(Grade of recommendation: C)**

Further high-quality RCTs are needed.

Table 32. Summary of data on acupuncture vs no active treatment or other treatment

Author, year	Comparator	N (randomised)	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss to follow-up…)
Chen (2015) (185)	Electroacupuncture (45) vs PFMT (45)	90	SUI	Electroacupuncture: 30-min electroacupuncture at bilateral BL35 and BL33 plus scalp acupuncture with a continuous wave of 80-100 Hz, daily for 8 weeks. PFMT: 15-30 min PFM contractions, 3s hold/3s rest, 2-3 sets a day for 8 weeks.	Self-reported cure: 10/45 vs 4/45 Self-reported improvement: 37/45 vs 39/45 QoL: NR Adverse effects: NR	8-weeks	Loss of follow-up: None
Zheng (2015) (189)	Electrovacua-puncture (33) vs PFMT (33)	66	SUI	Electroacupuncture: 20-min electroacupuncture at CV3, CV4, and bilateral KI12, BL23, and BL33, twice a week for 4 weeks. PFMT: 10 PFM contractions, 3s hold/3s rest, 5 sets a day for 4 weeks.	Cure (based on 1-h pad test): 15/33 vs 3/33 Improvement (based on 1-h pad test): 31/33 vs 18/33 QoL: NR Adverse effects: NR	4-weeks	Loss of follow-up: None

Author, year	Comparator	N (randomised)	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss to follow-up…)
Liu (2017) (186)	Electroacupuncture (252) vs Sham electroacupuncture (252)	504	SUI	Electroacupuncture: 30-min electroacupuncture at bilateral BL35 and BL33 with a continuous wave of 50 Hz and a current intensity of 1 to 5mA, 3x per week for 6 weeks. Sham electroacupuncture: 30-min sham electroacupuncture without electricity output, at bilateral sham BL35 (1 cun≈20 mm horizontal to BL35) and BL33 (1 cun≈20 mm lateral to BL 33), 3x per week for 6 weeks.	Cure: NR Self-reported improvement: N=492 at 6-weeks (end of treatment), 210/246 vs 75/246; N=482 at 18-week, 185/243 vs 66/239; N=482 at 30-week, 183/243 vs 68/239. QoL: NR Adverse effects: N=496, adverse effects include subcutaneous hematoma, fatigue, pain, and palpitation. 4/247 vs 5/249	30-weeks	Loss of follow-up: 9 patients in electroacupuncture group and 13 patients in sham electroacupuncture group.
Wang (2020) (187)	Acupuncture (45) vs Sham acupuncture (45)	90	SUI	Acupuncture: 30-min acupuncture session at bilateral BL 54 through ST 28, once a day for 10 days. Sham acupuncture: 30-min non-permeable sham acupuncture at bilateral BL 54, once a day for 10 days.	Cure: NR Improvement: NR QoL via I-QOL: N = 88 at 10-days (end of treatment), mean difference 41.05;95% CI 36.44 to 45.66 N = 88 at 4-week, mean difference 41.93; 95% CI 37.1 to 46.76. Adverse effects: NR	4-weeks	Loss of follow up: 1 patient in acupuncture group and 1 patient in sham acupuncture group.
Wang (2016) (188)	Electroacupuncture (90) vs Drug treatment (midrodine) (90)	180	SUI	Electroacupuncture: 30-min electroacupuncture at bilateral BL23, BL32 and BL35 with a disperse-dense wave of 50-70 Hz 6x per week for 4 weeks. Drug treatment: midrodine 2.5mg, 3x per day for 4 weeks.	Cure (based on ICIQ-SF and 1-h pad test): 30/90 vs 20/90 Improvement (based on ICIQ-SF and 1-h pad test): 78/90 vs 62/90 QoL: NR Adverse effects: NR	4-weeks	Loss of follow up: None

Abbreviations: PFMT: pelvic floor muscle training; SUI: stress urinary incontinence; QoL: quality of life; NR: not reported; PFM: pelvic floor muscles; ICIQ-SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form

8.2.1.2. OAB, UUI, MUI

In this update, four new studies including 684 women were identified (49, 193-195). One trial was excluded because it did not report data for women and men separately (193). The characteristics of the other three new studies (N= 584) are presented in Table 33. One trial compared electroacupuncture to sham electroacupuncture in 50 women with OAB that were refractory to anticholinergics (195). In a pilot study, 34 women with MUI were randomised to three groups including acupuncture, PFMT and waitlist control (49). See section on PFMT (II.2.3.1) for more details. Finally, a non-inferiority trial tested electroacupuncture versus PFMT plus solifenacin in 500 women with MUI (194). In the three new trials and five previous trials, it was inappropriate to combine study findings as there was heterogeneity in the control intervention or sample populations.

Quality of data

Randomisation was considered appropriate in the three new studies (194, 195). Allocation concealment was considered adequate in only two of the three studies (49, 194). In terms of blinding, one study proposed a single-blind design (195), while the two others were non-blinded (49, 194). One study reported the complete data (194), while two other trials only reported the data for participants who completed the study (49, 195). In particular, the dropout rates in the study by Solberg (2016) were 25%, 40% and 50% in acupuncture, PFMT, and the waiting list group respectively (49), which could have biased the results.

Results

No included studies reported information on cure or improvement rates. In the two previous trials, no statistically significant differences were detected for improvement of UI frequency when comparing acupuncture with sham or placebo treatment (196, 197). A new trial showed that electroacupuncture was associated with improved OABSS, KHQ and urodynamic parameters compared to a sham acupuncture treatment (P<0.01) in women with refractory OAB to anticholinergics (195). For women with MUI, a pilot trial found no statistically significant difference in ICIQ-UI SF scores between acupuncture and PFMT or between acupuncture and no treatment after the intervention. However, this trial was small and possibly underpowered (49). Results from two previous trials showed few differences between acupuncture and antimuscarinic treatment (oxybutynin or tolterodine) for frequency, urgency and UUI improvement (198, 199). Findings from a non-inferiority trial showed that electroacupuncture was not inferior to PFMT combined with solifenacin, with a between-group difference (-1.34%, 95% CI, -9.78% to 7.10%, P<0.001) for the reduction of UI episodes in women with MUI (194).

Summary

Three trials on the effect of acupuncture on OAB, UUI and MUI compared with no active treatment and another treatment were assessed. When pooling these data with previous trials, four trials (small to medium size) of varying quality found limited to no benefit of acupuncture compared to various sham treatments for MUI and OAB\UUI in women. (**Level of evidence: 2**)

Several factors limit these results, including a small sample size, moderate to high ROB and heterogeneity of active and sham treatments.

Two trials comparing acupuncture to DT in women with OAB, UUI and MUI found no difference between treatments. **(Level of evidence: 2)**

One moderate-quality trial suggested electroacupuncture was not inferior to PFMT plus DT for the treatment of MUI. **(Level of evidence: 2)**

Recommendations

Either electroacupuncture or anticholinergic drugs can be recommended for the treatment of OAB, UUI and MUI in women. **(Grade of recommendation: B)**

Table 33. Summary of data on acupuncture vs no active treatment or other treatment

Author, year	Comparator	N (randomised)	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Zhang (2015) (195)	Electroacupuncture (25) vs Sham electroacupuncture (25)	50	OAB refractory to anticholinergic	Electroacupuncture: 30-min electroacupuncture at bilateral BL32, BL33 and BL34 with a disperse-dense waves of 4/20 Hz, 5x per week for 6 weeks. Sham electroacupuncture: 30-min sham electroacupuncture without electricity output, at non-points located 15 mm lateral to each point, 5x per week for 6 weeks.	Cure: NR Improvement: NR QoL via KHQ: N= 45 at 6-weeks (end of treatment), mean difference -260; 95% CI -314.6 to - 205.4. Adverse effects: N= 45, adverse events include minor pain at the needling sites 3/23 vs 2/22	6-weeks	Loss of follow-up: 2 patients in electroacupunc-ture group and 3 patients in sham electro-acupuncture group.

Author, year	Comparator	N (randomised)	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Solberg (2016) (49)	Acupuncture (12) vs PFMT (10) vs Waiting list (12)	34	MUI	Acupuncture: 30-min acupuncture alternately at 2 groups of points. Group 1 included CV3, CV4, CV6, and bilateral SP6, KI3, KI7, (PC6, LR3 and SP3 with related symptoms), Group 2 included GV4, GV20, and bilateral BL 23, BL 28, BL31, BL32, BL33, BL34, SP6, (BL 14, BL18 and BL20 with symptoms), 1-2x per week for 12 sessions over 12 weeks. PFMT: 25 min of PFMT, following a 20-min general exercise program (no details were provided). Waiting list: no treatment	Cure: NR Improvement: NR QoL: NR Adverse effects: N=34, adverse events included tiredness, symptoms worsening. 1/12 vs 1/10 vs 0/12	12-weeks	Loss of follow-up: 3 patients in acupuncture group, 4 patients in PFMT group, and 6 patients in waiting list group
Liu (2019) (194)	Electroacupuncture (250) vs PFMT plus solifenacin (250)	500	MUI	Electroacupuncture: 30-min electroacupuncture at bilateral BL33 and BL35 with a sparedense wave, 10/50 Hz, 0.1 to 5.0 mA, three times a week for 12 weeks. PFMT +solfenacin: PFMT (intensive exercises at the hospital and home exercises) + Solifenacin, 5 mg daily. Intensive exercises include PFM contractions, 8s hold/8s rest + 4 rapid 1-2s contractions a minimum of 12x for each posture (supine, sitting, and standing). Home exercises include additional 12 contractions 3x per day at home.	Cure: NR Self-reported improvement: N=478 at 12-weeks, 236/244 vs 223/234; N=480 at 36-weeks, 235/245 vs 225/235. QoL via ICIQ-SF: N = 497 at 12-weeks, mean difference -0.23; 95% CI -0.74 to 0.27; N = 497 at 24-weeks, mean difference -0.47, 95% CI -1.13 to 0.19; N = 497 at 36-week, mean difference -0.26, 95% CI -0.9 to 0.39. Adverse effects: N = 497, adverse events included subcutaneous hematoma, dry mouth, constipation, stomach ache, diarrhoea, dyspepsia, heartburn, upper respiratory tract infection, cough, dizziness, hypogeusia, blurred vision, headache, herpes zoster, lower back pain, pruritus, urinary tract infection, dysuria, dry eye, facial oedema 43/249 vs 91/248	36-weeks	Loss of follow-up: 4 patients in electroacupunc-ture group and 8 patients in PFMT plus solifenacin group.

Abbreviations: OAB: overactive bladder; NR: not reported; QoL: quality of life; KHQ: King's Health Questionnaire; PFMT: pelvic floor muscle training; MUI: mixed urinary incontinence; ICIQ-SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form

8.2.2. What is the most effective acupuncture protocol?

No studies were found addressing this question.

8.2.3. Yoga

Yoga is a mixture of physical and mental exercises that originated in ancient India. In this update of the 6th ICI, a Cochrane systematic review (200), which included two trials (201, 202), and an additional trial (203) were identified, and 105 participants were involved. The characteristics of the three studies are presented in Table 34. One trial compared yoga to mindfulness-based stress reduction in 30 women with predominant UUI (201). Huang *et al.* performed two studies comparing yoga to no active treatment. This included a pilot study involving 19 women with UI that explored the efficacy of yoga for six weeks compared with no treatment (202). The other trial assessed the effectiveness of yoga in 56 women with UI over three months compared to a non-specific muscle stretching and strengthening programme as the control (203).

Quality of data
Randomisation was considered appropriate in the three studies (201-203). Allocation concealment was considered adequate in two out of three studies (201, 203). One study did not describe the methods used for allocation concealment (202). In one trial, the investigators and all staff involved in abstracting data were blinded, although participants were not blinded (203). Two other studies were not blinded (201, 202). Only one trial reported the complete data (201), while the two other trials only reported data on participants who completed the study (202, 203).

Results
In the 2019 Cochrane systematic review, data from two trials were not combined into a meta-analysis due to the difference in comparators. Uncertainty about the effectiveness of yoga was also addressed (200). Both studies included in the Cochrane review and the additional trial did not report information on cure or improvement rates. Pooled data from two studies in which yoga was compared with no active treatment suggested that yoga resulted in a statistically significant decrease in UI episode frequency compared to no active treatment (N=68, MD-1.21, 95% CI -2.07 to -0.35, P=0.006, I^2=0%) (202, 203). One study reported that yoga resulted in a statistically significant improvement QoL as evaluated by the UDI-6 (P<0.01) (202), while another study found no statistically significant difference between yoga and no active treatment (203). One study found that yoga was associated with fewer symptoms and improvement in QoL than mindfulness-based stress reduction for managing predominant UUI in women (201).

Summary

The three included studies had a small sample size (19-56 participants) and a moderate to high ROB. Pooled data from two studies on women with UI suggest that yoga may be more effective than no active treatment in improving symptoms, although the effect on QoL was inconsistent. **(Level of evidence: 2)**

For women with predominant UUI, evidence from one small trial suggests that yoga might be associated with reduced improvement of symptoms and QoL compared to mindfulness-based stress reduction. **(Level of evidence: 3)**

Recommendations

On the present evidence, no recommendation on the use of yoga on UI is possible. **(Grade of recommendation: D New)**

More randomised controlled trials with large sample sizes and clear and consistent reporting of core outcome data would be beneficial in reaching a firm conclusion on the effectiveness of yoga over other treatments.

Table 34. Summary of data on yoga vs no active treatment or other treatment

Author, year	Comparator	N (randomised)	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Baker (2014) (201)	Yoga therapy (15) vs MBSR (15)	30	Predominant UUI	Yoga therapy: participants were taught by a certified yoga instructor in a weekly yoga class for 8 weeks. The class focused on the "Asanas" or physical practice and how to prevent injury and promote relaxation of the muscles. MBSR: The 8-week MBSR program is a structured program that teaches participants a variety of meditation practices, mindfulness-yoga, walking meditation, and discussions on the relationship between stress, illness, and health.	Cure: NR Improvement: NR QoL via OAB-HRQL: N= 24 at 8-weeks (end of treatment), median change from baseline 8.7% vs 29.27%; N= 20 at 6-month, 8% vs 43.9%; N= 21 at 1-year, 13.04% vs 36.09%. Adverse effects: NR	1 year	Loss of follow-up: NR

Author, year	Comparator	N (randomised)	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Huang (2014) (202)	Yoga therapy (10) vs Waitlist control (9)	19	All types of UI	Yoga therapy: participants were scheduled to attend two 90-minute group yoga classes per week for 6 weeks, led by a certified instructor. The program focused on a core set of 8 postures. Waitlist control: no treatment	Cure: NR Improvement: NR QoL via BDI-6: N = 18 at 6-weeks (end of treatment), mean difference -0.9, 95% CI -1.4 to -0.3. Adverse effects: N=18, no details were described. 2/9 vs 2/9	6 weeks	Loss of follow-up: 1 patient in yoga group dropped out.
Huang (2019) (203)	Yoga therapy (28) vs Nonspecific muscle stretching and strengthening program (28)	56	All types of UI	Yoga therapy: participants were scheduled to attend two 90-minute group yoga classes per week for 6 weeks, led by a certified instructor. The program focused on a core set of 15 postures. In addition to attending group classes, participants were asked to practice yoga at home at least 1 additional hour per week. Nonspecific muscle stretching and strengthening program: participants were scheduled to attend two 90-minute group classes per week for 6 weeks, led by an instructor. The program focused on nonspecific muscle stretching and strengthening and avoided engaging the pelvic floor or promoting mind relaxation. In addition to attending group classes, participants were asked to practice exercises at home at least 1 additional hour per week.	Cure: NR Improvement: NR QoL via BDI-6: N = 50 at 3-month (end of treatment), percentage change from baseline 53% vs 37%. Adverse effects: N=56; included gastrointestinal, genitourinary, musculoskeletal, neurological or psychological, ophthalmologic, and respiratory adverse events. (no specific adverse events were listed) 23/28 vs 25/28	3 months	Loss of follow-up: 1 patient in yoga group and 5 in control group dropped out.

Abbreviations: MBSR: Mindfulness-based stress reduction; UUI: urge urinary incontinence; UI: urinary incontinence; NR: not reported; QoL: quality of life; OAB-HRQL: overactive bladder symptom and health-related quality of life questionnaire; BDI-6: Beck Depression Inventory

8.2.4. Herbal Therapy

Available evidence on herbal therapy was limited. In the sixth ICI, no trials were identified. In this update, three trials including 278 women were identified (204-206). The characteristics of the three studies are presented in Table 35. All three studies used placebo as the control (204-206). As the three new trials had little duplication in the outcomes or sample populations it was inappropriate to combine study findings.

Quality of data

Randomisation was considered to be appropriate in the two studies (204, 206), whereas the third study did not provide sufficient information on the method of randomisation (205). Allocation concealment was considered to be adequate in two studies (204, 206), while another one did not describe methods used for allocation concealment (205). All three studies were double-blinded (204, 206). Additionally, all three studies only reported data on participants who completed the study (204-206).

Results

No trials reported information on cure or improvement rates. For women with OAB, a study showed that cranberry may result in a statistically significant reduction of daily micturition (-1.91, 95% CI -3.74 to -0.88, p<0.05) and urgency episodes (-2.81, 95% CI -4.82 to -0.80, p<0.01) at 24 weeks of follow-up compared with placebo (204). For women with UI, findings from two other trials showed that herbal therapy was associated with a significant reduction in the ICIQ-UI SF score compared to placebo (205, 206). Additionally, a study reported that herbal therapy resulted in a statistically significant improvement in QoL in UI patients as evaluated by ICIQ-UI SF's question 5 (205), while another study found no significant difference in QoL between herbal therapy and placebo, evaluated by the OABQ-SF HRQL sub-score and SQOL-F (204).

Summary

Three trials assessed the effect of herbal therapy on OAB and UI compared with no active treatment and another treatment. Data from the three small- to moderate-sized studies of moderate quality suggest that herbal therapy could be more effective than no active treatment in improving UI and LUTS, although the effect on QoL was inconsistent. **(Level of evidence: 3)**

Recommendations

Herbal therapy could be recommended over no therapy for improving UI and LUTs symptoms in women with OAB and UI but not for improvements in QoL. **(Grade of recommendation: C New)**

More randomised controlled trials with large sample sizes and clear and consistent reporting of core outcome data would be beneficial in reaching a firm conclusion on the effectiveness of herbal therapy.

Table 35. Summary of data on herbal therapy vs no active treatment or other treatment

Author, year	Comparator	N (randomised)	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Cho (2020) (204)	Herbal therapy (46) vs Placebo (52)	98	OAB	Herbal therapy: 1 pill of dried cranberry powder (500 mg of proprietary full spectrum dried cranberry fruit), orally 1x per day for 24 weeks Placebo: 1 placebo pill (500 mg proprietary mixture of maltodextrin and food grade colours), orally 1x per day for 24 weeks	Cure: NR Improvement: NR QoL via OABQ-SF HRQL subscore: N = 60 at 24-weeks (end of treatment), mean difference -3.11; 95% CI -8.14 to 1.92. QoL via SQOL-F: N = 60 at 24-week (end of treatment), mean difference -2.16, 95% CI -8.15 to 3.82. Adverse effects: NR	24-weeks	Loss of follow-up: 11 patients in herbal therapy group and 6 in control group.
Niktabe (2018) (205)	Herbal therapy (44) vs Placebo (45)	99	SUI or MUI	Herbal therapy: 2.3 mL of qost oil (Hydro alcoholic extract from dried roots of Saussurea costus) was used by local application to the area between the navel and pubic region without massage 2x per day for 6 weeks. Placebo: 2.3 mL of cold pressed sesame oil was used by local application to the area between the navel and pubic region without massage 2x per day for 6 weeks.	Cure: NR Improvement: NR QoL via ICIQ-SF Question 5: N = 82 at 6-weeks (end of treatment), mean difference -2.81;95% CI -3.93 to -1.69; at 10-week (follow-up), mean difference -2.83;95% CI -4.07 to -1.59. Adverse effects: NR	10-weeks	Loss of follow-up: 1 patient in yoga group

Author, year	Comparator	N (randomised)	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Palacios (2020) (206)	Herbal therapy (41) vs Placebo (40)	81	All type of UI	Herbal therapy: 1 pill of Femaxeen (cytoplasmic extracts of pollen 160 mg, pumpkin seed extract 300 mg and vitamin E 10 mg), 1x per day for 90 days, taken orally. Placebo: 1 placebo pill per day for 90 days, taken orally.	Cure: NR Improvement: NR QoL: NR Adverse effects: N=76, adverse events include elevated transaminases, increased cholesterol levels, and headache. 2/38 vs 1/38	90-days	Loss of follow-up: 3 patients in herbal therapy group and 2 in control group

Abbreviations: MUI: mixed urinary incontinence; UUI: urge urinary incontinence; SUI: stress urinary incontinence; UI: urinary incontinence; NR: not reported; QoL: quality of life; OABQ-SF: overactive bladder questionnaire short form; OAB-HRQL: overactive bladder symptom and health-related quality of life questionnaire; BDI-6: Beck Depression Inventory

9. SUMMARY CONSERVATIVE MANAGEMENT OF UI IN WOMEN

9.1. Lifestyle interventions

Prevention

Based on the secondary analysis of a large RCT, a dietary intervention with high fruit, vegetable, and whole grain content as well as a moderate caloric intake can be recommended to postmenopausal women to prevent UI. **(Grade of recommendation: B New)**

Based on one longitudinal study, higher levels of physical activity (≥43.2 MET hours/week) coud be recommended to continent parous middle-aged women. **(Grade of recommendation: C New)**

Treatment:

Behavioral weight loss should be recommended to obese and overweight women with UI. **(Grade of recommendation: A)**

A physical activity programme for the reduction of abdominal fat could be recommended to young overweight women with UUI to reduce LUTS (**Grade of recommendation: C New)**

A low-fat and high-fruit, vegetable and whole grain diet could be recommended as it has a small effect in decreasing UI symptoms independently of weight change, age, ethnicity, and hormone replacement use. **(Grade of recommendation: C New)**

Vitamin D supplementation can be recommended to decrease UUI episodes in post-menopausal women in women of certain ethnicity. **(Grade of recommendation: B)**

An adequate fluid intake and the reduction of caffeine consumption can be recommended for people with UI and related LUTS symptoms. (**Grade of recommendation: B)**

9.2. PFMT

Childbearing women

Prevention

Continent, pregnant women should be offered a supervised PFMT programme (including regular health professional contact) that is intensive and aimed at strengthening PFMs to prevent antepartum and postpartum UI (up to 6 months) UI. **(Grade of recommendation: A)**

Treatment

PFMT should be offered as first line conservative therapy to women with persistent UI symptoms, two to three months after delivery. **(Grade of recommendation: A)**

An 'intensive' PFM strength training programme (in terms of supervision and exercise content) can be recommended as it is related the treatment effectiveness. **(Grade of recommendation: B)**

Prevention and treatment

Health providers should carefully consider the costs and benefits of population-based approaches, such as professionally taught antepartum or postpartum PFMT. PFMT should be provided to all pregnant or postpartum women by a health professional regardless of their current or prior continence status.

(Grade of recommendation - antepartum PFMT: A)

(Grade of recommendation - postpartum PFMT: B)

Women Others

Prevention

Evidence suggest that PFMT is effective in the prevention of UI in younger athletes and menopausal women, immediately after the intervention. (**Level of evidence 2)** Supervised PFMT can be offered to prevent UI in women. **(Grade of Recommendation: B New)**

Treatment

Supervised PFMT should be offered as a first line conservative therapy for women of all ages with UI. **(Grade of recommendation: A)**

Clinicians should offer and provide the most intensive health professional-led PFMT programme possible within service constraints. **(Grade of recommendation: A)**

Supervised individual or group PFMT with confirmation of adequate PFM contraction can be considered in postmenopausal women with SUI and MUI. **(Grade of recommendation: B New)**

Direct PFMT as opposed to indirect PFMT can be recommended **(Grade of recommendation: B New)**

There is no clear benefit for adding other modalities (i.e., motor learning, abdominal or hip muscle training, intra-vaginal resistance devices and adherence strategies) to PFMT and therefore they cannot be recommended. **(Grade of recommendation: B)**

There is no clear benefit for adding clinic- **(Grade of recommendation: B changed)** or home-based biofeedback (**Grade of recommendation: B) or both (Grade of recommendation: A New)** to a PFMT programme. However, biofeedback may be considered for sub-groups of women presenting an important PFM weakness, atrophy, or reduced proprioception.

PFMT and VC are both effective as conservative therapies for SUI, although PFMT can be favoured because a subset of women is unable to use VC and there are side effects associated with their use. **(Grade of recommendation: B)**.

VC with supervised training sessions by a trained health professional can be offered to women with SUI who can and are prepared to use them. **(Grade of recommendation: B)**

PFMT should be preferentially offered over EStim as first line conservative therapy for women with SUI, UUI and MUI. **(Grade of recommendation: A New)**

PFMT can be preferentially offered over BT as a first line conservative therapy for women with SUI, UUI and MUI. **(Grade of Recommendation: B)**

Oxybutynin cannot be recommended over PFMT as a first line therapy in women with UUI and MUI. **(Grade of recommendation: B)**

PFMT and drug therapy (i.e., alpha-adrenergic agonist, tolterodine) interventions showed significant benefits for UI outcomes, although drug therapy results in more adverse effects and a higher dropout rate. PFMT can be offered as the first line therapy **(Grade of recommendation: B)**

Surgery is more effective than PFMT for SUI, but the potential benefits should be weighed against the potential adverse events and cost. PFMT can be offered as the first line therapy because it is less invasive. **(Grade of recommendation: B)**

Both PFMT and continence pessaries can be considered for the treatment of UI as both showed significant benefits for women. **(Grade of recommendation: B)**

Based on limited evidence, combining PFMT with either VC or EStim may not add any benefits and could not be routinely recommended. **(Grade of recommendation: C)**

For the treatment of SUI, UUI, or MUI in women, one could consider the addition of PFMT to BT, which provides additional benefits compared to BT alone. **(Grade of recommendation: C)**

When treating women with SUI and vaginal atrophy, combining PFMT and intravaginal oestrogen over oestrogen alone could be considered. **(Grade of recommendation: C)**

For treatment of UUI (tolterodine) and SUI (duloxetine), adding PFMT to drug therapy can be considered. **(Grade of recommendation: B New)**

Adding PFMT to mid-urethral tape can have potential benefits and could be considered in women with MUI and SUI. **(Grade of recommendation: B New)**

When treating stress-predominant incontinence, adding PFMT to a continence pessary can be considered. (**Grade of recommendation: B)**

9.3. Cones

Treatment

For women with SUI, VC with supervised training sessions by a trained health professional can be offered as a first-line conservative therapy to those who can and are prepared to use them. **(Grade of recommendation: B)** Assessment by a trained health professional is recommended. **(Grade of recommendation: D)**

VC and EStim can be equally recommended in the treatment of SUI and MUI**. (Grade of re-commendation: B)** However, side effects and discomfort appear to limit their utility in clinical practice. **Grade of recommendation: D).**

9.4. EStim

Treatment

EStim can be considered over no treatment to improve symptoms and QoL in women with SUI. **(Grade of recommendation: B)**

EStim can be considered for treatment to improve symptoms for UUI. **(Grade of recommendation: B)** However, this recommendation should be viewed with caution until the findings are supported or refuted in longer-term follow up.

For women with SUI and UUI, pudendal EStim could be recommended as it may be more effective than transvaginal EStim in improving symptoms. **(Grade of recommendation: C)**

External EStim and transvaginal EStim can be recommended to improve SUI in short term. **(Grade of recommendation: B New)**

Transcutaneous TNS may be slightly better than parasacral EStim and therefore could be recommended. **(Grade of recommendation: C)**

There is a need for studies to elucidate the purpose and biological rationale for EStim in different diagnostic groups. More RCTs are needed.

Medical treatments appear to be less effective than EStim or a combination of PFMT and EStim for SUI and therefore cannot be routinely recommended. **(Grade of recommendation: B)**

Propantheline bromide in women with UUI or oxybutynin and tolterodine for DO cannot be routinely recommended for UUI as they are less effective than EStim. **(Grade of recommendation: B)**

For SUI, the addition of EStim to PFMT or biofeedback-assisted PFMT programmes cannot be routinely recommended as there appears to be no additional benefit. **(Grade of recommendation: B)**

For OAB or MUI, the addition of EStim to BT or BT plus biofeedback can be considered as this adds benefit to the treatment **(Grade of recommendation: B)**

9.5. MStim

Treatment

For women with SUI, MStim can be recommended over no active treatment. **(Grade of recommendation: B New)** However, this recommendation should be viewed with caution until the findings are supported or refuted in further trials with large sample sizes and clear and consistent reporting of core outcome data.

Adding MStim to PFMT does not appear to be beneficial and therefore could not be recommended **(Grade of recommendation: C)**

9.6. TNS

Treatment

For women with UUI or OAB, TNS could be considered over no active treatment in symptom control. **(Grade of recommendation: C)**

For women with urgency UI or OAB, transcutaneous and percutaneous TNS could be recommended as each appears to be equally effective treatments. Transcutaneous TNS is associated with fewer adverse effects. **(Grade of recommendation: C)**

Transcutaneous TNS or percutaneous TNS can be considered for symptom control in combination with other effective treatments by women with urgency UI or OAB. **(Grade of recommendation: B New)**

9.7. Scheduled voiding regimens

Treatment

BT should be recommended as first line conservative therapy for UI in women. **(Grade of recommendation: A)**

Clinicians should provide the most intensive BT supervision that is possible within service constraints. **(Grade of recommendation: D)**

Either BT or anticholinergic drugs can be recommended for women with OAB or UUI **(Grade of recommendation: B)**.

BT may be preferred by women and clinicians because of the absence of drug related adverse effects. **(Grade of recommendation: D)**

EStim or EStim plus biofeedback can be recommended as an adjunct treatment to BT, although further studies are needed. (**Grade of recommendation: B New**)

The addition of written information on BT to an antimuscarinic drug cannot be routinely recommended as it does not appear to further improve UI in women with OAB. **(Grade of recommendation: B)**

Timed voiding with a two-hour voiding interval could be considered as a sole intervention for women with mild UI or infrequent voiding patterns. **(Grade of recommendation: C)**

The routine addition of a “simplified” BT to DT should be considered in the treatment of voiding frequency in women with UI and OAB. **(Grade of recommendation: A New)**

BT can be offered to treat urinary frequency. **(Grade of recommendation: B)**

Either BT and/or an anticholinergic drug can be recommended as both are effective intreating frequency in women. **(Grade of recommendation: B)**

Combining EStim, to BT but not biofeedback can be recommended and may provide additional benefits for treating frequency. **(Grade of recommendation: B New)**

BT can be offered as treatment for nocturia. **(Grade of recommendation: B)**

Combining EStim and BT cannot be recommended over BT alone for treating nocturia. **(Grade of recommendation: B New)**

Moxibustion could be considered in addition to BT for treating nocturia. **(Grade of recommendation: C New)**

BT alone or with anticholinergic drugs can be considered for treating nocturia (with OBA), as they appear equally effective. **(Grade of recommendation: B)**

9.8. Complementary and alternative medicine

Treatment

Acupuncture could be recommended as an optional treatment over no treatment for women with SUI. **(Grade of recommendation: C)**

Either electroacupuncture or anticholinergic drugs can be recommended for the treatment of OAB, UUI and MUI in women. **(Grade of recommendation: B)**

Herbal therapy could be recommended over no active treatment for improving UI and LUTs in women with OAB and UI, but not for QoL.(**Grade of recommendation: C New)**

III. PELVIC ORGAN PROLAPSE

Pelvic organ prolapse (POP) refers to the descent of one or more of the anterior vaginal wall, posterior vaginal wall, uterus, cervix or vaginal vault (cuff scar after hysterectomy). The presence of any such sign should be correlated with relevant prolapse symptoms (207). Women with prolapse commonly have a variety of pelvic floor symptoms. The more common symptoms are: the feeling of (or seeing) a vaginal bulge, a feeling of something coming down, pelvic pressure, low backache, urinary tract symptoms (e.g. frequency, incomplete emptying), anorectal symptoms (e.g. incomplete emptying, having to digitate to empty) and sexual symptoms (e.g. dyspareunia, vaginal laxity) (207). The prevalence of symptomatic POP in the general population is 11.4% (4–12.2%) (208), but this increases to 41% in women over the age of 50 (209). The aetiology of prolapse is multi-factorial. Risk factors include pregnancy, childbirth, congenital or acquired connective tissue abnormalities, denervation or weakness of the PFM, ageing, menopause and factors associated with chronically raised intra-abdominal pressure (e.g., heavy lifting) (210-213). Treatment depends on the severity of the prolapse and its symptoms, and the woman's general health (214). Conservative treatment is generally considered for those with a lesser degree of prolapse, those who wish to have more children, those with frailty or those unwilling or unable to undergo surgery. The aims of conservative treatment in the management of prolapse are threefold and include:

- Preventing the prolapse worsening;
- Decreasing the frequency or severity of symptoms caused by prolapse (i.e., pelvic pressure, vaginal bulging, backache, urinary, bowel and sexual dysfunction);
- Avoiding or delaying of the need for surgery.

Study selection criteria for inclusion in the update

The evidence presented in this section is drawn from recent Cochrane systematic reviews (215), and literature identified from this chapter search strategy (Appendix 1). As the number of studies employing higher quality study designs has continued to increase in the field, we have *included only* RCTs. Because the focus of this chapter is treatment and prevention of prolapse, the main focus of the outcome measures selected are on prolapse signs and symptoms. Therefore, only RCTs that report at least one prolapse outcome were included.

Quality of data

The methodological quality for included trials was assessed using the Cochrane ROB tool (216). Trials were independently assessed by 2 of the authors of this chapter, and judged as either at 'low risk', 'unclear' or 'high risk' across six domains (selection, performance, detection attrition, reporting and other potential sources of bias). The ROB is summarised graphically for each trial in Appendix 2.

Summary of new studies included in the update

We have identified 42 new RCTs as suitable for inclusion. Four of these studies were published outside our search dates (217-220), but were not previously included in earlier versions of this chapter, so we have included this evidence here for completeness. Most of the studies employed a parallel group RCT design (36/43) and were carried out in the USA (9/43) and China (8/43). Multi-arm RCT data are presented as randomised paired comparisons indicated as i, ii or iii. For example, data from Berzuk *et al.* (2015) are presented as three trials of (i) Enhanced education vs standard education; (ii) Standard education vs control (no treatment) and (iii) Enhanced education vs control (no treatment).

We have presented **updated** evidence for the use of conservative management of prolapse in three sections:

- **Section 1. Educational and lifestyle interventions**: seven studies (35, 40, 218, 221-224) of which five studies (seven randomised comparisons) (35, 40, 218, 223, 224), were aimed at prevention of prolapse and two studies focused on treatment of prolapse (221, 225) (see Table 37: Characteristics of included studies for Educational / lifestyle interventions),
- **Section 2. Physical interventions**: 22 studies (30, 73, 91, 217, 219, 220, 226-241). Of these 11 studies aimed at prevention of prolapse (30, 91, 217, 219, 220, 226-231) (see Table 38; Characteristics of included studies of physical interventions for prevention of prolapse) and 11 studies focused on prolapse treatment (73, 232-241) (see Table 39; Characteristics of included studies of physical interventions for treatment of prolapse),
- **Section 3. Pessaries**: 13 studies (242-254), of which one study aimed at prevention (242), and the remaining 12 studies focused on treatment (243-254) (Table 40. Characteristics of included studies for pessaries).

Groupings were broadened to allow data to accumulate within comparisons, to provide stronger and more clinically useful evidence. Consequently, within each of these sections we have divided the evidence into studies aimed at prevention of prolapse and treatment trials. For ease of use, we have summarised the volume of evidence identified earlier editions alongside the new evidence identified in this update in Table 36.

Table 36. Summary of the volume of evidence identified in this update and earlier version of this chapter

	Intervention	Comparator	Number of prevention studies included in previous ICI reviews	New prevention studies identified in this update (References)	Number of treatment studies included in previous ICI reviews	New Treatment studies (References)
Section 1. Educational and lifestyle interventions	Educational / lifestyle intervention (alone or in combination)	No treatment/ usual care/ no active treatment	45 observational studies. No RCTs.	3 studies [35, 40, 223]	1 secondary analysis of an RCT	No studies identified
	Educational / lifestyle intervention (alone or in combination)	An active treatment (or combination)		3 studies [40, 218, 224]		2 studies [221, 225]
Section 2. Physical interventions	Physical intervention (alone or in combination)	No treatment/ usual care/ no active treatment	2 RCTs	6 studies [30, 217, 219, 220, 227, 256]	13 RCTs	1 study [239]
	Physical intervention (alone or in combination)	An active treatment (or combination)		7 studies [30, 91, 226, 228, 229, 230, 256]		5 studies [73, 232, 234, 236, 240]
	A physical intervention combined with a non-conservative adjunct	An active treatment (or combination)	No RCTs	No studies identified	6 RCTs	5 studies [233, 237, 238, 241, 263, 264]
Section 3. Pessaries	Pessary (alone or in combination)	Control / waiting list or no active treatment	No RCTs	1 study [242]	No RCTs	No studies identified
	Pessary (alone or in combination)	An active treatment (or combination)		No studies identified	Preliminary data from 2 RCTs and data from a small trial with recruitment issues	2 studies [244, 248]
	Pessary (alone or in combination)	Surgery		No studies identified	No studies	1 study [254, 268]
	Pessary (alone or in combination)	Another pessary		No studies identified	No studies identified	3 studies [247, 252, 253]
	Studies aimed at optimising pessary management or reducing pessary-related complications			No studies identified	No studies identified	6 studies [243, 245, 246, 249, 250, 251]

Abbreviations: RCT: randomised controlled trial

1. EDUCATIONAL AND LIFESTYLE INTERVENTIONS

Lifestyle and educational interventions seek to avoid the onset and exacerbation of prolapse by decreasing intra-abdominal pressure. For example, heavy (or incorrect) lifting, being overweight and being constipated can cause chronically increased intra-abdominal pressure, which in turn may lead to the development or worsening of prolapse. Education and lifestyle interventions for prolapse might include the following:

- education/advice relating to the effects of body weight/weight reduction,
- education/advice relating to the effects of exacerbating activities (e.g., lifting, coughing),
- education/advice relating to the effects of straining to defecate,
- education/advice relating to the effects of diet and fluid,
- education about the pelvic floor anatomy and conditions.

1.1. Prevention

1.1.1. An educational/lifestyle intervention (alone or in combination) versus no treatment/ usual care/ no active treatment

In this update, three new trials (four randomised comparisons) of lifestyle and educational interventions (either on their own or in combination with other treatments) were identified (35, 40, 223). Salient features of each trial are summarised in Table 37 and the ROB for each trial is presented in Appendix 2.

Quality of data

Berzuk and Shay (2015) (40) (ii) (iii) conducted a 3-arm RCT to assess whether a pelvic floor health education presentation could improve female office workers' knowledge about their pelvic floor and raise their awareness of pelvic floor dysfunction (PFD), including prolapse. Women were randomly allocated to one of three groups: enhanced educational intervention; standard educational intervention or no intervention. The enhanced educational intervention comprised a 60-minute educational presentation on female pelvic health and PFM function including verbal instruction in a home PFM strengthening programme. The session included definitions and risk factors for PFD, the impact of neglect or injury on the PFMs, and available treatments. Healthy behavioural strategies such as proper toileting postures and habits, and bladder and bowel-friendly diet information were presented. Approximately two months following the education intervention, the enhanced educational intervention group were asked to attend a second presentation. The purpose of this second 60-minute presentation was to review the information previously presented to determine the effect of a 'reminder' or 're-education' variable. Women in the standard educational intervention did not get a repeat presentation two months later. Women in the control group received no intervention. Online surveys using validated tools including the Prolapse and Incontinence Knowledge Quiz, PFDI-20, PFIQ-7 and PFM exercise items were completed by all groups on three occasions (at baseline, after the first educational presentation and two months later).

In the PREPARED trial, Hyakutake and colleagues (35) conducted a RCT to assess whether attending a pregnancy workshop would improve pregnant primiparous women's postpartum pelvic floor health knowledge and symptoms. Women with a first singleton gestation were randomised to receive either an education intervention (i.e., 2-hour pelvic floor health workshop delivered while the women were still pregnant) or routine prenatal care. The workshop covered a variety of topics including anatomy, definitions, risk factors, the effect of various modes of delivery, PFMT, preventive strategies, and treatments for PFD. Women were given a workbook with diagrams, tables, and resources. The main outcomes were assessed using questionnaires to measure the difference between groups in knowledge scores; PFMT-specific knowledge and practice; prolapse (POPDI-6) and pelvic floor symptoms (PFDI-20) and condition-specific quality of life (PFIQ-7); and mode of and satisfaction with delivery. Questionnaires were completed by women when they were recruited and again at 6-weeks postpartum.

Takacs and colleagues (2020) (223, 255) conducted a RCT to investigate the effects of an oral dietary supplement aimed at improving postpartum recovery of pelvic floor injuries (and other related symptoms). Postpartum women who had no complications during their pregnancy and who had a first-time normal vaginal delivery were enrolled within 48 hours of delivery. Women were randomised to receive either a specially formulated postpartum supplement plus routine prenatal vitamin (intervention) or a routine prenatal vitamin (control). Women in the treatment group were asked to take a daily oral dose of the supplement (4g leucine, 30 mg zinc, 900mg omega-3 fatty acids) for six weeks. Secondary outcomes included POPDI-6 and UDI-6 symptom questionnaires and POP-Q. Questionnaire data were collected at baseline (immediately following delivery) and 6 weeks post-delivery. POP-Q data were collected at 6 weeks postpartum.

Results

One hundred and sixty-one female volunteers were randomised in the Berzuk (2015) trial (40); 54 received enhanced education, 55 received the standard education intervention, and 52 were allocated to the no treatment group. Of these, 145 completed the trial; 6 women dropped out of the enhanced education group. Seven women dropped out of the standard education group. Three women dropped out of the control arm. Women who received both education interventions (iii), and those receiving only the first education intervention (ii) had significantly better knowledge of pelvic floor anatomy and awareness compared with the control group. The groups receiving education also had significantly fewer pelvic floor symptoms (on PFDI-20) accompanied with significantly better quality of life (on PFIQ-7).

One hundred women were randomised in the PREPARED trial (35): 50 were allocated to each group. Postpartum data were available for 37 women per group. Thirteen women dropped out of the pelvic floor health workshop group. In the control group, 13 women did not return their questionnaires. Women in the intervention arm scored significantly higher on a pelvic floor knowledge questionnaire, reported performing daily PFMT more frequently than women in the control group and were more confident in performing PFMT. Women in the intervention group also reported significantly fewer bowel symptoms than women in the control group. However, there were no differences in urinary or prolapse symptoms, mode of delivery, complications, or satisfaction with delivery between the two groups.

Takacs and colleagues (2020) (223, 255) randomised 66 women: 32 received the intervention, and 34 received the control. Five women in the intervention group did not complete the trial. Eight women dropped out from the control group. There was no significant difference in any of the individual POP-Q measurements between groups at 6 weeks postpartum. However, when the POP-Q data were dichotomised, the authors reported a statistically significant difference in anterior vaginal wall prolapse at or beyond the hymenal ring in the control group compared to the treatment group. No statistically significant difference was found between the groups on POPDI-6, UDI-6, or zinc serum levels at six-weeks. However, the authors note that statistically significantly more women reported bothersome bulge symptoms (based on Q3 from the POPDI-6) in the control group compared with women receiving the intervention.

Summary of the evidence from the previous edition

In this update we have only included evidence from RCTs.

Summary of the evidence identified in this update

Three new studies were included in this comparison.

- A small-medium size study with a moderate-high ROB delivering an educational workshop led to better knowledge of pelvic floor anatomy compared to no intervention, and fewer pelvic floor symptoms (40). **(Level of evidence: 2)**
- A small study with a moderate-high ROB showed women who took part in a pelvic health workshop during pregnancy had better knowledge and better PFMT adherence postpartum compared to controls but there were no differences in delivery outcomes or symptoms. **(Level of evidence: 2)**
- A small study with a moderate ROB evaluating a postnatal oral dietary supplement did not show any difference in women's prolapse symptom scores compared to controls although women receiving the supplement were significantly less like-

ly to have anterior prolapse beyond the hymen or to report a bothersome bulge. **(Level of evidence: 2)**

Recommendations

Improving pelvic floor knowledge in healthy women could be recommended to reduce pelvic floor symptoms **(Grade of recommendation: C New)**

1.1.2. An educational/lifestyle intervention (alone or in combination) versus another active treatment (or combination)

In this update, three trials of lifestyle and educational interventions (either on their own or in combination with other treatments) compared with another active treatment (or combination) were identified (40, 218, 224). Salient features of each trial are summarised in Table 37 and the ROB for each study is presented in Appendix 2.

Quality of data

Our review identified one randomised paired comparison (Berzuk 2015) (i) that compared the effectiveness of an enhanced educational intervention with a standard educational intervention, discussed above (40).

Gozukara and team (2014) (218), conducted a RCT comparing the effects of weight loss on pelvic floor symptoms, prolpase and UI. Overweight and obese women with UI were randomly allocated to a six month behavioural weight loss programme, or a structured education programme (218). Women in both groups were asked to agree not to initiate new treatments for incontinence or weight reduction during the trial. All women were provided four 1-hour group education sessions in the preceding month *prior* to randomisation. Each session included about 20 women, and they consisted of information about the beneficial effects of weight loss, physical activity, and healthy eating on urinary complaints provided by an internist, dietitian, and urogynecologists. In addition, women allocated to the weight loss programme received information about a calorie and fat restricted diet of 1,200–1,800 kcal daily, depending on initial weight, with less than 30% of calories from fat, designed to produce an average loss of 7–9 % of initial body weight within 6 months. The women also met monthly for 6 months in groups of 15–20 for 1-hour sessions that were led by an internist in nutrition, exercise, and behaviour change. Women were provided with sample meal plans suited for their calorie restrictions. They were also encouraged to gradually increase their physical activity. Monthly consultations with women employed behaviour modification techniques (e.g., self-monitoring of diet and exercise) throughout the programme. Women were assessed using the PFDI, including POPDI-6 subscale, and POP-Q at baseline and again at 6 months.

Tuuli and colleagues (2020) (224) conducted a RCT to determine the impact of pushing timing (immediate vs delayed) during the second stage of labour on women's pelvic floor. Primiparous women at term were randomly allocated (at complete cervical dilation with neuraxial analgesia) to either immediate pushing or asked to delay pushing for an hour. Outcome measures included rate and extent of prolapse using POP-Q, PFDI-20 and PFIQ-7, in their subscales including POPDI-6 and POPIQ-7. Data were collected at baseline (questionnaires only) and at six weeks and six months postpartum.

Results

Berzuk and Shay (2015) (40) compared an enhanced educational intervention compared with standard educational intervention. Descriptions of the intervention and details of the dropouts are summarised in 1.1.1. The enhanced educational intervention group had statistically significantly greater pelvic floor knowledge compared with the standard educational group.

In the Gozukara *et al.* (2014) (218) study 378 women were randomised, with 189 women allocated to each group. Of these 321 women completed the trial; 26 women dropped out of the intervention group (lost to follow-up or declined to continue) and 31 women dropped out of the control group (lost to follow-up or declined to continue). Women in the intervention group lost significantly more weight than women in the control group. Women in the weight loss intervention group also had significantly lower totalPFDI-20 score and POPDI-6 subscore at six months. The genital hiatus, perineal body, and Ap measurements on POP-Q were significantly lower in the weight loss group compared with the control group after 6 months.

Tuuli and colleagues (2020) (224) randomised 2414 women; of which 941 completed the questionnaires at baseline (452 women in the immediate pushing group, and 489 women in the delayed pushing group). At the six-week follow-up, 38 women immediate group and 40 women from the delayed pushing group had dropped out; at six months a further 27 women had dropped out of the immediate group and 37 women from the delayed pushing group. There was no significant difference between groups on the POP-Q at six weeks or six months postpartum. No significant difference was seen between groups on the PFDI-20 or PFIQ-7 questionnaires.

Summary of the evidence identified in this update

Three new trials were included in this comparison.

- A small-medium sized study with a moderate-high ROB found an enhanced educational presentation led to better knowledge of pelvic floor anatomy compared to standard educational presentation (40). **(Level of evidence: 2)**
- A large study with generally low ROB showed that a weight loss programme resulted in improved POP symptoms and POPQ measurements in women with UI (218). **(Level of evidence: 2)**
- A large study with an unclear ROB comparing the impact of immediate versus delayed pushing timing during labour on women's pelvic floor outcomes showed no difference on prolapse severity or symptoms, nor on other pelvic floor symptoms. **(Level of evidence: 2)**

Recommendations

An enhanced educational intervention may be recommended to improve healthy women's knowledge of their pelvic floor. **(Grade of recommendation: D New)**

A weight loss programme in overweight women with UI could be considered for improved prolapse symptoms and severity. **(Grade of recommendation: C New)**

1.2. Treatment

1.2.1. Educational / lifestyle interventions (alone or in combination) with no treatment, usual care or no active treatment were identified

In this update, no new trials were identified.

Summary of the evidence from the previous edition

No trials identified

Summary of the evidence identified in this update

No trials were identified highlighting a gap in evidence.

Recommendations

None

1.2.2. Educational / lifestyle intervention (alone or in combination) with another active treatment (or combination)

Two trials of lifestyle and educational interventions (either on their own or in combination) were identified (221, 225). Salient features of each trial are described in Table 37. ROB is summarised in Appendix 2.

Quality of data

The RECOUP trial conducted by Mueller *et al.* (2017) (225) compared the effects of two different prescribed postoperative activity recommendations after reconstructive prolapse surgery. Women undergoing reconstructive pelvic surgery for prolapse (stage II or greater) were randomised to receive recommendations that were either 'liberal' (i.e., no restrictions on lifting or high-impact activities) or restricted (i.e., instructions recommending limited activity). Recommendations for each group were given verbally, detailing their assigned postoperative activity recommendations. Women in the liberal activity group were told to resume activity postoperatively "at their own pace with no restrictions on lifting or high-impact activity (including running, aerobics, sit-ups, and other high-impact activities). Those assigned to restricted activity recommendations were told to abstain from heavy lifting or high-impact activities for 3 months". Women in both groups were given the same recommendations for other activities like walking and stairs and sexual intercourse. Each group also received identical written postoperative instructions except for the activity recommendation section before surgery by a clinic nurse or advance practice nurse. The primary outcome was patient satisfaction. Secondary outcomes included POP-Q measurements, PFDI-20 and PFIQ-7 questionnaires for pelvic floor symptoms, including their prolapse subscale, and QOL. Data were collected pre-operatively, and at two weeks, six weeks and three months after surgery.

In a similar study, Arunachalam (2020) (221) conducted an RCT comparing the impact of postoperative activity instructions on disease specific symptom bother and impact on quality of life. Women were randomised to receive either liberal or restricted instructions following pelvic reconstructive surgery. Details of the instructions were not described. Women were asked to complete PFDI-20 and PFIQ-7 questionnaires, including the prolapse subscales. Questionnaire data were collected at six weeks post-surgery.

Results

The RECOUP study (225) randomised and allocated 108 women to the trial interventions, of which 95 (n=45 liberal, n=50 restricted) completed the primary outcome. Eight women dropped out of the liberal intervention: six did not receive the allocated intervention and two were lost to follow-up. Five women dropped out of the restricted group. Satisfaction with the result of the surgery was equally high in both groups three months after surgery. Women in the liberal postoperative instruction group had statistically significantly fewer prolapse symptoms using the prolapse subscale score of the PFDI-20 compared with women in the restricted group. There was no significant difference between the groups on the PFIQ-7 or its prolapse subscale, or the POP-Q except for point Bp measurements which was statistically significantly better in the liberal group.

Arunachalam (2020) (221) recruited 157 women, of which 146 women completed the study: 72 women in the liberal group and 74 in the restricted group. There was a significant difference between the two groups in prolapse symptom score in favour of the liberal group as measured by the POPDI-6, but no significant difference in quality of life as measured by the PFIQ-7.

Summary of the evidence identified in this update

Two new trials were included in this comparison. Both studies compared the effectiveness of post discharge instructions (restricted activities compared to liberal activities) in women, after prolapse surgery. The findings from the two studies agree that liberal post-operative activity recommendations lead to fewer prolapse symptoms. **(Level of evidence:2)**

Recommendations

Liberal post-operative instructions could be recommended rather than restricted activities for reducing post-operative prolapse symptoms. **(Grade of recommendation: C New)**

Table 37. Characteristics of included studies for educational / lifestyle intervention

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes and key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Arunachalam (2020) (221)	RCT Liberal post-operative activity recommendations vs restricted post-operative recommendations	146	Women scheduled for prolapse surgery USA	Liberal or restricted instructions following pelvic reconstructive surgery. No other details about the intervention are provided.	Outcomes: Activities Assessment Scale, accelerometer readings, PFDI-20 and PFDI-7 Key findings: no significant difference between the liberal or restricted groups on physical activity between the groups, but women in the liberal instruction group reported significantly less symptom distress on POPDI-6 compared with women in the restricted group at 6 weeks follow-up.	PA measures were collected at baseline, 2 weeks and 6 weeks FU surgery. Questionnaires data collected 6 weeks post-surgery	Publication: FT Dropouts: NR AE: not described
Berzuk (2015) (i) (40)	3-arm RCT Three randomised paired comparisons	109	Women working in a large corporation who volunteered (no incentive) for a women's health research study Canada	Enhanced education: 60-minute educational presentation on PFH and PFM function including instruction in home PFM strengthening program + 60-minute presentation 2 months later to review previous information Standard education: 60-minute educational presentation on PFH and PFM function including instruction in home PFM strengthening program CG: no treatment	Outcomes: primary outcome was Pelvic Floor Knowledge measured using Prolapse and Incontinence Knowledge Quiz, 24 true or false statements, score 0 to 24 converted to %, higher score indicates better knowledge. Secondary outcomes: Pelvic floor symptoms and QoL measured using the PFDI-20 and PFIQ-7 Key findings: participants in the two groups receiving education showed significantly better knowledge ($p<0.001$), PFD symptoms ($p<0.001$), and QoL ($p<0.05$), compared with those in the control group.	T1 (baseline), time 2 (24 hours after the first presentation), T3 (following the second presentation to group A – 2 months after the first presentation	Publication: FT Dropouts: accounted for. 10/161 withdrew post-randomisation; data from a further 6 women was excluded because they didn't attend a presentation or fully complete a survey. AE: none (personal communication)
Gozukara (2014) (218)	RCT Behaviour weight loss program + Structured education program vs Structured education program	378	Overweight/ obese women (i.e., BMI> 25 kg/m2) who also had >5 or more episodes of any UI in a-3-day voiding diary Turkey	Behaviour weight loss program – calorie and fat restricted diet plus behavioural modification techniques delivered over 6 months. All women were provided 4x 1-hour group education sessions in the preceding month prior to randomisation. Each session included about 20 women, and they consisted of information about the beneficial effects of weight loss, physical activity, and healthy eating on urinary complaints provided by an internist, dietitian, and urogynecologists.	Outcomes: POP-Q, PFDI-20 (Turkish version), number of UI episodes Key findings: women in the weight loss group had a significantly higher weight loss compared to the control group ($p<0.001$), and a reduction in SUI. POPDI-6 and total PFDI scores were significantly reduced in the weight loss group compared with the control group. There was little difference between groups on POP-Q measurements with women in the weight loss group only showing significantly lower measurements on the genital hiatus, perineal body and Ap measurements.	Data were collected at baseline and at 6 months (i.e., immediately post-intervention)	Publication: FT Dropouts: 26/189 women in the weight loss group and 31/189 in the structured education group declined to continue or were lost to follow-up. No reasons were given for why women declined AE: none described in the paper

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes and key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Hyakutake (2018) (35)	RCT PREPARED trial Pelvic floor health workshop delivered during pregnancy vs usual care	100	Primiparous women aged 20 years +, with a singleton pregnancy, with maternity providers including obstetricians, mid- wives, and family physicians Canada	IG: Two-hour workshop on pelvic floor health, and given a workbook with diagrams, tables, and resources. CG: received routine prenatal care	Outcomes: primary outcome was pelvic floor health knowledge questionnaire at 6 weeks PP. Secondary outcomes included PFME specific knowledge and practice of PFMEs, PFDI-20, POPDI-6, CRADI-8, UDI-6, PFIQ-7, CRAIQ-7, UIQ-7 mode of delivery and satisfaction with the delivery 6 weeks PP. Key findings: women in the pelvic floor health workshop group had significantly more pelvic floor knowledge (p=0.02), performed daily PFMT more frequently (p=0.002) and were significantly more confident in performing PFMT (p=0.004) and had fewer bowel symptoms (p=0.046) than women in the control group. No significant differences in prolapse symptoms between groups.	Questionnaires were completed at recruitment and 6 weeks PP	Publication: FT Dropouts: 40/50 received the intervention; 5 were lost to follow-up, 3 developed pregnancy related complication and 2 women withdrew for personal reasons; only 37 women returned their questionnaires Drop-out details not reported for the control group; only 37 women in this group returned their questionnaires. AE: none described in the paper
Mueller (2017) (225)	RCT Liberal post-operative activity recommendations vs restricted post-operative recommendations	108	Women undergoing reconstructive pelvic surgery for stage II or greater prolapse USA	Women in the liberal group were told to resume postoperative activity at their own pace with no restrictions on lifting or high-impact activity (including running, aerobics, sit-ups, and other high-impact activities). Women in the restricted group were told to abstain from heavy lifting or high-impact activities for 3 months. Each group received identical written postoperative instructions with the exception of the activity recommendation section before surgery. Women then underwent planned surgery. On discharge from the hospital, women were provided with a duplicate of the appropriate postoperative instructions, again detailing their assigned postoperative activity recommendations.	Outcomes: primary outcomes included patient satisfaction after surgery based on women's responses How satisfied are you with the result of your prolapse surgery? Secondary outcomes: POP-Q, PFDI, PFIQ, health-related quality of life as assessed by the Patient-Reported Outcomes Measurement Information System profile, Activity Assessment Scale, women to quantify their high-impact activity by asking the following question: During the past month, on average, on how many days in each week did you do strenuous or very hard exercise; that is, exercise that caused you to work up a sweat and made your heartbeat fast. For example, high- impact activities such as aerobics, dancing, jogging, or tennis. Women also provided an answer of minutes per day spent performing these activities. Key findings: At 3 months, satisfaction with surgery was equally high in both groups. Women in the liberal postdischarge instruction group had significantly fewer prolapse symptoms using the prolapse subscale score (PFDI-20) compared with women in the restricted group (p=0.13). There was no significant difference between the groups on POP-Q stage except for point Bp measurements which was significantly improved in the liberal group.	Routine clinical postoperative appointments were conducted at 2 weeks, 6 weeks, and 3 months after surgery.	Publication: FT Dropouts: Restricted intervention: 5 women did not receive the intervention (dropped-out); none lost to FU. Liberal group: 5 not eligible, 1 dropped out; 2 lost to FU. AE: not described

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes and key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Takacs (2020) (223, 255)	RCT Oral dietary supplement + routine prenatal vitamin vs routine prenatal vitamin	66	PP women who had no complications during the course of their pregnancy with a normal first-time birth with vaginal delivery Hungary	IG: Supplement was a multi-vitamin composition aimed to promote healing of muscular injuries following delivery (prenatal vitamin, 4g leucine, 30 mg zinc, 900mg omega-3 fatty acids) once a day for six weeks CG: prenatal vitamin	Outcomes: primary outcomes included vaginal squeeze pressure and levator muscle injury. Secondary outcomes included POPDI-6, UDI-6, zinc serum samples and POP-Q. Key findings: significantly fewer women reported bothersome bulge in the supplement group at 6 weeks pp (p=0.02), but there were no differences between groups on POP-Q measurements.	Questionnaire data were collected at baseline (immediately following delivery) and 6 weeks post-delivery. Serum samples and POP-Q were collected at 6 weeks PP	Publication: AB, FT Dropouts: 5/32 women in the IG did not complete the trial; 2 were lost to FU and 3 withdrew because of minor AE. 8/34 dropped out from the CG; four were lost to FU, two withdrew consent before starting, one developed a minor AE, and one woman refused the clinical examination at the six-week FU. AE: minor AE reported in both groups including a rash (one case from each group), inability to swallow the tablets in one woman (IG) and one woman thought her infant's vomiting was related to the supplement in the IG
Tuuli (2020) (224)	RCT Immediate pushing vs delayed pushing during second stage of labour	941	Nulliparous women at term USA	At complete cervical dilation with neuraxial analgesia) women were asked to either immediate pushing or asked to delay pushing for an hour	Outcomes: rate and extent of prolapse using POP-Q, and PFDI-20, PFIQ-7 and Fecal Incontinence Severity Index questionnaires Key findings: no significant differences between groups on PFDI-20 total scores at 6 weeks (p=0.18) or 6 months (0.09) or PFIQ-7 total scores at 6 weeks (p = 0.27) or at 6 months (p=0.30)	Data were collected at baseline (questionnaires only) and at six weeks and six months PP	Publication: AB Dropouts: 6-week FU, 38/452 women from the immediate group; and 40/489 women from the delayed pushing group had dropped out; at six months a further 27 women had dropped out of the immediate group and 37 women from the delayed pushing group. Reasons for dropouts are NR AE: not described

Abbreviations: AB: abstract; AE: adverse events; CARP: commercially available ring pessary; CG: control group; CRADI-8: Colorectal-Anal Distress Inventory; CRAIQ-7: Colorectal-Anal Impact Questionnaire; EMLA: (eutectic mixture of lidocaine 2.5% and prilocaine 2.5 %); FI: faecal incontinence; FT: full-text; FU: follow-up; IG: intervention group; IIQ-7: Incontinence Impact Questionnaire; ND: new vaginal device; NR: not reported; PA: physical activity; PFD: pelvic floor disease; PFDI-20: Pelvic Floor Distress Inventory; PFH: pelvic floor health; PFIQ-7: Pelvic Floor Impact Questionnaire; PFM: pelvic floor muscle; PFMT: pelvic floor muscle therapy; PGI-I: Patient Global Impression of Improvement-Incontinence; PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire; POP: pelvic organ prolapse; POPDI-6: Pelvic Organ Prolapse Distress Inventory; POPIQ-7: Pelvic Organ Prolapse Impact Questionnaire; PP: postpartum; PRC: Peoples Republic of China; PUS: perineal ultrasound; QoL: quality of life; RCT: Randomised controlled trial; SA: Staphylococcus aureus; UDI-6: Urinary Distress Inventory; UI: urinary incontinence; UTI: urinary infection; VAS: visual analogue scale

2. PHYSICAL INTERVENTIONS

The PFMs play a critical role in giving structural support to the pelvic organs and pelvic openings. It is hypothesised that improving PFM function may improve this structural support. Physical interventions predominantly include PFMT. A programme of supervised PFMT includes assessment of the woman's PFMs and her ability to contract these muscles; education about the PFMs and how they support the pelvic organs; instruction in how to correctly perform PFM exercises and "the Knack". An individualised exercise programme is prescribed for the woman to follow. Adjuncts to PFMT (such as biofeedback) or other physical therapies (such as neuromuscular EStim) may be used. Other interventions, which are hypothesised to work indirectly on the PFM, also fit under the heading of physical interventions. Examples of these interventions are transversus abdominis muscle contraction and hypopressive exercises.

2.1. Prevention

2.1.1. Physical intervention (alone or in combination) vs no treatment/ usual care/ no active treatment

In this update, six studies (10 randomised comparisons) of physical interventions were identified (30, 217, 219, 220, 227, 256). Key features of each trial are described in Table 38. ROB is summarised in Appendix 2.

Quality of data

Fritel and colleagues (227) conducted a RCT to examine the postnatal effect of prenatal supervised PFMT with written instructions in nulliparous pregnant women. Women between 20 and 28 weeks of gestation were randomised into two groups. The prenatal PFMT group received individual supervised exercises conducted during the 6th and 8th month of pregnancy. Women were seen individually by a specialist physiotherapist once a week for 8 weeks. Each 20 to 30-minute session consisted of standing contractions (5 minutes), lying contractions (10 minutes) and learning how to start a pelvic floor contraction just before exerting intra-abdominal pressure (the 'knack'). Women also had their PFM contractions assessed through a vaginal examination in each session. Women were encouraged to perform the PFMT daily but were given no specific instructions about the number or intensity of each. The control group received written information about the anatomy of the pelvic floor and pelvic floor contraction exercises. Both groups received written instructions about how to perform exercises at home. Women were assessed at baseline, end of pregnancy, and 2 and 12 months postpartum. The primary outcome measured was the severity of UI assessed using the ICIQUI-short form questionnaire (validated in French). Other outcomes included the Female Pelvic Floor Questionnaire (with bladder, prolapse, bowel and sex subscales), a clinical examination with the POP-Q and a 24-hour pad test which were performed at baseline and at the 2-month postpartum visit.

Glazener (2014) (217) reported prolapse outcomes from the PROLONG study which aimed to improve postnatal urinary and faecal incontinence. Women (primiparous and multiparous) were randomly allocated to receive either a nurse-led intervention (after delivery) comprised of PFMT and BT or standard care in this large multicentre trial. PFMT was delivered by specially trained nurses and involved three individual, face-to-face instruction (with BT if indicated) at 5, 7 and 9 months after the birth. Data were collected at trial entry, and at 1 and 6 years (257, 258). In 2014, Glazener and colleagues presented the data from the 12-year follow-up, which included data about women's prolapse symptoms (using the POP-SS) for the first time.

Kou and colleagues (2013) (220) conducted a RCT evaluating the effectiveness of postpartum pelvic floor rehabilitation in women 6 weeks after giving birth. The study was published in Chinese and a translation was available. Women aged between 25-35 years were randomly divided into two groups: the intervention group received PFMT and EStim, and women in the control group received standard postnatal care. The intervention involved PFMT consisting of 150-200 contractions of 3-s, performed 2-3 times per day. Each session lasted 20-30 minutes and used the Phenix EStim device, twice a week. The authors measured POP-Q at 6 weeks and 12 months postpartum.

Liu and colleagues (219) conducted a single centre RCT that compared PFMT during pregnancy with standard care in low risk primigravida women. The study was published in Chinese and a translation was available. Women were recruited during their first pregnancy visit (16-30 weeks' gestation) and were randomly allocated to receive either PFMT or usual care (standard educational information). Pelvic floor physiotherapists supervised the PFMT. Women were asked to repeat a contraction of 5 to 10 seconds, follow by 5 to 10 seconds rest, then fast contractions 10-15 times. They were encouraged to perform this sequence for 15-20 minutes, 2-3 times daily and continued for 8 weeks. POP-Q was measured at 6 weeks after delivery.

In the Yang 2017 (30) 3-arm single-centre RCT, primiparous women aged between 20-35 years and with an episiotomy or second-degree tear were randomly assigned to one of three groups:

- a *'training group'* that received PFMT and other pelvic exercises from two days postpartum until three months postpartum. Two specialists provided the 20-minute training session, which consisted of teaching a programme of five second contractions followed by five seconds of relaxation. The vaginal palpation method was employed to ensure that women performed the exercises correctly. Women were also instructed to complete other pelvic movement exercises (swinging bent legs from left to right; pulling a bent knee towards the chest followed by gentle swaying). When the women were judged to have correctly mastered the exercises, they were then allowed to complete them at home and encouraged to complete them 2-3 times per day.
- a *'combination group'* who received the same rehabilitation exercises as the training group, plus 15 sessions of transvaginal EStim at low voltage, low frequency, beginning at week 6 postpartum. EStim sessions were delivered 3 times a week and lasted 30 minutes. Two specialist trained staff members delivered the stimulation using the PHENIX Neuromuscular Stimulation Therapy System. Current frequency was 60–80 Hz. The ratio of the EStim duration (contraction) and interval time (relaxation) was individualised and adjusted depending on the woman's response.
- A '*control group'* who were given routine postpartum guidance (two hours postpartum) delivered by two specially trained staff members. Guidance included information on appropriate physical and sport activity to promote postpartum recovery, dietary advice (e.g., eating more vegetables and fruits) to avoid constipation, general advice to avoid forceful coughing and lifting heavy objects, and advice on breastfeeding.

Data were collected during the third month after delivery. Outcomes that were measured included prolapse severity using POP-Q.

Zhang and colleagues (256) conducted a 4-arm RCT that randomised primiparous women 6 weeks after a vaginal delivery into one of the following:

- Control group (standard care)
- PFM exercise group
- Weighted vaginal cones ('vaginal dumbbell group')
- Biofeedback combined with electrostimulation (subdivided into two groups: individual vs traditional)

Details about each of the interventions were limited as no full text paper is currently available. Data were collected at baseline (6 weeks postpartum), 3 months postpartum and 9 months postpartum (i.e., 6 months' post-intervention). Outcomes measured at these timepoints included severity of prolapse using the POP-Q and PISQ-12.

Results

Of the 282 women recruited in the multicentre RCT conducted by Fritel and colleagues (227), 140 nulliparous pregnant women were randomised to the physiotherapy group and 142 to the control group. By the end of the pregnancy, 224 women had completed the study; at 2 months post-partum 212 women were still enrolled in the study and by 12 months post-partum 190 women completed the study. The authors reported no difference in prolapse or pelvic floor symptoms at baseline, end of pregnancy, and at 2 and 12 months postpartum between the groups.

Glazener and colleagues (2014) originally randomised 747 women, of which 371 were allocated to the PFMT group and 376 to the standard care arm. At the 12-year follow-up, 230 women in the PFMT arm responded and 241 women in the standard care group responded. One hundred and forty-one women dropped out of the PFMT group and 145 women dropped out of the standard care group. The prevalence or severity of prolapse symptoms or number of women having surgery for prolapse did not differ between groups at the 12-year follow-up. The researchers objectively measured POP-Q in a subsample of women (35%) at 12 years (76 women in PFMT group and 89 women in standard care) and found no evidence of a difference in prolapse severity between the groups.

One hundred and fifty women were randomised in the Kou (2013) study (220); of these, 80 women received the intervention and 70 were enrolled in the control arm. No dropouts were reported. The incidence of stage I POP was significantly lower in the intervention group at 12 months postpartum compared with women in the control group.

Liu 2013 (219) randomised 360 pregnant women (180 women in each group) but data were only reported for 329 women as 31 women (14 PFMT group; 17 control) were lost to follow-up six weeks after delivery: the reasons were not provided. Significantly more women in the treatment group exhibited stage 0 prolapse and significantly fewer had stage II prolapse at 6 weeks post-partum compared with women in the control group; however, there were no differences between groups in the percentage who had stage I prolapse.

In this section we also consider the findings from two randomised paired comparisons comparing the effectiveness of a physical intervention with standard care:

- Yang 2017 (i) training group vs control group,
- Yang 2017 (iii) combination group vs control group.

The findings from the third randomised comparison (i.e., combination group vs training group) is considered later in section III.2.1.2.

Of the 240 women randomised across the three study arms, a total of 189 women were seen for follow-up measurements at 3 months after delivery. Seventeen women from the training group; 14 women from combination group and 20 women from the control group withdrew from trial or were lost to follow-up. Women in the training and combination group were significantly more likely to have had an improvement in the stage of prolapse, compared to women who received standard postpartum care (30).

Our review also identified three relevant randomised paired comparisons (Zhang (i, iv and vi) (256) that compared the effectiveness of:

- Zhang 2016 (i) PFM exercises vs control group
- Zhang 2016 (iv) weighted vaginal cones vs control group
- Zhang 2016 (vi) biofeedback plus EStim (subdivided into two groups: individual vs traditional) vs control group.

The results from three other randomised comparisons from this study (256) are presented later in section III.2.1.2. In this trial 2700 women were enrolled; 675 women were randomly allocated to each of the four study arms and 2403 women were evaluated after 6 weeks treatment. Reasons for dropouts were not fully reported but recorded as "lost to follow-up" (69 in control group, 74 in PFM exercise group, 81 in vaginal cones group and 73 in the biofeedback plus EStim group). Data reported in the abstract are limited and authors concluded that "biofeedback combined with EStim has advantages over the PFM exercises", but no statistical data were available to compare data across groups, and we anticipate that the results from this large-scale multicentre trial will be available in the next update.

Summary of the evidence from the previous edition

PFMT is shown to prevent symptoms of prolapse which develop in the longer term after childbirth, but not immediately after childbirth. **(Level of evidence: 1)**

Summary of the evidence identified in this update

Conflicting evidence from two large trials of ante-natal PFMT with high ROB reported less severe prolapse stage at 6 weeks' postpartum (219) and no difference in prolapse stage or symptoms in the postpartum period up to 12 months compared to control (227).

Evidence from two large uncertain to high ROB trials of postpartum PFMT +/- EStim (30, 220) reported a difference in prolapse stage between groups in favour of the intervention. **(Level of evidence: 2)**

Recommendations

Antenatal PFMT cannot be routinely offered for prevention of postnatal prolapse**. (Grade of Recommendation: B)**

Postnatal EStim in addition to PFMT could be recommended as beneficial in preventing prolapse in women in the post-partum period. (**Grade of recommendation: C New)**

2.1.2. Physical intervention (alone or in combination) vs an active treatment (or combination)

In this update, seven studies (9 randomised paired comparisons) of physical interventions were identified (30, 91, 226, 228-230, 256). Key features of each trial are described in Table 38. ROB is summarised in Appendix 2.

Quality of data

Artymuk and colleagues (226) conducted a RCT comparing PFMT using two different devices. Women who had delivered a baby in the preceding 12 months were randomly allocated to either PFMT using the EmbaGYN pelvic floor training device or to perform assisted PFMT using Magic Kegel Master pelvic floor training device. Women in both groups were asked to use the "postpartum" exercise setting. Women were asked to perform PFMT for 20 minutes per day over 4 weeks. The researchers contacted the women in both groups to offer support and encouragement. Questionnaires (PFDI-20 and FSFI) were administered at baseline and immediately post-intervention.

Bergman and colleagues (2020) (91) conducted a RCT that compared PFMT with perineorrhaphy in women with a poorly healed (more than 6 months postpartum) second-degree perineal tear. Women were randomly allocated to receive either PFMT or surgical treatment. Women in the PFMT group were initially referred to a physiotherapist for an assessment of their PFM strength. Women were educated about their PFMs and taught how to perform a PFM contraction. Biofeedback or EStim was used, if needed, to help women correctly perform PFM exercises. They were given a home-based exercise programme which involved women gradually building up 10 maximal contractions, (5 seconds long), three times per day and one maximal contraction of 30–60 seconds. Women were then scheduled for 1–3 follow-up visits. Women in the surgical group were scheduled for perineorrhaphy with distal posterior colporrhaphy which was standardised prior to the commencement of the trial. Surgeries were performed in the outpatient surgical ward by one of five urogynecologists. Primary outcome was treatment success, defined by PGI-I. Secondary outcomes included the PFDI-20 and PFIQ-7 (and their prolapse subscales), the Pelvic Organ Prolapse/UI Sexual Questionnaire, POP-Q and HADS. Data were collected at baseline and at 6 months.

Huan (2020) (228) recently conducted a RCT comparing PFMT plus EStim, biofeedback compared with PFMT. Postpartum women (4-6 weeks postpartum) with no pregnancy complications were randomly assigned to receive either individualised, tailored PFMT plus EStim, biofeedback or PFMT alone. Women in the PFMT alone intervention received group education about the symptoms and causes of pelvic floor disorders and PFMT training methods. Women were then taught to do PFM exercises at home. Exercises were performed in the horizontal position and involved contracting PFMs for 5-seconds and relaxing for 5-seconds with three rapid contractions at the end of the session. Each session lasted approximately 15 minutes. Women were asked to perform the exercises twice a day, and gradually increase the frequency and intensity over 6 months. After discharge, women were phoned every two weeks for the first three months, and then every four weeks in the last three months of the intervention. Women in the PFMT plus EStim biofeedback group received tailored PFMT training combined with EStim biofeedback therapy. A total of 10 biofeedback therapy sessions were delivered: three times per week with each session lasting 20 mins. Four weeks later the individualised PFMT training was delivered as described for the PFMT alone group. Women were phoned every two weeks for the first three months, and then every four weeks in the last three months of the intervention. Outcomes included PFDI-20 and PFIQ-7 (prolapse subscales not reported), PISQ-12 and POP-Q. Data were collected at baseline and at six months.

Juninger (2018) (229) conducted an RCT comparing a bladder neck effective PFM rehabilitation programme with PFMT with EMG-biofeedback in women with SUI. The authors argued that PFMT programmes can vary in approach and that comparison was necessary to determine the effectiveness of one approach against another. Women with SUI who were able to perform a PFM contraction were randomised to either the bladder neck effective PFM rehabilitation programme or EMG-biofeedback augmented PFMT. Women in the bladder neck effective PFM rehabilitation programme were given perineal ultrasound for visual biofeedback for teaching and practicing bladder neck support and elevation as well as PFM precontraction daily for three months. Women in the EMG-biofeedback augmented PFMT group were given an EMG-biofeedback device with a vaginal probe for performing daily home exercises for three months. A specialist physiotherapist checked the performance of women in both groups three times. Women were then offered to switch groups after three months according to their preference. The primary outcome measure was subjective improvement-cure rate after 3 months. Secondary outcomes included changes in a validated German pelvic floor questionnaire (Bladder, Bowel, Prolapse and Sex subscales). Data were collected at baseline and immediately post-intervention.

Sun and colleagues (2015) (230) conducted a RCT to examine whether PFMT could prevent or improve women's pelvic floor function postpartum. Although the trial was published in Chinese, a translation was available. Women who had given birth to a single child at term were randomised to receive EStim plus PFMT with biofeedback (intervention) or PFMT at home (control). Women in the intervention group started the intervention at 6 weeks postpartum. EStim was tailored but commenced at a frequency of 8 -33 Hz (pulse width 320-740 microns) in the first two weeks and increased in weeks 3 – 4 to 20-80 Hz (pulse width 20-320 microns). Women were seen twice a week for four weeks, and each session lasted approximately 20 minutes. Outcome measures included prolapse severity using POP-Q, PFIQ-7 and PISQ-12. Data were collected at 6 weeks, 6 months and 12 months postpartum.

Our review identified also one randomised paired comparison Yang 2017 (ii) (30) (Table 38) that compared the effectiveness of combination training with training alone in primiparous women. Details of this trial, dropouts and methodological quality are described earlier in section III.2.1.1 (see Yang (i/iii) (30), Table 38).

Our review also identified three relevant randomised paired comparisons (Zhang (ii, iii and v) (256) that compared the effectiveness of:

- Zhang 2016 (ii) PFM exercises vs weighted vaginal cones
- Zhang 2016 (iii) PFM exercises vs biofeedback plus EStim (subdivided into two groups: individual vs traditional)
- Zhang 2016 (v) weighted vaginal cones vs biofeedback plus EStim (subdivided into two groups: individual vs traditional).

Details of this trial, dropouts and methodological quality are described earlier in section III. 2.1.1.

Results
Eighty women in the postpartum period were randomised in the Artymuk trial (226) (40 in each group). Of these, 34 women completed the study in the EmbaGYN group, and 36 women completed the study in Magic Kegel Master group. The reasons for drop-out were not clearly reported but the authors reported that these women were excluded from the analysis because of poor adherence. Immediately post-intervention, there were no significant differences between the groups for any of the outcomes.

Seventy women were randomised in the Bergman (2020) study (91); 35 women were allocated to each group. In the PFMT arm, 33 women received the intervention, one woman did not receive the allocated intervention and crossed over to the surgical arm and one woman was reported as not meeting the inclusion criteria as she had a history of grade 4 perineal tear. In the surgical arm, 30 women received the intervention; 4 did not receive the allocated intervention (three did not undergo surgery and one crossed over to the PFMT arm) and one woman did not adhere to the protocol as she had a concomitant mid-urethral sling. No woman was lost to follow-up in either arm. Surgical treatment had a significantly higher treatment success rate – defined as "much better" and "very much better" on the PGI-I questionnaire, and significantly greater improvement in all secondary endpoints at 6 months of follow-up.

Huan (2020) (228) randomised 124 women of which 62 were allocated to the PFMT +biofeedback and EStim and 62 received routine PFMT. No dropouts were reported. The POP-Q stage of women in the PFMT + biofeedback and EStim group was significantly better than women who received PFMT alone. There was no significant difference in PFDI-20, PFIQ-7 and PISQ-12 scores between the two groups.

Juninger (2018) (229) randomly allocated 83 women: 47 to the bladder neck effective PFM rehabilitation programme and 36 women to the PFMT with EMG-biofeedback arm. Nineteen women did not start treatment because of time constraints and illness, leaving 32 women allocated to each group. No further dropouts were reported. Data were difficult to interpret based on the results reported in the abstract and the prolapse symptom score was significantly different between groups at baseline. The prolapse score was presented as divided into two groups (so losing the randomisation) and we were unable to draw any conclusions.

Three hundred and twenty four women were randomised in the Sun and colleagues (2015) trial (230) (200 women in intervention group and 124 in control group). The POP-Q staging point Aa showed a statistically significantly greater improvement in the treatment group compared with the control group; no other difference was seen for any of the other POP-Q points. There was no statistically significant difference between groups on the QoL questionnaire or sexual life questionnaire.

Yang 2017 (ii) (30) (Table 38) compared the effectiveness of combination training with training alone in primiparous women. Details of this trial, dropouts and methodological quality are described earlier in section III.2.1.1. (see Yang (i/iii) (30), Table 38). Women in the combination group had significantly better stage of prolapse, compared to women who received rehabilitation exercises alone. However, based on the limited statistical data, this does not appear to be statistically significantly different between the groups.

Data reported in the Zhang 2016 (ii, iii and v) abstract (256) are limited with no statistical data available to compare data across groups, and we anticipate that the results from this large-scale multicentre trial will be available in the next update.

Summary of the evidence from the previous edition

No trials identified.

Summary of the evidence identified in this update

Seven trials (9 comparisons) were included in this update, however for three trials (5 comparisons) no conclusions could be drawn (30, 229, 256). The remaining four trials (91, 226, 228, 230) were conducted in postnatal women. One of these was a small, high ROB study which showed no difference between two different types of PFMT device (226). Another small, moderate ROB showed that surgery was better than PFMT at six months follow-up for treatment of post-natal tears (91)idence. One moderate size study with an uncertain ROB found no difference in symptoms between PFMT + EStim and PFMT alone but POP-Q was better with combined (PFMT + stimulation) treatment (228). One large study with a moderate ROB showed that POP-Q was better at 12 months post-partum in the EStim and PFMT + biofeedback group compared to PFMT alone (230). **(Level of evidence: 2)**

Recommendations

A combination of EStim plus PFMT, or EStim plus PFMT and biofeedback given preventatively postpartum could be recommended as this combination is shown to improve the stage of prolapse compared with PFMT alone. (**Grade of recommendation: C New)**

2.1.3. A physical intervention combined with a non-conservative adjunct vs no treatment/ usual care/ no active treatment

In this update, no new trials were identified.

Summary of the evidence from the previous edition

No trials identified.

Summary of the evidence identified in this update

No trials were identified highlighting a gap in evidence.

Recommendations

None.

2.1.4. A physical intervention combined with a non-conservative adjunct vs an active treatment (or combination)

In this update, no new trials were identified.

Summary of the evidence from the previous edition

No trials identified.

Summary of the evidence identified in this update

No trials were identified highlighting a gap in evidence.

Recommendations

None.

Table 38. Summary of key characteristics of prevention studies of women with POP and physical interventions

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Artymuk (2020) (226)	RCT Device assisted PFMT trainer vs device assisted PFMT trainer	70	Women in post-partum period Russia	Women in both groups asked to perform assisted PFMT exercises for 20 mins/day over 4 weeks. Group 1 used the EmbaGYN and Group 2 used the Magic Kegel Master device.	Outcomes: PFDI-20, FSFI, PFM strength measured Key findings: No significant differences between groups for on any outcomes.	Baseline and at 4 weeks (immediately post-intervention)	Publication: FT Dropouts: 10 women were excluded from the analysis due to non-adherence to the exercise program (p2) AE: Not described in the paper.
Bergman (2020) (91)	RCT PFMT vs surgical treatment (perineorrhaphy)	70	Women with a poorly healed (more than 6 months postpartum) second-degree perineal tear Sweden	PFMT assessment provided with education about PFM and biofeedback and/or electrstimulation if needed. Home-based exercise program involved gradual build-up to 10 maximal contractions, (5 seconds long), three times per day and one maximal contraction of 30–60 seconds. Women in surgical treatment group received perineorrhaphy with distal posterior colporrhaphy.	Outcomes: primary outcome treatment success, defined by PGI-I. Secondary outcomes included the PFDI-20, PFIQ-7, the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire with three additional unvalidated questions for vaginal symptoms, POP-Q and HADS Key findings: Surgical treatment had a significantly higher treatment success rate – defined as much better and very much better on the PGI-I questionnaire, and significantly greater improvement in all secondary endpoints at 6 months of follow-up	Baseline and at 6 months	Publication: FT Dropouts: 2/35 women in PFMT did not receive the intervention; 5/35 women in the surgical arm did not receive the intervention and one woman did not adhere to the protocol AE: Not described

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Fritel (2015) (227)	RCT Prepartum PFMT vs written PFMT instructions	282	Nulliparous pregnant women randomised in 2nd trimester France	Women in the physiotherapy group were given 8 sessions of individually supervised exercises delivered by a trained physiotherapist or midwife Both groups of women were given written PFMT instructions	Outcomes: primary outcome was ICI-UI short form questionnaire (validated in French). Secondary outcomes included clinical examination with the POP-Q, clinical assessment of PFM strength and a 24-hour pad test were performed at baseline and at the 2-month postpartum visit. Key findings: no difference in UI severity, prevalence, or pelvic floor symptoms at baseline, end of pregnancy, and at 2 and 12 months postpartum between the groups.	Baseline, end of pregnancy, and 2 and 12 months postpartum.	Publication: FT Dropouts: 93/140 women in the physiotherapy group and 97/142 had a primary outcome available at 12 months. AE: None related to the treatment were reported in the PFMT group.
Glazener (2014) (217)	RCT (PROLONG study) PFMT and bladder training vs standard care	471 (original RCT randomised 747)	Women in post-partum period	Specially trained nurses. Individual PFMT instruction (with bladder training if indicated) at 5, 7 and 9 months after the birth Standard care	Outcomes: primary outcome was the incidence of UI, secondary outcomes FI and POP-SS Key findings: prevalence or severity of prolapse symptoms or number of women having surgery for prolapse did not differ between groups at 12-year follow-up	Baseline, year 1, year 6 and 12 years (collected POP-SS data for first time)	Publication: FT Dropouts: 141 dropped out of the PFMT group (1 died, 31 moved and 109 did not respond) and 145 women dropped out of the standard care group (1 died, 42 moved and 92 did not respond). AE: none related to PFMT reported

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Huan (2020) (228)	RCT PFMT plus electrical stimulation biofeedback vs PFMT	124	Women in post-partum period PRC	PFMT alone: group education about PFD and PFMT, taught PFM exercises at home (individual) comprised of contracting PFM for 5-seconds and relaxing for 5-seconds with three rapid contractions at the end of the session, 2 sessions / day (each session lasted approx. 15 mins) gradually increasing in frequency and intensity. Intervention delivered over 6 months. PFMT plus electrical stimulation biofeedback: received tailored PFMT training (as described above) combined with electrical stimulation biofeedback therapy (10 biofeedback therapy sessions were delivered: three times per week with each session lasting 20 mins). Four weeks later the individualised PFMT training was delivered as described for the PFMT alone group.	Outcomes: PFM strength, A3 reflex, POP-Q, PFDI20, PFIQ-7 and PISQ-12. Key findings: POP-Q score of women in the PFMT and electrostimulation group significantly better than women who received PFMT alone. No significant difference in PFDI-20, PFIQ-7 and PISQ-12 scores between groups	Baseline and at six months	Publication: FT Dropouts: none AE: not described in the paper
Jung-inger (2018) (229)	RCT Bladder neck effective PFM rehabilitation program vs PFMT with EMG-biofeedback (BFB)	83	Women with SUI Germany	Bladder neck effective PFM rehabilitation program: perineal ultrasound for visual biofeedback for teaching and practicing BN-support and elevation as well as PFM precontraction daily for 3 months PFMT with EMG-biofeedback (BFB): given an EMG-BFB device with a vaginal probe for performing daily home exercises for three months. Specialist physiotherapist checked the performance of women in both groups three times	Outcomes: primary outcome measure was subjective improvement-cure rate after 3 months. Secondary outcomes included changes in a validated German pelvic floor questionnaire (Bladder, Bowel, Prolapse and Sex subscales) Key findings: Data is difficult to interpret based on the abstract and the prolapse symptom score was significantly different between groups at baseline. The prolapse score was presented as divided into two groups (so losing the randomisation) and we are unable to draw any conclusions	Baseline and immediately post-intervention	Publication: AB Dropouts: 19 women did not start treatment (time constraints and illness). No further dropouts reported. AE: Not described in the paper.

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Kou (2013) (220)	RCT PP pelvic floor rehabilitation device combined with PFMT vs standard PP rehabilitation education only	150	Women recruited at 6 weeks PP with POP stage I-III PRC	PFMT plus use of the Phenix device for electrostimation. PFMT regimen was 2-3 times / day for 20-30 mins for each session or 150-200 contractions (3 seconds for each contraction then relax). Women also received electrostimulation twice/ week. Control group: standard PP education only	Outcomes: Vaginal resting and vaginal squeezing pressure, Incontinence rate and POP-Q measured at 6 weeks PP and 12 months PP Key findings: PFM strength measures were significantly different between the two groups at 6 months. This difference between groups was sustained at 12 months. The incidence of stage I POP was also significantly lower in the intervention group at 12 months postpartum (21/80) compared with women in the control group (30/70). The number of women with stress UI was also significantly lower in the intervention arm at 6 months postpartum (2.5% vs 12.86%), and at 12 months postpartum (3.75% vs 14.29%).	Baseline (6 weeks PP), 6 months PP and 12 months PP	Publication: AB available in English. Original paper in Chinese; translation provided. Dropouts: no dropouts reported. AE: Not described in the paper.

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Liu (2013) (219)	RCT PFMT vs standard care	360	Women recruited 16-30 gestation week, first pregnancy PRC	IG: PFMT supervised by pelvic floor physiotherapists. PFMT regimen included repeat contraction of 5 to 10 seconds, follow by 5 to 10 seconds rest, then fast contractions for 10-15 times, perform the above sequence for 15-20 minutes, 2-3 times daily for 8 weeks. CG: standard care	Outcomes: measured pelvic muscle tension with Phenix equipment, on vaginal squeezing pressure, vaginal resting pressure and POP-Q for detecting pelvic prolapse conditions Key findings: PFM strength was significantly higher in the PFMT group compared with women in the control group at the end of the intervention. In addition, significantly more women in the treatment group reported either no prolapse or stage II prolapse compared with women in the control group; however, there were no differences between groups for those with stage I prolapse.	Baseline (first pregnancy visit), At labour (first, second and total stages of labour), PFM tension measures were measured at 8 weeks and POP-Q was measured at 6 weeks after the delivery	Publication: AB available in English. Original paper in Chinese; translation provided. Dropouts: 31 dropouts reported (IG:14, CG: 17; reasons for drop-out not provided) AE: Not described in the paper.
Sun (2015) (230)	RCT Electrostimulation plus biofeedback treatment vs PFMT exercises at home	324	Women who gave birth to a single child at term, first reviewed at day 42 PP PRC	IG: received electrical stimulation plus biofeedback. Stated at 6 weeks PP, two sessions (20 mins each) / week CG: performed PFMT exercises at home but no details were given	Outcomes: primary outcome tool was PFIQ-7. Secondary outcomes included PISQ-12, pelvic floor muscle strength (type I and II fibres), vaginal dynamic pressure, POP-Q Key findings: Significant improvement in muscle fibre strength in treatment group compared with the control group at 6 weeks PP which was sustained at 6 and 12 months postpartum. POP-Q staging point Aa showed a significant improvement in the treatment group compared with the control group; no other difference was seen for any of the other points. No significant difference between groups on the quality-of-life questionnaire or sexual life questionnaire.	Baseline: 6 weeks PP, 6months PP and 12 months PP	Publication: AB is available in English. Original paper in Chinese; translation provided. Dropouts: at 6 weeks (Total:6, I: 0, C: 6), 6 months (Total:17, I: 10, C: 7), 12 months (Total: 207, I: 128, C: 79) Reasons: 6 weeks (incomplete baseline information), 6 months (4 gravidity, 7 loss to follow up), 12 months most unclear (5 gravidity, 11 loss to follow up) AE: Not described in the paper.

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Yang (2017) (30)	3-arm RCT Individuals were randomised across three groups resulting in 3 randomised paired comparisons	240	Primiparous women aged between 20-35 years and with an episiotomy or second-degree episiotomy tear PRC	Training group: received PFM exercises and other pelvic exercises from two days PP until three months PP. Each session was 20-minutes which consisted of five second contractions followed by five seconds of relaxation, asked to perform 2-3 times per day. Combination group: received the same rehabilitation exercises as the training group, plus 15 sessions of direct vaginal low voltage, low frequency electrostimulation beginning at week 6 PP. Control group: routine PP guidance (two hours PP) delivered by two specially trained staff members.	Outcomes: POP-Q, degree of incontinence score, pad test, pubic symphysis clearance, and PFM electrophysiological measures Key findings: Limited statistical data available (see text)	Data were collected during the third month after delivery ne	Publication: FT Dropouts: 189/240 women were seen for follow-up measurements at 3 months after delivery. 17 women from the training group; 14 women from combination group and 20 women from the control group withdrew from trial or were lost to follow-up AE: none described
Zhang (2016) (231, 256)	4-arm RCT Individuals were randomised across four groups resulting in 6 randomised paired comparisons	2700	Primiparous women 6 weeks after a vaginal delivery PRC	PFM exercise group Weighted vaginal cones ('vaginal dumbbell group') Biofeedback combined with electrostimulation Control group (standard care)	Outcomes: POP-Q, PISQ-12 and measures of PFM strength. Key findings: Limited data available	Baseline (6 weeks PP), 3 months PP and 9 months PP (i.e., 6 months' post-intervention)	Publication: AB Dropouts: unclear Adverse events: not reported

Abbreviations: AB: abstract; AE: adverse events; CARP: commercially available ring pessary; CG: control group; CRADI-8: Colorectal-Anal Distress Inventory; CRAIQ-7: Colorectal-Anal Impact Questionnaire; EMLA: (eutectic mixture of lidocaine 2.5% and prilocaine 2.5 %); FI: faecal incontinence; FT: full-text; FU: follow-up; IG: intervention group; IIQ-7: Incontinence Impact Questionnaire; ND: new vaginal device; NR: not reported; PA: physical activity; PFD: pelvic floor disease; PFDI-20: Pelvic Floor Distress Inventory; PFH: pelvic floor health; PFIQ-7: Pelvic Floor Impact Questionnaire; PFM: pelvic floor muscle; PFMT: pelvic floor muscle training; PGI-I: Patient Global Impression of Improvement-Incontinence; PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire; POP: pelvic organ prolapse; POPDI-6: Pelvic Organ Prolapse Distress Inventory; POPIQ-7: Pelvic Organ Prolapse Impact Questionnaire; PP: postpartum; PRC: Peoples Republic of China; PUS: perineal ultrasound; QoL: quality of life; RCT: Randomised controlled trial; SA: Staphylococcus aureus; UDI-6: Urinary Distress Inventory; UI: urinary incontinence; UTI: urinary infection; VAS: visual analogue scale.

2.2. Treatment

2.2.1. A physical intervention vs no treatment, placebo control or sham

One trial comparing a physical intervention with standard care met the selection criteria for inclusion in this comparison (239). Key features of this study are shown in Table 39. ROB is summarised in Appendix 2.

Quality of data

Orhan and team (239) conducted a RCT comparing PFMT plus biofeedback with standard care. Women with prolapse were randomly allocated to receive either PFMT combined with biofeedback or standard care (details not reported). Women in both groups were given lifestyle advice. The intervention was delivered for 12 weeks. The primary outcome measure was self-reported perception of improvement. Secondary outcomes included severity of prolapse symptoms measured using the POP-SS and PFDI-20 questionnaires. Data were collected at baseline and immediately post-intervention at 12 weeks.

Results
In the Orhan (2017) trial (239), 22 women were randomised. Drop-outs were not reported in the abstract. At the study conclusion, there was a statistically significant difference between the groups for self-reported symptom questionnaires (PFDI-20 and POP-SS) favouring the intervention.

Summary of the evidence from the previous edition

Previous editions have reported evidence from 13 RCTs. These trials compared PFMT with a "minimal intervention control" arm (e.g., lifestyle advice, self-instruction manual or other type of exercise / general fitness). These studies provided evidence of the benefit of PFMT in reducing prolapse and pelvic floor symptoms in women. **(Level of evidence: 1)** There was some evidence that PFMT had an effect on prolapse stage and some that there was not.

Summary of the evidence identified in this update

One new study was included in this comparison.

A small size study (239) with an unclear ROB compared PFMT plus biofeedback with standard care and found significant improvement in prolapse symptoms and pelvic floor symptoms more broadly. **(Level of evidence: 2)**

No new studies were found for this comparison on the effect of PFMT on prolapse stage, therefore the evidence remains contradictory **(Level of evidence 2)**

Recommendations

PFMT can be offered to women with symptomatic prolapse as it is associated with a reduction in prolapse symptoms and pelvic floor symptoms. (**Grade of recommendation: A)** It is uncertain whether PFMT reduces prolapse stage (**Grade of recommendation: B)**

PFMT plus biofeedback may be recommended as this combination is shown to improve prolapse symptoms and pelvic floor symptoms compared with standard care**. (Grade of recommendation: C New)**

2.2.2. A physical intervention (alone or in combination) vs an active treatment (or combination)

In this update, five studies (seven randomised comparisons) were identified (73, 232, 234, 236, 240). Salient features of each trial are described in Table 39. ROB is summarised in Appendix 2. Two other studies are also judged as relevant to this comparison (see Cheung 2016 (244) and Panman 2016 (248). The quality of data and results from these studies are summarised in the section on pessaries (see III.3.2.2).

Quality of data
Ahadi 2017 (232) conducted a pilot RCT to evaluate the impact of biofeedback on quality of life in women diagnosed with stage I-II prolapse. The authors argued that while biofeedback was frequently used alongside PFMT, little was known about the effectiveness of biofeedback-assisted PFMT compared with PFMT alone. Women were randomised to a home-based PFMT programme, lifestyle advice leaflet and biofeedback (intervention group) or PFMT and lifestyle advice leaflet (control group). Women were initially seen by a physician who performed a physical examination and taught the women how to perform the exercises. Women in both groups received the same home exercise protocol comprised of 10 repetitions of a 5 second squeeze followed by a 5 second release. Women were asked to perform five sets per day for 12 weeks. A lifestyle advice leaflet was also given to all women. Women in the intervention group also received two 30-minute sessions of pressure biofeedback each week delivered over 4 weeks (total of 8 sessions). The primary outcome measure was the validated Persian (Farsi) version of P-QoL questionnaire (including a prolapse severity subscale). Secondary outcome measures included stage of prolapse using POP-Q system. Data were collected at baseline and 4-5 weeks and 12 weeks follow-up.

Caagbay 2020 (234) recently published an RCT evaluating the impact of lifestyle advice and PFMT instruction on quality of life in Nepali women. They argued that while there is growing evidence for the use of PFMT in a wide range of populations, the evidence of effectiveness for women living in rural communities in low-and-middle income countries is still lacking. Caagbay (2020) (234) recruited women who were attending a reproductive health screening camp in Kathmandu Valley, who were diagnosed with stage I-III prolapse. Women were then randomised to receive lifestyle advice and PFMT instruction (intervention) or usual care (control). Women in both groups had an initial physical examination conducted by an experienced gynaecologist. During this examination, women were asked to perform a PFM contraction by "squeezing their muscles around the gynaecologist's finger as though they were trying to avoid passing gas". They were also given additional verbal instruction and biofeedback using digital pressure to ensure they were performing the contraction correctly. Women in the intervention group received individual, face-to-face education using an informational flipchart. This included information about how to correctly perform PFM contractions and how to perform the 'knack'. Women were advised to perform PFMT daily and to work up gradually to complete a set of ten PFM squeezes and a 10-second hold. Lifestyle advice included information about conservative management of prolapse. Women were also taught about pelvic anatomy, prolapse (definition, causes, symptoms) and treatment options and where to get help. The flipchart took 20 minutes to complete, and women were encouraged to ask questions. Women in the control group received usual care, which comprised of brief verbal instruction about PFMT like that provided to women in the intervention group. The primary outcome measure was the change from baseline in the P-QoL domains measured at 6 weeks, 12 weeks and 6 months' post-intervention. Secondary outcomes included POP-Q, which was assessed clinically at baseline and 6 months. Women were also asked to keep an exercise diary to document PFMT exercise adherence.

Gorji and colleagues (2020) (236) conducted an RCT to explore the addition of hip muscle exercises to a PFMT exercise regime. This built on previous work which hypothesised that prolapse causes lumbo-pelvic-hip musculoskeletal weakness in addition to the functional failure to support pelvic organs (259). Women with stage II or III prolapse were randomised to receive either PFMT and postural or positional inversion exercises (intervention group) or PFMT alone (control). Women in both groups had a total of 12 sessions delivered over 4 weeks (3 sessions per week). The PFMT included exercises as described by Hagen *et al.* (2014) (260). Women in the intervention group were also

asked to perform 10 repetitions of four postural or positional inversion exercises using an inversion wedge. These additional exercises are described in more detail in Table 39. Outcome measures included POP-Q stage, ICIQ-FLUTS, P-QoL (including prolapse severity) (Persian version). Data were collected at baseline and immediately post-intervention.

Navarro and colleagues recently published their findings from a 3-arm RCT which aimed to compare the effectiveness of hypopressive exercises with PFMT and to a combination intervention (Hypopressive exercises plus PFMT) (73). Women with self-reported signs or symptoms of stress or MUI, anal incontinence, and/or a gynaecologist diagnosis of stage I-II prolapse were randomly divided into three groups:

- *PFMT:* women received individualised PFMT instruction based on components of the PERFECT scheme (261). Within each session, women were encouraged to perform 10 repetitions of 10 maximal effort, rapid contractions lasting one second each to maintain an isometric contraction up to 10 seconds. Training was tailored for each woman based on progression at each session, and EStim, biofeedback, resistance training and dynamometric devices were used if the physiotherapist felt it was appropriate. PFMT instruction was delivered twice a week for 8 weeks. Each session was approximately 45 minutes' duration. Following each session, women were instructed to perform the daily exercises at home aiming for one to three sets of 5-10 repetitions between one and three times per day.

- *Hypopressive exercises:* women were instructed to perform hypopressive exercises using methods reported by Caufriez (262). Women were initially taught to do the "hypopressive manoeuvre" which involved maximal exhaling, then breath-holding, expanding rib cage drawing their abdomen inward and upward without breathing in, sustaining this for 10 seconds before resuming normal breathing. The hypopressive manoeuvre was performed in different positions: standing, kneeling, sitting and lying and women were taught a total of 33 exercises. Training was delivered twice a week for 8 weeks with each session lasting approximately 45 minutes. During the final week of training, the physiotherapist and each woman selected three exercises for home-based exercise. Women were asked to repeat each exercise three times per set and to perform 1 to 3 sets per day. Women in this group were also given feedback on PFM contractions (during their vaginal palpation assessment) and were taught the knack but were asked not to perform any specific PFMT exercise.

- *Combination training:* women in this group received a combination of PFMT and hypopressive exercises as described above. Women in the combination group split their session equally between PFMT and hypopressive exercise but PFM contractions were never combined with hypopressive exercises. Women were asked to exercise at home alternating between PFMT and hypopressive exercises.

Women in all groups were also taught about the anatomy and physiology of the pelvic floor using printed materials and 3-D models. They were also given lifestyle advice and given instruction about toileting habits and taught to use the knack manoeuvre when doing any task that could increase intra-abdominal pressure. Interventions were delivered individually and face-to-face by the same (unblinded) specialist physiotherapist. The primary outcomes measures included: PFIQ-7 and PFDI-20. Data were collected at baseline, immediately post-intervention and at 3-, 6- and 12-months post-intervention.

Resende and colleagues (2019) (240) also examined the effectiveness of hypopressive exercises compared with PFMT. In their study, they randomised women with stage II untreated and symptomatic prolapse to receive either PFMT or hypopressive exercises. Women in the PFMT group were given three training sessions. In session one, they were taught about the anatomy and physiology of the pelvic floor. They were then asked to contract their PFM using a mirror while lying in a supine position. The physiotherapist observed the movement to make sure it was correct. Later in the session, they were then given lifestyle advice. In the second session, a weighted vaginal cone was used to improve the woman's awareness of the PFM with the physiotherapist removing the cone while the woman attempted to keep it inside the vagina using PFM contractions. Later in the same session each woman received vaginal palpation. In the final session PFMT was performed using the home exercise protocol in three positions (lying, sitting, standing). Women were asked to perform three sets of 8 – 12 maximum voluntary contractions, hold for six seconds each and 12 seconds rest between contractions followed by three fast contractions. Women in the hypopressive exercise group also participated in three sessions. In addition to learning about pelvic floor anatomy and physiology they were also taught about the transverse abdominal muscles and how to activate these muscles. In the second session, women were instructed how to do the hypopressive manoeuvre (262) as reported earlier in this section (see Navarro (2020)). Women were discouraged from performing voluntary PFM contractions. In the final session, women were trained in the home hypopressive exercise protocol in lying and standing positions. Women were asked to complete two sets of 8-10 repetitions per day (one in each position) holding each contraction for 5- 8 seconds, with each session lasting approximately 40 minutes. Women in both groups were then asked to perform their daily exercises at home for 12 weeks. They received a call from the physiotherapist once a week and were seen individually for a face-to-face appointment twice a month. All women received standardised lifestyle advice. The physiotherapist delivering the intervention was given training before the beginning of the trial. The primary outcome measured was prolapse symptoms using P-QoL; secondary outcomes recorded were prolapse severity using POP-Q. Data were collected at baseline and immediately post intervention.

Results

In the Ahadi (2017) (232) study, forty women were randomised (20 to each group) of which 38 completed the trial. One woman in the intervention group did not receive the intervention as she was pregnant and one woman in the control group was lost to follow-up due to a hysterectomy. Women in the intervention group had statistically significantly more improvement in seven of the nine P-QoL domains (prolapse impact, role limitation, physical limitation, personal relation, emotion, sleep/energy and severity measures) compared to control. These findings were observed at the 4-5 weeks follow-up and sustained at 12 weeks follow-up. There were no significant differences at either follow-up time-point between the two groups for either PFM strength or stage of the prolapse.

Of the 140 women initially randomised in the Caagbay (2020) study, 136 were allocated (n=69 intervention; n=67 control). Four women were excluded because they had a stage IV prolapse. At the 6-month telephone follow-up, 102 women were reviewed; trialists were unable to contact 15 women in the intervention group and 17

women in the control group. Data were reported as missing from two additional women in the control group. At six months, there were statistically significant differences between groups in six out of nine P-QoL domains (general health, prolapse impact, physical limitations, emotions, sleep and severity measures) and for prolapse, bladder and bowel symptoms, favouring the intervention group. Only 27/136 women attended for the 6-month examination, with women citing insufficient time to visit the clinic, consequently secondary outcomes could not be analysed.

Forty women were randomised in the Gorji (2020) study; 20 women in each arm (236). No dropouts were reported. Women receiving PFMT and postural or positional inversion exercises had statistically significantly better scores in three domains of the P-QoL questionnaire (general health, physical limitation and social limitation).

In the Navarro (2020) (73) study, 99 women were randomised equally across the three arms (33 in each group). One woman from the PFMT group and one woman in the hypopressive exercise group did not complete the intervention because they became pregnant. Three women (one in the hypopressive group and two in the combined group) were lost to follow-up. There was no statistically significant difference between groups immediately post-intervention or at 3-, 6- and 12-months post-intervention in any prolapse or pelvic floor symptom measures or related quality of life. However, the authors presented data to show that these measures did improve *within* groups.

Resende 2019 (240) randomly assigned 70 women (35 in each group). Nine women were lost to follow-up (5 from PFMT group; 4 from hypopressive exercise group) because of motivational problems or other health problems. Women in the PFMT group showed statistically significantly more improvement in five symptoms (vaginal bulge/lump, heaviness or dragging on the lower abdomen, straining to empty bladder, stress incontinence, vaginal bulge interfering with emptying bowel) and in four out of nine P-QoL domains (prolapse impact, role limitations, social limitations and personal limitations) compared to women in the hypopressive exercise group. Women in the PFMT group also exhibited more improvement in prolapse severity compared with women who received the hypopressive exercise training.

Summary of the evidence from the previous edition

Earlier editions of this chapter synthesised the evidence for all PFMT interventions and are described at the beginning of section III (Table 36).

Summary of the evidence identified in this update

Five new studies were included in this comparison:

- Two medium size trials with low ROB compared PFMT with hypopressive exercises, and with a combination of the two. One found PFMT to be more effective in treating prolapse symptoms and severity than hypopressive exercises, while the other found no significant difference between the two, nor between either intervention, or a combination of PFMT plus hypopressive exercises. The benefit of hypopressive exercises as an alternative, or an addition to, PFMT is uncertain for treatment of prolapse. **(Level of evidence: 2)**
- One small, moderate ROB trial found no significant difference in prolapse stage or PFM strength for women treated with PFMT plus biofeedback compared to PFMT alone. **(Level of evidence: 2)**
- One large, moderate ROB trial found a significant prolapse symptom and quality of life benefit for Nepali women receiving an educational session including lifestyle advice and PFMT instruction, compared to verbal instruction in PFMT. **(Level of evidence: 2)**
- One small, moderate ROB trial found a significant quality of life and PFM strength benefité, but no prolapse symptom benefit, for women receiving postural exercises plus PFMT compared to PFMT alone. **(Level of evidence: 2)**

Recommendations

PFMT plus biofeedback does not offer benefit compared to PFMT alone for treatment of prolapse and may not be routinely recommended**. (Grade of recommendation: D New)**

An educational session including lifestyle and PFMT instruction may be considered as it does offer benefits over verbal PFMT instruction alone when treating prolapse. **(Grade of recommendation: D New)**

Postural exercises in addition to PFMT may be considered as they offer benefit over PFMT alone in treating prolapse. **(Grade of recommendation: D New)**

2.2.3. A physical intervention combined with a non-conservative intervention vs an active (non-conservative) treatment (or combination)

For this update, five studies (seven randomised comparisons) were identified (218, 233, 237, 241, 263, 264). Salient features of each trial are described in Table 39. ROB is summarised in Appendix 2.

Quality of data

Brandt (2019) (233, 264) conducted a three-arm RCT that compared the impact of PFMT or core training or usual care on prolapse in women scheduled for prolapse surgery. Women who were waiting for pelvic reconstructive surgery to manage their prolapse were randomly allocated to three groups: PFMT programme, core stability programme or control. Further descriptions of the interventions were not available in the abstracts. Each intervention was delivered for six months (from pre-to-postoperative). Outcome measures included P-QOL and POP-Q. It is unclear from the abstract when data were collected.

In a conference abstract, Dawson and colleagues (2017) (263) presented their findings from an RCT which aimed to evaluate whether PFMT offered post-operatively would improve women's quality of life following prolapse surgery. Women having pelvic reconstructive surgery to manage their prolapse were randomly assigned to PFMT immediately post-surgery (intervention) or standard post-operative care (control). A trained pelvic floor physiotherapist delivered a six-week standardised protocol of PFMT. Women in the control group received routine postoperative care. Outcome measures included PFIQ-7 and PFDI-20 (total scores only), and POP-Q. Data were collected at

baseline, immediately post-intervention and 6 weeks' post-intervention.

Duarte and colleagues (241) conducted a RCT comparing the effectiveness of incorporating perioperative PFMT training on prolapse symptoms after surgery. Women who were candidates for prolapse surgery (stage II-IV) were randomly allocated to receive either perioperative PFMT (intervention) or surgery only (control). The intervention group received a 9-week PFMT protocol with four intensive, supervised sessions before the surgery (twice a week for 2 weeks), and received seven supervised sessions, 40 days after the surgery. The PFMT was delivered by a physiotherapist with more than 10 years' experience. Each session comprised four sets of maximum contractions (7 second hold, 7 second rest) performed in a variety of positions. Women were encouraged to perform the contractions at home at least three days per week. The control group received surgery and usual post-operative care. The primary outcome was the PFDI-20 questionnaire. Secondary outcomes included PGI-I. Data were collected at baseline (15 days before surgery) and at day 40 and day 90 after surgery.

Jelovsek and colleagues (2018) (237) published the five year outcomes from the OPTIMAL trial which was reported in the 6th ICI. This extended OPTIMAL (E-OPTIMAL) trial aimed to follow-up women who took part in the original trial 5 years after their index surgery from April 2011 through June 2016. Women in the OPTIMAL trial were allocated to perioperative behavioural therapy with PFMT or usual care. The primary outcomes for the PFMT intervention were time to surgical failure defined as (a) apical descent greater than one-third of total vaginal length or anterior or posterior vaginal wall beyond the hymen or retreatment for prolapse (anatomic failure), or (b) bothersome bulge symptoms (based on change from baseline preoperative POPDI scores). The primary behavioural outcomes were time to anatomical failure and POPDI.

Nyhus and colleagues (2020) (218) conducted a RCT to evaluate the effectiveness of preoperative PFMT in women waiting for prolapse surgery. Women were randomised to receive either daily PFMT following enrolment into the trial until their surgery, or to receive no intervention while waiting. Women in the PFMT arm were asked to perform daily PFMT consisting of 8-12 contractions (duration of 6-8 seconds in 3 sets). Women were seen by a specialist physiotherapist (in weeks two and six) for a vaginal examination to ensure that the exercises were being done correctly. Women were also offered weekly group exercise sessions. They were also given lifestyle advice information and asked to perform contractions in situations that could increase intra-abdominal pressure. Women in the control were scheduled for surgery but received no other intervention. Outcomes included sensation of vaginal bulge. Data were collected at baseline (day of inclusion), day of surgery and at six months.

Results

Eighty-one women were randomised to receive either PFMT (24 women), core stability programme (28 women) or control (18 women) in the Brandt (2019) study (233, 264). Dropouts are not reported in the abstract. There were no significant differences across groups for any of the measures reported, except for a significant difference in P-QoL total score, with better scores for women in the core stability group.

In the Dawson study (263) 46 women were enrolled, however only 34 women completed the study (16 in PFMT; 18 in control). Reasons for the dropouts were not reported. There were no significant differences between the two groups for severity of prolapse or prolapse symptoms.

Duarte and colleagues (241) randomised 96 women with prolapse: allocating 48 to the perioperative PFMT group and 48 to the control group (no PFMT). In the perioperative PFMT group, two women were lost to follow-up (unable to be contacted) by day 40. There were no dropouts from the control group. Both groups reported a marked improvement in prolapse symptoms after surgery but there was no between group difference in pelvic floor symptoms at day 40 or at day 90 on the PFDI-20 total score, or on any of the subscales including prolapse symptoms (POPDI-6, CRADI-8, UDI-6). There was no significant difference between groups on PFIQ-7 or any of the subscales of PISQ-12. Women who received the additional perioperative PFMT protocol perceived marginally greater global improvement compared with women in the control group by day 90 on PGI-I but this was also not statistically significant.

In the E-OPTIMAL trial reported by Jelovsek *et al.* (237) 309 women were eligible for follow-up in the extended trial, of these 285 enrolled and 244 completed the extended trial. There were no differences between groups on either primary outcome. Almost two-thirds of women met *a priori* trial definitions of failure 5 years after surgery with no significant difference between perioperative behavioural muscle training and usual care on rates of anatomic failure and prolapse symptom scores.

Nyhus (238) randomised 159 women of which 81 were allocated to the intervention arm and 78 were allocated to the control group. Six women dropped out of the intervention group before the day of surgery; three did not want any further examinations and three women cancelled surgery. Two women dropped out of the control group and cancelled their surgery as their symptoms improved. At the post-operative follow-up there was no statistically significant between group difference in any outcome including vaginal bulge.

Summary of the evidence from the previous edition

Six trials have previously been published evaluating PFMT and surgery; none of the trials showed evidence of an effect of PFMT. **(Level of evidence: 1)**

Summary of the evidence identified in this update

Five new studies (six comparisons) were included:

No significant differences were evident in four comparisons of peri-op physical intervention (PFMT or core stability exercises) with surgery versus surgery alone (233, 237, 241, 264). The ROB was low or uncertain and the sample size small to large. **(Level of evidence: 1)**

One comparison of pre-op PFMT with surgery vs surgery alone, with low ROB and a large sample size (238) showed no significant difference between groups post-op. **(Level of evidence: 2)**

One comparison of post-op PFMT with surgery vs surgery alone (263), with uncertain ROB and a small sample size, showed no significant difference. **(Level of evidence: 2)**

Recommendations

Adding a physical intervention to prolapse surgery, pre-, peri- or post-operatively did not improve symptoms or severity and cannot be recommended routinely. **(Grade of recommendation: B New)**

Table 39. Summary of key characteristics of treatment studies of women with prolapse and physical interventions

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Ahadi (2017) (232)	RCT Home-based PFMT exercise program plus lifestyle advice plus biofeedback vs Exercise group (PFMT+lifestyle advice)	40	Women aged 18-75 years with stage I-II prolapse Iran	Home based PFMT protocol consisted of five sets and each set included 10 repetitions of a 5-s squeeze followed by a 5-s release. Participants also given a lifestyle advice sheet. Biofeedback program included eight 30 min-sessions of pressure biofeedback which were accomplished by Enraf- NONIUS (Mymed632x) device. PFMT consisted of 5 sets per day over 12 weeks; biofeedback: twice a week for 4 weeks (8 x 30 min sessions)	Outcomes: primary outcome was Persian (Farsi) version of P-QOL questionnaire. Secondary outcomes included PFM strength and POP-Q Key findings: Women in the intervention group had a significant improvement in 7/9 P-QoL domains at the 4-5 weeks follow-up and sustained at 12 weeks follow-up. No significant differences at either follow up time-point between the two groups for either PFM strength or stage of the prolapse	Baseline, 4-5 weeks and 12 weeks follow-up	Publication: FT Dropouts: 1 woman did not receive the allocated intervention in the experimental group (home-based PFMT + LA +biofeedback) due to pregnancy; 1 dropout in the control group (PFMT+lifestyle) due to hysterectomy AE: authors reported no adverse effects
Brandt (2019) (233, 264)	3-arm RCT Individuals were randomised across three groups resulting in the following randomised paired comparisons: Brandt (2019) (i) PFMT or usual care Brandt (2019) (ii) Core training vs usual care Brandt (2019) (iii) PFMT vs core training	81	Women scheduled for prolapse surgery South Africa	PFMT program, core stability program or control. Further descriptions of the interventions were not available in the abstracts. Each intervention was delivered for six months (from pre-to-postoperative).	Outcomes: P-QoL, SF-36, 2-D ultrasound, POP-Q, the PERFECT scale, EMG, Sahrmann scale and PBU. Medical and exercise history, exercise compliance and the Visual Faces Scale for pain assessment were also recorded. Key findings: no significant differences across groups for any of the measures reported, except for a significant improvement in PQoL scores for women in the core stability group.	Unclear – insufficient information	Publication: AB Dropouts: not reported in the abstracts AE: not described in the publication

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Caagbay (2020) (234)	RCT PFMT plus lifestyle advice vs standard care	136	Women attending a reproductive health screening camp in Kathmandu Valley, diagnosed with stage I-III prolapse Nepal	Individual, face-to-face education using an informational flipchart (20 mins) about how to perform PFMT and how to perform the knack) trained in PFMT (given a physical exam plus biofeedback using digital pressure) plus lifestyle advice which included information about conservative management. Asked to perform PFMT daily and to work up gradually to complete a set of ten PFM squeezes and a 10-second hold. Usual care comprised brief verbal instruction about PFMT similar to that provided to women in the intervention group	Outcomes: primary outcome was the PQoL. Secondary outcomes included POP-Q, modified Oxford scale and exercise diary Key findings: Women in the intervention had significant improvement in 6/9 P-QoL domains and for prolapse, bladder and bowel symptoms at six months. Only 27/136 women attended for the 6-month examination, with women citing insufficient time to visit the clinic, consequently secondary outcomes could not be analysed. No women completed the exercise diary.	P-QoL was measured at baseline, 6 weeks, 12 weeks and 6 months post-intervention. Secondary outcomes were collected at baseline and 6 months	Publication: FTvand PhD thesis Dropouts: 136/140 were allocated (4 women had stage IV prolapse and were excluded); At the 6-month telephone follow-up, 102 women were reviewed; trialists were unable to make contact with 15 women in the intervention group and 17 women in the control group. Missing data from 2 women in the control group. Only 27/136 women attended for the 6-month examination, with women citing insufficient time to visit the clinic AE: not described in the publication
Cheung (2016) (244)	See Table 40 for details	-	-	-	-	-	-
Dawson (2017) (235)	RCT Postoperative PFMT vs standard postoperative care	46	Women who presented with prolapse and desired vaginal reconstructive surgery for resolution of their condition USA	PFPT consisted of a 6-week standardised protocol with a trained pelvic floor physical therapist, no other details available. Standard postoperative care: not described	Outcomes: PFIQ-7, PFDI-20, VAS for daily pain and sexual pain, FSFI, and the WHOQOL-BREF questionnaires prior to surgery; 6-week postoperative visit, patients were given the VAS and WHO-QOL-BREF; 12-week visit patients were given PFIQ-7, PFDI-20, FSFI, WHOQOL-BREF and VAS Key findings: no significant differences between the two groups for WHO QOL-BREF or severity of prolapse.	Baseline, 6-week follow-up (immediately post-intervention) and 12-week follow-up (6 weeks post intervention)	Publication: abstract Dropouts: 46 women were enrolled in the study however only 34 women completed the study; 18 in the standard post-operative arm and 16 in the postoperative PFMT arm. Reasons for dropouts were not reported. AE: not described in the publication

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Duarte (2020) (241)	RCT Prolapse surgery with perioperative PFMT or a control group (prolapse surgery only)	96	Women aged between 35 and 80 years with prolapse symptoms (bulging); surgical indication to undergo anterior, apical and/or posterior repair; and prolapse stage II- IV Brazil	Perioperative PFMT: Four sessions of intensive supervised PFMT twice a week for 2 weeks preoperatively and returned 40 days postoperatively for an additional seven sessions, giving a total of 11 supervised individual PFMT sessions Sessions included four sets of 10 repetitions of maximum voluntary contractions with a 7-second hold and a 7-second rest period between each contraction Prolapse surgery: standard follow up	Outcomes: primary outcome: PFDI-20 including its subscales POPDI-6, CRADI-8 and UDI-6. Secondary outcomes: PFM strength was measured using a Peritron manometer (peak, endurance and mean strength); PFIQ-7, including its subscales UIQ-7, CRAIQ-7 and POPIQ-7; PSIQ-12; PGI-I Key findings: no between group difference in prolapse symptoms at day 40 or at day 90 on the PFDI-20 total score or on any of the subscales (POPDI-6, CRADI-8, UDI-6). No significant difference between groups on any of the secondary outcomes (PFM strength, PFIQ-7 or any of the subscales of PISQ-12)	Baseline: 15 days before surgery; 40 days after surgery; and 90 days after surgery	Publication: FT Dropouts: 96 women were randomised, 48 to each group. At day 40 postoperative 2 were lost to follow-up (not contactable) in the intervention group. No dropouts in the control group. No dropouts reported at day 90 AE: not described in the publication
Gorji (2020) (236)	RCT PFMT plus postural or positional inversion exercises (intervention group) vs PFMT alone	40	Women with stage II or III prolapse Iran	PFMT included exercises as described by Hagen et al (2014) (267). Women in the intervention group were also asked to perform 10 repetitions of four postural or positional inversion exercises using an inversion wedge. Both groups had a total of 12 sessions delivered over 4 weeks (3 sessions per week).	Outcomes: POP-Q stage, ICIQ-FLUTS, PQoL (Persian version) and PFM strength (cm H2O) Key findings: Women receiving PFMT and postural or positional inversion exercises showed significant improvement in three domains on the PQoL questionnaire. (general health, physical limitation and social limitation). PFM strength was significantly greater in the intervention group compared with the control group	Baseline and immediately post-intervention (at 4 weeks)	Publication: FT Dropouts: none AE: not described in the publication

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Jelovsek (2018) (237)	Five-year outcomes from the Extended-OPTIMAL (E-OPTIMAL) Perioperative BPMT group vs usual care	285	Followed up women in the original trial 5 years from surgery to compare surgical failure, changes in quality of life, and complication rates of the 2 surgical and 2 behavioral treatment groups USA	Women randomided to perioperative BPMT visited centrally trained pelvic floor therapists 2 - 4 weeks before and 2, 4, 6, 8, and 12 weeks after surgery. Women practiced PFMT exercises and received individualised education on behavioural strategies to reduce urinary and colorectal symptoms during each visit. Maximum of 45 contractions per day, duration ranging from 1 to 3 seconds / contraction. Postoperatively the interventionist adjusted the patient's exercise regimen by gradually increasing the number (maximum ranging from 45 to 60 per day) and duration (maximum = 10 seconds) of each contraction. At the final postoperative session, the interventionist provided patients with a maintenance exercise program consisting of 15 contractions per day at the maximum contraction duration achieved during the intervention period	Outcomes: primary behavioural outcomes were time to anatomic failure (defined as POP-Q points Aa, Ba, Ap, or Bp beyond the hymen, point C descending >one-third of total vaginal length, or retreatment) and change from baseline (preoperative) and POPDI scores Key findings: no significant difference between perioperative behavioural muscle training and usual care on rates of anatomic failure and symptom scores. No meaningful difference in secondary outcomes including UDI, CRADI, PGI-I or adverse events.	Annual evaluation during postoperative years 3-5. Each visit and interview occurred within 3 months of the anniversary of the index surgery	Publication: FT Dropouts: The OPTIMAL trial (Barber et al. 2014 (273) previously reported in 5th Edition ICI chapter. At year 5: 309/374 women from the original study were eligible for this extended trial. 285 women enrolled in E-OPTIMAL and 244 (86%) completed the trial. Dropouts are accounted for in Figure 2.

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Navarro (2020) (73)	3-arm RCT Individuals were randomised across three randomised paired comparisons	99	Women with PFD – other details not available Spain	PFMT alone: Pelvic floor muscles exercises guided throw vaginal palpation and intravaginal biofeedback. Women were encouraged to perform 10 repetitions of 10 maximal effort, rapid contractions lasting one second each to maintain an isometric contraction up to 10 seconds. PFMT instruction was delivered twice a week for 8 weeks; session lasted 45 mins Hypopressive exercises: Thirty-three hypopressive exercises described by Caufriez 1997 (269). Women were taught the hypopressive manoeuvre which was performed in different positions: standing, kneeling, sitting and lying and women were taught a total of 33 exercises. Training was delivered twice a week for 8 weeks; sessions lasted 45 mins. During the final week of training, the physiotherapist and each woman selected three exercises for home-based exercise. Women were asked to repeat each exercise three times per set and to perform 1 to 3 sets per day. Combination training: PFMT guided throw palpation and biofeedback + hypopressive exercises. All women received the same educational strategy and were instructed in the knack manoeuvre. All interventions were carried out by the same physiotherapist for 8 weeks. A qualitative study was nested in the RCT; 31 women were interviewed. Interviews were recorded, transcribed manually, and thematic analysis was conducted.	Outcomes: PFDI-20, PFIQ-7 and PFM strength Key findings: no statistically significant difference between groups immediately post-intervention or at 3-, 6- and 12-months post-intervention.	Baseline, 3, 6- and 12-months post-intervention	Publication: FT Dropouts: One woman from the PFMT group and one woman in the hypopressive exercise group did not complete the intervention because they became pregnant. Three women (one in the hypopressive group and two in the combined group) were lost to follow-up AE: reported in the three intervention groups with one woman reporting exacerbated back pain in the combined intervention group and five women in the hypopressive exercise group who needed to modify the exercise because the intervention caused pain, or they were unable to perform them correctly

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Nyhus (2020) (238)	RCT Daily PFMT following enrolment into the trial until their surgery vs no intervention while waiting for surgery	151	Women scheduled for prolapse surgery Norway	PFMT: daily PFMT consisting of 8-12 contractions (duration of 6-8 seconds in 3 sets). Women were seen by a specialist physiotherapist (in weeks two and six) for a vaginal examination to ensure that the exercises were being done correctly. Women were also offered weekly group exercise sessions; given lifestyle advice and asked to perform contractions in situations that could increase intraabdominal pressure Control group: scheduled for surgery but received no other intervention	Outcomes: PFM strength using the modified Oxford scale, vaginal manometry, ultrasound and sensation of vaginal bulge. Adherence was recorded in a training diary Key findings: no statistically significant difference between groups at postoperative follow-up on any outcome.	Baseline (day of inclusion), day of surgery and at six months	Publication: FT Dropouts: Surgery group - 6 women dropped out before surgery; 3 did not want any further examinations and 3 women cancelled surgery. Control group: 2 women cancelled their surgery as their symptoms improved. AE: two major complications after surgery; an intestinovaginal fistula after laparoscopic sacrocolpopexy and one haemorrhage which required a second operation. 3 women reported postoperative infections and one woman had complications with persisting residual urine
Orhan (2020) (239)	RCT PFMT plus biofeedback vs usual care	22	Women with prolapse Turkey	PFMT combined with biofeedback using the Myomed 632 biofeedback device to instruct women about how to perform the exercise for 12 weeks Control group: usual care Women in both groups were given lifestyle advice	Outcomes: primary outcome was self-reported perception of improvement. Secondary outcomes measures included POPP-SS and PFDI-20 questionnaires, and PFM strength and endurance. Key findings: statistically significant difference in the change of PFM strength, PFDI-20 and POP-SS scores between PFMT plus biofeedback and control groups ($p<0.05$)	Baseline and immediately post-intervention (at 12 weeks)	Publication: abstract Dropouts: not described AE: not described in the publication
Panman (2016) (248)	See Table 40 for details	-	-	-	-	-	-

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes (side effects, loss of follow up…)
Resende (2019) (240)	RCT PFMT vs Hypopressive exercises	70	Symptomatic women with untreated stage II prolapse Brazil	PFMT group: 3 training sessions including provision of information about the pelvic floor, instructed about how to make the correct PFM contraction, life-style advice, use of a weighted vaginal cone to improve awareness of the PFM, vaginal palpation and PFMT performed using the home exercise protocol in three positions (lying, sitting, standing). Women were asked to perform three sets of 8 – 12 maximum voluntary contractions, hold for six seconds each and 12 seconds rest between contractions followed by three fast contractions. Hypopressive home exercise programme: bimonthly sessions with a physiotherapist. The protocol included 3 sessions to learn how to perform the exercises correctly followed by 3 months of exercise with monthly progression. Women in both groups were then asked to perform their daily exercises at home for 12 weeks	Outcomes: primary outcomes included PQoL, and specific questions (yes/no response) to investigate POP symptoms (bulge/ lump, pelvic heaviness, backache) and other potentially related POP symptoms (e.g bladder and bowel symptoms). Secondary outcomes were POP-Q, PFM function and electrical activity (Oxford, Endurance and MVC SEMG). Key findings: Women in the PFMT group showed significantly more improvement in five symptoms (vaginal bulge/lump, heaviness or dragging on the lower abdomen, straining to empty bladder, stress incontinence, vaginal bulge interfering with emptying bowel) and in 4/9 P-QoL domains compared to women in the hypopressive exercise group. Women in the PFMT group also exhibited more improvement in prolapse severity and PFM function compared with women who received the hypopressive exercise training.	Baseline and after 3 months of treatment	Publication: FT Dropouts: 5 women dropped out in the PFMT group (3 with motivational problems and 2 due to other health conditions); 4 women dropped out in the Hypopressive exercise group (2 with motivational problems and 2 due to other health conditions) AE: not described in the publication

Abbreviations: AB: abstract; AE: adverse events; CARP: commercially available ring pessary; CG: control group; CRADI-8: Colorectal-Anal Distress Inventory; CRAIQ-7: Colorectal-Anal Impact Questionnaire; EMLA: (eutectic mixture of lidocaine 2.5% and prilocaine 2.5 %); FI: faecal incontinence; FT: full-text; FU: follow-up; IG: intervention group; IIQ-7: Incontinence Impact Questionnaire; ND: new vaginal device; NR: not reported; PA: physical activity; PFD: pelvic floor disease; PFDI-20: Pelvic Floor Distress Inventory; PFH: pelvic floor health; PFIQ-7: Pelvic Floor Impact Questionnaire; PFM: pelvic floor muscle; PFMT: pelvic floor muscle training; PGI-I: Patient Global Impression of Improvement-Incontinence; PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire; POP: pelvic organ prolapse; POPDI-6: Pelvic Organ Prolapse Distress Inventory; POPIQ-7: Pelvic Organ Prolapse Impact Questionnaire; PP: postpartum; PRC: Peoples Republic of China; PUS: perineal ultrasound; QoL: quality of life; RCT: Randomised controlled trial; SA: Staphylococcus aureus; UDI-6: Urinary Distress Inventory; UI: urinary incontinence; UTI: urinary tract infection; VAS: visual analogue scale.

3. PESSARY INTERVENTIONS

A vaginal pessary[1] is a device that provides structural support for the vaginal walls and pelvic organs that lie behind them (215). Pessaries are frequently used as a first-line option for women who do not wish to have surgery, or in women who have a higher risk of surgical complications or women with recurrent prolapse. There is currently no evidence to support the use of a specific type of pessary, and choice is largely based on clinical experience and trial and error. However, it is generally accepted that the ring pessary should be tried first because of ease of insertion and removal, and if this fails, other pessaries can be investigated (265). A Cochrane review by Bugge *et al,* published in 2013 (266) identified one RCT that compared two different types of pessaries (ring versus Gellhorn), and the authors concluded that there is no consensus on the use of different types of device, the indications nor the pattern of replacement and follow-up care. Consequently much of the evidence for the effectiveness of pessaries presented in previous editions has relied heavily on observational studies (265). Here, we present the current evidence-base drawing on the recently updated Cochrane review published in 2020, which identified four new RCTs for inclusion (215). We have also included nine additional RCTs, which were not included in the Cochrane review, as they fell outside the scope of the review of effectiveness. This additional body of evidence is focused on optimising pessary management or reducing some of the well-known barriers to successful pessary usage (e.g., common side effects). Key features of each study are described in Table 40. The ROB for each of the studies is presented in Appendix 2.

3.1. Prevention

3.1.1. Pessary (alone or in combination) versus control, waiting list or no active treatment

In this update, one trial evaluating a pessary intervention compared with no treatment focussed on prevention of prolapse was identified (242). Key features of this trial are described in Table 40 The ROB is summarised in Appendix 2.

Quality of data

Baessler and colleagues (242) piloted an RCT to determine whether women receiving a pessary early (i.e. 1 to 3 days after their first vaginal birth with stage II prolapse) would report an improvement in their prolapse symptoms. The authors argued that a study to explore early intervention was necessary because 39% of women had a stage II prolapse at 6 weeks postpartum; with almost a third of women still describing prolapse symptoms 12 months postpartum. In this study, women diagnosed with stage II prolapse following their first vaginal delivery were randomised to receive either a vaginal ring pessary for 6 weeks postpartum or standard care (i.e., no intervention). Preference groups were established for women who declined randomisation. The authors measured POP-Q, Australian Pelvic Floor Questionnaire (German version) at 6 weeks and 12 months postpartum. Complications such as reduced lochia or infection were also recorded.

Results

Forty-four women were initially enrolled in the Baessler trial (242); three preferred the pessary and seven preferred standard care. Thirteen women were randomised to the vaginal ring pessary and 21 women received standard care. Pessary placement was not possible in two women. At 12 months, three women were lost to follow-up in the pessary group and 10 women in the standard care group. The authors stopped the trial early because of 'slow' recruitment and pessary problems, which the authors reported as resolving once the pessary was removed. In the abstract, data for the preference and randomised groups are presented together, but Bugge (2020) (215) presents the separated data (personal communication) at 12 months. There was no significant difference in perceived improvement in prolapse symptoms in women in the pessary group compared to women in the standard care group at 12 months on the Australian Pelvic Floor Questionnaire. There was no significant difference between groups on the severity of prolapse as measured by POP-Q at 12 months.

Summary of the evidence from the previous edition

No RCTs were identified for the prevention of prolapse.

Summary of the evidence identified in this update

One new study was included in this comparison. A small size study with a moderate ROB (242) that compared a postpartum vaginal ring pessary with standard care showed no difference in the severity of prolapse for women with stage II prolapse postnatally or women's perceived improvement in prolapse symptoms. **(Level of Evidence: 2)**

Recommendations

Vaginal ring pessary cannot be recommended routinely in women early after delivery to prevent or improve prolapse. **(Grade of recommendation: B)**

3.1.2. Pessary (alone or in combination) versus an active treatment (or combination)

In this update, no new trials were identified.

Summary of the evidence from the previous edition

No RCTs were identified.

Summary of the evidence identified in this update

No trials were identified in this comparison highlighting a gap in evidence.

Recommendations

None.

3.2. Treatment

3.2.1. Pessary (alone or in combination) versus control, waiting list or no active treatment

In this update, no new trials were identified.

Summary of the evidence from the previous edition

The previous update was based on prospective case-controlled cohort studies, which suggested that pessaries are a viable op-

[1] In this chapter, we do not include pessaries used to support pregnancy.

tion for women who complain of a symptomatic prolapse and can be recommended. **(Level of evidence: 3, Grade of recommendation: B)**

Summary of the evidence identified in this update

No trials were identified in this comparison highlighting a gap in evidence.

Recommendations

None.

3.2.2. Pessary (alone or in combination) vs another active treatment (or combination)

In the previous edition, preliminary data for two relevant studies (244, 267) were reported. Since then both trials have been fully reported and are now included in the recent Cochrane review update (215). Consequently, a more comprehensive description is presented below. Salient features of each trial are described in Table 40 and the ROB is profiled in Appendix 2.

Quality of data

Panman and colleagues 2017 (248, 267) conducted a large multicentre RCT comparing the long-term effectiveness and cost-effectiveness of pessary treatment compared with PFMT in menopausal women diagnosed with symptomatic POP. Women in the PFMT arm received PFMT, supervised by an experienced registered physiotherapist. They were initially educated on pelvic floor function, and then taught how to contract their PFMs. Women received feedback about their contractions using digital palpation or myofeedback using EStim if required. All women were initially asked to do the same exercise protocol. This 'basic exercise' programme included a series of graded exercises initially starting with three blocks of 8–12 fast contractions (1-sec each) followed by 1 second of relaxation; 30–60 seconds of rest between each block; building up to a (nearly) maximal contraction (hold 6–10 seconds); 3–5 fast contractions (1 second on top of the maximal contraction). They were asked to repeat this three times with 1-2 minutes' rest between exercises. The basic exercise programme was later tailored for each woman based on specific needs identified during their pelvic floor examination, and additional exercises were included. Women were given advice about going to the toilet (e.g., keeping their feet flat on the floor, not to strain, etc.). Women were also provided with lifestyle advice (e.g., use the 'knack' exercise, avoid heavy lifting, avoiding constipation, etc.), and a lifestyle leaflet at their 3-month follow-up. The PFMT lifestyle and exercise programme are documented in a supplementary online file (see Table 40). Women were then asked to perform the exercises at home 2-3 times per day, 3 – 5 times per week.

Women enrolled in the pessary arm tried a pessary for two weeks (ring pessary). A refit was offered using different types of pessaries as required: a ring with support followed by a Gellhorn or Shaatz pessary. Women were offered a maximum of three refits. The pessary intervention was provided by one of four research physicians who had been trained by an experienced urogynecologist. Women were seen every three months by their GP or by the research physician to clean and replace the pessary and record any side effects. The primary outcome was distress experienced due to pelvic floor symptoms measured using the PFDI-20 questionnaire, and its subscales including POPDi-6, at 24 months. Secondary outcomes included pelvic floor related quality of life; costs; prolapse stage; and participants' perceived symptom improvement. Women were followed up at 3, 12 and 24 months after starting PFMT or having a successful pessary fitting.

Cheung and colleagues carried out a RCT in women with symptomatic POP (stage I-III) who had never received previous treatment (244). Women were randomised to receive either a ring pessary plus PFMT, or PFMT alone (244). Women in the pessary plus PFMT group were assessed by a specialist gynaecologist and then fitted with a vaginal ring pessary, using the largest pessary that was comfortable for the woman. Reinsertion of the same pessary (or the next size) was performed up to a maximum of three times. Women were contacted by phone two weeks later to see how successful the pessary fitting was. If women reported that the pessary had slipped out, they were offered a reassessment and replacement. Women in both groups were taught PFMT by specialist nurses (who were also trained as continence advisors). The standardised PFMT course included a teaching session (within two weeks after the first consultation) and three individual training sessions delivered at 4, 8, and 16 weeks. Women were encouraged to perform two sets of 8–12 exercises per day (with 8–10 exercises per session *at least* twice per week). The specialist nurses continued to encourage women to perform the PFMT at each follow-up session. The trial had two primary outcomes: change in prolapse symptoms measured using the PFDI-20 (Chinese version) and change in PFIQ-7 (Chinese version) at 6 and 12 months. Secondary outcomes included the discomfort of prolapse symptoms using a visual analogue score, severity of prolapse using POP-Q. Desired treatment for the prolapse in the first consultation before any intervention and at the 12-month follow-up and complications were also documented.

Results

Of the 162 enrolled in the Panman study (267), 80 women were randomised to PFMT and 82 to a pessary. Four out of the 80 women in the PFMT group did not attend any PFMT appointments and another 10 discontinued (Table 40). Pessary fitting was successful in 47/82 women; 35 women did not receive pessary treatment mostly due to an unsuccessful fitting (Table 40). There was aa statistically significant between group difference in the adjusted POPDI-6 scores at 24 months but the authors concluded that this was not clinically meaningful. The meta-analyses presented in Bugge (215), based on unadjusted data showed no difference between groups in perceived improvement in the PFDI-20 or POPDI-6 prolapse subscores at 12 or 24 months. The number of women reporting an improvement in symptoms was not statistically significantly different between groups at 12 or 24 months. There was also no difference in prolapse-specific quality of life measures between the groups at 12 or 24-month follow-up. The number of women with complications and adverse events (vaginal bleeding, voiding difficulty) were presented as a *per protocol* analysis. No adverse effects were reported in the PFMT group, but of the 35 women who were still using a pessary at 24 months, 21 reported one or more side effects including vaginal discharge (n=14), increased UI (n=5), and irritation / erosion of the vaginal wall (n=10). Based on their meta-analysis, the authors concluded that pessaries may substantially increase the risk of adverse events compared with PFMT. Pessary treatment was reported as less expensive than PFMT ($309/woman in pessary group vs $437/women in the PFMT arm) over the two-year period (248).

Of the initial 311 women recruited to the Cheung trial (244), 276 were randomised, 137 to PFMT treatment and 139 to vaginal pessary plus PFMT. Seven women dropped out of the pessary plus PFMT group (3 were lost to follow-up, 1 with cervical cancer and 3 with missing data). Nine women dropped out of the PFMT alone group (7 were lost to follow-up and 2 with missing data). Women in the pessary plus PFMT group reported statistically significantly fewer prolapse symptoms compared with women who received PFMT alone at both 6 and 12 months on POPDI-6. Women in the pessary plus PFMT had a statistically significantly improved prolapse-specific quality of life compared with women in the PFMT alone group at 12 months based on their POPIQ scores. Fifty-six women out of 132 (42%) in the pessary plus PFMT group failed to retain a pessary but their data appear to have been included in the final analysis. Nine women (9/132) had abnormal vaginal bleeding and 6/132 had unusual or bothersome vaginal discharge. Complications reported in the PFMT alone group included: 4/128 women with abnormal vaginal bleeding and 2/128 unusual or bothersome vaginal discharge (244). While there was no statistically significant difference between the groups for abnormal vaginal bleeding, Bugge (215) concluded that *"Pessary plus PFMT may slightly increase the risk of abnormal vaginal bleeding compared with PFMT alone (RR 2.18, 95% CI 0.69 to 6.91; 1 study; 260 women; low-certainty evidence".*

Summary of the evidence from the previous edition

Preliminary data from two relevant studies (244, 267) were reported. Since then both trials have been fully reported and are now included in the recent Cochrane review update (215).

Summary of the evidence identified in this update

Two new studies were included in this comparison.

A moderate-large size study with a low ROB that comparing PFMT with pessary showed no difference between groups in clinical outcomes including prolapse symptoms, but PFMT was more expensive and pessary had more adverse events (267). **(Level of evidence: 2)**

A moderate-large study with very low ROB comparing PFMT with PFMT plus pessary showed better prolapse symptom and quality of life outcomes in the combined group with no significant difference in complications (244). **(Level of evidence: 1)**

Recommendations

Pessary and PFMT could both be recommended as treatment for prolapse, but cost and adverse events need to be taken into consideration. **(Grade of recommendation: C New)**

The combined use of a vaginal pessary plus PFMT, rather than PFMT alone, can be recommended for treatment of prolapse. **(Grade of recommendation: B New)**

3.2.3. Pessary and Surgery

In the previous chapter, there were no trials comparing the effectiveness of pessary use with surgery. This update includes one study (254, 268), which is also described in Bugge (2020) (215).

Quality of data

Coolen *et al*. (2018) (254, 268) conducted a trial to compare women with symptomatic prolapse (stage II or greater) according to their preference for either a pessary (Portex ring) or prolapse surgery (254). They aimed to conduct an RCT, however of the 113 women recruited to the trial, only six women were randomised; the remainder were treated according to patient preference and the study was subsequently reported as a prospective cohort study. Data from the women randomised were unavailable in the published studies, but Bugge (2020) stated that contact had been made with the trialists and these data would be presented in the next review update (215).

Summary of the evidence from the previous edition

No RCTs were identified.

Summary of the evidence identified in this update

Only 6 women were randomised in the trial identified. No conclusions can be drawn.

Recommendations

None

3.2.4. Pessary (alone or in combination) vs another pessary (alone or in combination)

In this section, we have identified three new RCTs (247, 252, 269); two of these were excluded by Bugge (2020) (215) because the data were presented from a mixed population and it was not possible to extract separate data for women with prolapse only (247), and one study had an adjunct component which meant that *"it would not be evidence of the effectiveness of the pessary itself"* (Bugge, 2020, p15) (215). We have chosen to include these here as they provide important evidence of the effectiveness of pessary usage. Salient features of each trial are described in Table 40. ROB is summarised in Appendix 2.

Quality of data

The cross-over RCT conducted by Ziv *et al.* (2019) was reported over multiple conference abstracts (253, 269, 270). Ziv and colleagues described a new disposable device for the management of POP which was evaluated clinically for its impact on vaginal microflora and *Staphylococcus aureus* (SA) levels compared to a commercially available ring pessary. The authors described the new disposable device as *"housed in small dimensions within an applicator and is self-inserted vaginally. Within the vagina the device opens to become a ring of up to 91 mm. Once inserted, the applicator can be discarded. The device can remain within the vagina for up to 7 days"*. To remove the device, women were instructed to pull the string, which causes the device to collapse. However, following publication of this trial, the clinical trial registry entry has been redacted as the clinical device has "not been approved or cleared by the US FDA".

Meriwether and colleagues (2015) (247) conducted a multi-centre RCT comparing the effect of hydroxyquinoline-based gel (TrimoSan – a mildly acidic vaginal lubricant) in first time pessary users (TrimoSan group) with new pessary users not using the gel (no treatment) to examine whether the gel could reduce the prevalence of bacterial vaginosis or other bothersome vaginal symptoms (vaginal

discharge, itching, pain, sores). The trialists also published a series of linked secondary analyses from this study exploring: sexual function and pessary management in women (271); changes in vaginal microenvironment (272, 273); and the continued use of pessaries in women from different ethnic backgrounds (274, 275). Prior to the pessary fitting, women were asked to complete questionnaires about vaginal symptoms, hormone therapy and had a bacterial vaginosis (BLUE) test and a vaginal secretion swab. Following pessary fitting women were then randomised to standard pessary care with the gel (twice weekly) or standard pessary care. Women were followed up at 2 weeks and 3 months, and the questionnaires, BLUE test and slide collection repeated.

A randomised trial carried out by Tontivuthikul (2016) (252) examined the effect of locally applied oestrogen cream on vaginal health. Post-menopausal women with prolapse who had successfully used a pessary for six weeks and who were using vaginal conjugated equine oestrogen cream (0.5g daily for the first two weeks following fitting, and then twice per week for the next four weeks) were enrolled in the study. During the first six weeks, women were also advised to remove their pessary every evening and reinsert in the morning. Women were then randomised to either continuing to use the oestrogen cream (0.5 g) once a week (treatment group) or asked to discontinue (control group) for 24 weeks. The primary outcome was a vaginal health assessment, which included a vaginal symptom score (dryness, soreness, itching/irritation and discharge), vaginal pH, and vaginal maturation. Secondary outcomes comprised difficulty in using the pessary and endometrial thickness. Data were collected at baseline, 12 and 24 weeks.

Results

The results reported by Ziv *et al.* 2019 (253, 269, 270) from a trial comparing a new device with a commercially available ring pessary are limited, and the dropouts are not fully reported. Women using the new devices showed an improvement in their prolapse in 95.3% of cases (see Table 40). The levels of vaginal microflora and *Staphylococcus aureus* levels were described as low in both groups.

A total of 184 women were randomised in the Meriwether (2015) study (247); 92 to the TrimoSan group and 92 to the standard care group. At the two-week follow-up, 111 women responded (64 in the TrimoSan group; 47 in the standard care group); at month three, 147 women attended for follow-up (73 TrimoSan group, 74 standard care group). Reasons for loss to follow-up are detailed in Table 40. The prevalence of bacterial vaginosis based on the swab test or on the questionnaire (based on the prevalence of at least one vaginal symptom) was not significantly different between the groups at 2 weeks or at 3 months. Women were also equally satisfied with their pessaries in both groups.

Of the 40 women who were randomised into the Tontivuthikul (2016) study (252), 20 were allocated to the vaginal conjugated equine oestrogen cream and 20 to the control group. There were no dropouts from either arm. The trialists reported no statistical difference between groups for the vaginal health assessment (vaginal symptom score, vaginal pH, and vaginal maturation) at any time point (baseline, 12 or 24 weeks). They also reported no significant difference between the groups for secondary outcomes, although data for endometrial thickness were only presented for 31 women.

Summary of the evidence from the previous edition

No RCTs were identified.

Summary of the evidence identified in this update

Three new studies were included in this comparison.

- A small size study with moderate-high ROB compared the use of a new disposable vaginal device with a commercially available ring pessary. Data from this trial are limited and not yet fully reported (253, 269, 270).
- A moderate size study with moderate ROB compared the use of hydroxyquinoline-based gel – a mildly acidic vaginal lubricant on the prevalence of bacterial vaginosis in first time pessary users with no treatment and found no statistically significant difference on any outcome (247) **(Level of evidence: 2).**
- A small size study with moderate ROB compared the extended use of oestrogen cream in post-menopausal women with women who were asked to discontinue the cream. No differences on vaginal health were found between the two groups (252). **(Level of evidence: 2)**

Recommendations

Use of hydroxyquinoline-based gel in first time pessary users may be considered according to expert's opinion but there is no evidence of benefit or harm. **(No recommendation possible)**

Extended use of oestrogen cream use in postmenopausal pessary users may be considered according to expert's opinion. There is evidence for neither harm nor benefit. **(No recommendation possible)**

3.3. Studies aimed at optimising treatment protocols in women with POP

In this update, six studies focussed on optimising pessary management or reducing pessary-related complications were identified (243, 245, 246, 249-251). Salient features of each trial are described in Table 40. ROB is summarised in Appendix 2.

Quality of data

Escobar 2017 (246) conducted a mixed methods study including a survey and a pilot RCT to assess whether simulation training delivered to medical professionals (residents) could improve pessary placement skills. Residents were randomised to either an enhanced education intervention or to a control group (standard education). Both groups received a didactic lecture on pessary sizing and placement, but residents in the enhanced education group received an additional hands-on tutorial regarding pessary sizing and placement on a small-scale pelvic model prior to the post-test written and practical examination. Outcomes included written and practical examination six months after initial testing.

In a conference abstract, Chinthakanan and colleagues (2019) (245) compared women's satisfaction with ultra-low dose estriol plus *Lactobacillus acidophilus* vaginal tablets (Estriol group) with a vaginal moisturiser (moisturisers group) in women who were able to -manage their own pessary over a two month follow-up period. The estriol group received a vaginal tablet daily for the first 6 days, then 2 tablets per week for 8 weeks. Women in the moisturisers group received one application every 3 days for 8 weeks. Outcomes were measured at 4- and 8-weeks

follow-up and included women's satisfaction using the Thai-version Patient Global Impression of Improvement - Incontinence (Thai PGI-I), subjective complaints (i.e., foul smell, vaginal discharge, vaginal irritation and abnormal vaginal bleeding), and objective outcomes of vaginal health (i.e., vaginal abrasion, pH) and number of adverse events.

Taege and colleagues (2017) (250) conducted a double-blind randomised placebo controlled trial that studied the effect of applying a topical anaesthetic cream at the time of routine pessary change. Women were randomised to receive either four grams of 5% EMLA cream (eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) or an equal volume of placebo cream (emollient cream containing purified water, white petrolatum, cetyl alcohol, stearyl alcohol, propylene glycol, glycerin, sodium lauryl sulfate, diazolidinyl urea, Iodopropynyl butylcarbamate). Women attended their routine urogynaecology outpatient appointment for pessary change, and the cream was applied. After five minutes the pessary was removed, a speculum exam was conducted, and the pessary insertion was performed. Outcomes included a satisfaction score for pessary use and a visual analogue scale pain score (0 = no pain to 10 = severe pain). The pain score was completed prior to placement of the study cream, immediately after pessary removal and immediately after pessary insertion. Physicians were also asked to mark their perception of women's pain using the same VAS score.

Propst (2018) conducted a randomised non-inferiority trial comparing the timing of routine pessary care appointments to determine the optimal interval for women to be seen by their healthcare providers to prevent pessary-related complications (249). Women who were existing pessary users (ring, Gellhorn or incontinence dish pessary to treat prolapse, incontinence or both) were invited to attend their routine outpatient appointment at 12 weeks (usual care group) or attend a routine appointment at an extended interval at 24 weeks (extended interval group). Pessary care included pessary removal and cleaning. Women were followed for 48 weeks. The primary outcome was the incidence of vaginal epithelial abnormalities (types 3 and 4) (i.e., an epithelial break or erosion). Secondary outcomes included rate of all types of vaginal epithelial abnormalities (i.e., epithelial erythema, granulation tissue, epithelial break, or erosion) at 24 and 48 weeks, patient satisfaction, degree of bother due to vaginal discharge, and number of unscheduled visits.

Tam and colleagues (2019) also undertook an RCT to examine the effect of time intervals on the replacement of pessaries (251). Existing users with a vaginal ring pessary for prolapse (stage I-IV) were randomised to either have their pessary replaced at 3 months (3 monthly treatment group) or at 6 months (6 monthly control group). Women in both groups received a pelvic examination and a new pessary was fitted at the baseline appointment. At the second visit, women received a speculum examination, and the pessary was replaced in the 3 monthly treatment group, or the same pessary was re-inserted after cleaning (6 monthly control group). Women in both groups were followed up at 3 and 6 months. The primary outcome was the complication rate – defined as complications arising from the use of vaginal pessary. Women were also asked to score their satisfaction with the use of a vaginal pessary using a visual analogue scale. Secondary outcomes included POP-Q, prolapse symptoms (aware of prolapse, vaginal soreness, dragging sensation, low back pain), urinary symptoms, bowel symptoms and sexual symptoms. The symptom questionnaires used were not reported.

Anglim and team (2020) (243) conducted an RCT to explore women's satisfaction with different models of pessary care, specifically comparing a 3-month follow-up with a 6-month follow-up. New users with a primary diagnosis of prolapse were randomised to receive either a follow-up appointment at three months or to a follow-up appointment at six months. Before taking part in the trial, all women received vaginal oestrogen (tablet or cream) for at least two weeks prior to being fitted with their pessary. The fittings followed standard procedures and a variety of pessaries were used (e.g., ring pessary, Gelhorn, Shaatz and Marland devices). Women were reassessed after two weeks and if the pessary was successful then they were randomised into one of the two trial arms. Follow-up outcomes were the same at both appointments and comprised discussion of pessary expulsion, bladder and bowel complications. The physician removed the pessary and performed a routine examination. The pessary was reinserted if there were no complications and notes made in the management plan. The primary outcome was the score on the Pessary Satisfaction Form at 12 months.

Results

Twenty-four medical residents completed the follow-up assessment at 6 months in the Escobar study (246). The authors reported a small but non-significant improvement within the intervention group, signalling improved retention of clinical skills on the practical assessment. The control group showed no improvement in their practical exam. No data comparing the two groups were reported, but 80% of residents reported that the simulation was a valuable learning experience.

In the Chinthakanan study (245), 60 women were randomised into two groups (30 women in each group). Attrition rate was low for the trial with one woman dropping out of the estriol group, but no reason was provided. No statistically significant difference for any outcomes (POP-Q, duration of pessary use or genitourinary symptoms (foul smell, vaginal discharge, vaginal irritation, abnormal vaginal bleeding), patient satisfaction) was evident between the groups at 4- or 8-weeks follow-up.

Fifty-four post-menopausal women were randomised to receive the topical anaesthetic (EMLA) cream (n=28) or placebo (n=26) in the Taege trial (250). One woman withdrew from the EMLA cream because of vaginal erosion preventing the reinsertion of her pessary. There was no statistically significant difference between the two groups on their baseline or reinsertion pain scores, but women receiving the EMLA cream reported significantly lower pain scores at pessary removal regardless of the experience level of the provider.

Of the 130 women enrolled in the Propst trial (249), 66 were randomised to receive extended interval pessary care (every 24 weeks) and 64 received usual care (every 12 weeks). Nine women discontinued the intervention in the extended arm, and 10 women withdrew from the usual care arm. The rate of type 3 and 4 vaginal epithelial abnormalities met the criterion for noninferiority of extended-interval pessary care. There was no difference in the incidence of vaginal epithelial abnormalities (of any type) between the two groups at any point in the study, with most women in the extended arm reporting that they preferred fewer appointments. Unscheduled visits were reported in both groups (14 women in the usual care group and 12 in the extended group), and usually occurred as a result of need to treat the vaginal epithelial abnormalities.

In the Tam study (251), sixty women were randomly allocated to each arm (30 women in each group). One woman was lost to follow-up in the 3-monthly treatment group. The complication rate, defined as adverse event necessitating discontinuation of the pes-

sary, was not statistically significantly different between groups. No statistically significant differences were evident between groups for patient satisfaction, change in self-reported symptoms or stage of prolapse.

In the EPIC trial, Anglim and team (243) assessed 203 women for eligibility and randomised 20 women; 9 women were allocated to the 3-month follow-up schedule and 11 women to the 6-month follow-up schedule. Three women from the 3-month schedule discontinued the study and 4 women from the 6-month schedule discontinued the study. The trial was stopped early after two years as the trialists did not reach their target sample size (n=70). Women in the 6-month group reported higher dissatisfaction with having to wait too long between visits, although the level of bother was low in both groups. Discomfort occurred more in the 3-month group and UI was common in both groups.

Summary of the evidence from the previous edition

No RCTs were identified.

Summary

Six new studies were included in this comparison:

- Three addressed the length of time between pessary appointments (only one small trial had low ROB, and one was stopped due to very low recruitment) providing some evidence that outcomes for longer follow up intervals are similar to those for shorter intervals. **(Level of evidence: 2)**
- One small unclear ROB trial evaluated pessary fitting training but reported no between group comparisons. **(Level of evidence: 4)**
- One small unclear ROB trial compared vaginal oestrogen plus lactobacillus acidophilus with a vaginal moisturiser found no difference between groups in POP-Q, symptoms, or satisfaction. **(Level of evidence: 2)**
- One small low ROB trial compared an anaesthetic cream with a placebo for pessary changes and found lower pain scores with the anaesthetic cream at pessary removal. **(Level of evidence: 1)**

Recommendations

A longer follow up interval for pessary users (e.g., 24 weeks, or 6 months) compared to a shorter interval (e.g., 12 weeks, or 3 months) could be recommended. **(Grade of recommendation: C New).**

The use of an oestrogen plus lactobacillus acidophilus vaginal tablet could not be recommended as there is no evidence of benefit. **(Grade of recommendation: C New)**

Use of an anaesthetic cream over placebo could be considered to reduce pain on pessary removal. **(Grade of recommendation: C New)**

Table 40. Summary of Pessaries and prolapse studies (Notes: * Key findings as extracted from Bugge et al. (2020) (215))

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes
Anglim (2020) (243)	RCT Pessary maintenance visit at 6 months FU vs pessary maintenance at 3 months FU	20	Women (age >18 yrs) with prolapse who opted for pessary management Canada	Variety of vaginal pessaries – common silicone pessaries incl. covered ring, Gelhorn, Shaatz and Marland. Women with successful pessary fitting were reassessed 1-2 weeks later and then randomised to either a 3- or 6-month FU	Outcomes: At each follow-up, women were asked about the following issues: recurrent pessary expulsion, discomfort, UI, vaginal bleeding, difficulty with defecation, and foul/ heavy discharge. Pessary difficulties (reinsertion, changes in management or discontinuation/withdrawal) was also documented. Pessary satisfaction form Key findings: only able to recruit 20 women, 35% dropped out, high satisfaction and similar between groups, UI was common in both groups 57-67%.	Baseline, 6 months, and 12-month follow-up	Publication: FT Dropouts: After 2 years, recruited 20 women of which 7 dropped out; 3/9 women dropped out of the 3-month FU schedule and 4/11 women dropped out of the 6-month FU group. Of these 2/7 shortened their FU interval and the remaining discontinued pessary usage. AE: bleeding, discharge and abrasion occurred in low numbers for both groups. Unable to reach sample size as most participants did not meet inclusion criteria (recruitment rate of 9.9% and target was 70 women
Baessler (2019) (242)	RCT Vaginal pessary ring vs standard PP care	44	Women 1-3 days after first vaginal birth with stage II prolapse Germany	Vaginal pessary ring (no other details available) Standard care: no interventions for 6 weeks	Outcomes: POP-Q, PUS, Australian Pelvic Floor Questionnaire (German version with validated PP module) Key findings*: Bugge reported no evidence of benefit or harm for any of the following outcomes at 12 months PP: site specific grading of prolapse using POP-Q (anatomical or posterior measurement of prolapse), Bladder problems compared with usual care; cure or improvement of of sexual problems	Baseline, 6 weeks PP and 12 months PP	Publication: AB but additional data presented in updated Cochrane review (218) Dropouts: 3 lost for follow-up in the pessary group and 10 lost for follow up in standard care. Pessary placement not possible in 2 women. Study was stopped early because of slow recruitment and occasional pessary problems AE: Two women reported reduced lochia and 1 reported vaginal pain

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes
Cheung (2016) (244)	RCT PFMT and insertion of a vaginal pessary (pessary group) vs Pelvic floor exercise training (control group)	276	Women with symptomatic stage I to stage III prolapse PRC	Vaginal ring pessary was inserted by a gynaecologist. The largest pessary that was comfortable for the women was used. If the vaginal pessary slipped out, reinsertion of same or next size of vaginal pessary was performed up to three times. A telephone hotline was given for both groups for early consultation if needed. Women in this group also received PFMT (detailed below) PFMT group: standardised PFMT training which included a teaching session within 2 weeks after the first consultation and three individual training sessions at 4, 8, and 16 weeks. Women were advised to practise daily with at least two sets of 8–12 preset exercise repetitions per day, with 8–10 exercises per session at least two times per week.	Outcomes: Primary outcomes: PFDI, PFIQ (Chinese validated versions). Secondary outcomes included distress caused by prolapse symptoms, desired treatment, and any complications Key findings*: Women in the pessary plus PFMT group reported a significant improvement in their prolapse symptoms compared with women who received PFMT alone at both 6 and 12 months on POPDI-6. Women in the pessary plus PFMT had a significantly improved prolapse-specific quality of life compared with women in the PFMT alone group at 12 months based on their POPIQ scores.	Baseline, 6 months, 12 months	Publication: FT and also reported in the updated Cochrane review (218) Dropouts: accounted for. In the pessary group 3 women were lost to follow-up and 1 had cervical cancer at 6 months: Missing data for 3 women at 12 months. In the PFMT alone group, 3 women were lost to follow-up at 6 months, 4 lost to follow up at 12 months and missing data for 2 women at month 12. AE: 56 women in the pessary plus PFMT group failed to retain a pessary, 9/132 had abnormal vaginal bleeding and 6/132 had unusual or bothersome vaginal discharge. Complications reported in the PFMT alone group included: 4/128 women with abnormal vaginal bleeding and 2/128 unusual or bothersome vaginal discharge
Chinthakanan (2019) (245)	RCT Vaginal moisturisers + pessary vs ultra-low dose estriol & Lactobacillus acidophilus vaginal tablets	60	Women able to take care, insert, and remove pessary by herself and did not use local oestrogen or vaginal moisturisers for 3 months Thailand	Estriol group received 1 vaginal tablet (ultra-low dose estriol & Lactobacillus vaginal tablets) daily for 6 days then 2 tablets per week for 8 weeks Moisturisers group received one application every 3 days for 8 weeks.	Outcomes: Primary outcome was patient's satisfaction using Thai-version Patient Global Impression of Improvement (Thai PGI-I). Secondary outcomes were subjective and objective outcomes of vaginal health Key findings: No significant difference between groups at 4 and 8 weeks for any of the following outcomes: age, BMI, POP-Q, duration of pessary used, and genitourinary symptoms. Patient satisfaction on the Thai PGI-I was equally high in both groups at 4 and 8 weeks (93.1% vs. 96.7%, P=0.487 at 4 weeks and 89.7% vs. 93.3%, P=0.484 at 8 weeks)	Baseline, 4 weeks and 8 weeks	Publication: AB Dropouts: one dropout; no reasons given AE: no serious events

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes
Coolen (2018) (254, 268)	RCT Pessary use vs prolapse surgery	6	Women with symptomatic prolapse (stage II or higher) The Netherlands	Pessary treatment (ring or a Falk pessary). Prolapse surgery: vaginal native tissue repair of compartments that affected according to the POP-Q score and required surgery.	Outcomes: Primary endpoint was disease specific quality of life at 12 months follow-up, according to the prolapse domain of the UDI. Key findings: Due to strong patient preference randomisation was not possible and only 6 women were randomised therefore no conclusions can be drawn.	Baseline and 12 months follow FU	Publication: FT, AB but only 6 women were randomized (2 to the pessary group and 4 to the surgery group) and a remaining 107 women took part in the prospective cohort study (72 choose pessary treatment and 35 choose surgery).
Escobar (2017) (246)	Survey and pilot RCT Hands-on teaching model + lecture vs lecture only	25	Resident physicians USA	IG: Hands-on training model using a small-scale size pelvic model to demonstrate proper pessary fitting (sizing and placement) plus lecture CG: received lecture only	Outcomes: Written exam, satisfaction survey Key findings: there was no significant difference between groups on the practical exam (immediately post-intervention) (p=0.66) or after 6 months (p=0.85)	Baseline, immediately post-intervention and 6 months FU	Publication: AB Dropouts: one resident physician dropped out; reasons not reported AE: not described
Meriwether (2016) (247, 271)	RCT Standard pessary care with the use of TrimoSan placed vaginally twice weekly or to standard pessary care without TrimoSan gel	184	Woment who were first time pessary users USA	IG: Hydroxyquinoline-based gel (TrimoSan – a mildly acidic vaginal lubricant) in first time pessary users (TrimoSan group); twice weekly CG: new pessary users not using the gel (standard care)	Outcomes: questionnaires about vaginal symptoms, hormone therapy, bacterial vaginosis (BLUE) test and a vaginal secretion swab Key findings: No significant difference in bacterial vaginosis on Nugent's criteria or on the BLUE testing at 2 weeks or 3 months. The prevalence of at least one vaginal symptom did not differ between groups at two weeks or at three months The TrimoSan group was equally likely to want to continue their pessary use compared with the standard care group at 2 weeks (90% vs 86%, p= 0.64) and 3 months (63% vs 60%, p= 0.76).	Baseline, 2 weeks and 3 months	Publication: FT Dropouts: At the two-week follow-up, 111 women responded (64 in the IG; 47 in the CG); at month 3, 147 women attended for follow-up (73 IG, 74 CG). Reasons for loss to follow-up across the trial included: no FU, partial FU (i.e. attended one visit but not another visit), no Gram stain results (only questionnaires, inadequate Gram stain and two women with unverified data AE: none reported but women were excluded from taking part in the trial if they had a known allergic or suspected adverse reaction to the gel.

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes
Panman (2016) (248, 267)	RCT PFMT vs pessary	162	Menopausal women diagnosed with symptomatic prolapse The Netherlands	PFMT: PFMT supervised by an experienced registered physiotherapist. Training and education; taught how to contract their pelvic floor exercises. Women received feedback about their contractions using digital palpation or myofeedback using electrostimulation if required. All women were taught the knack and there is supplemental material etc which is available online at: http://links.lww.com/MENO/A179 Pessary: trialled a pessary for two weeks (ring pessary). A refit was offered using different types of pessaries as required: a ring with support followed by a Gellhorn or Shaatz pessary. Women were offered a maximum of three refits. The pessary intervention was provided by one of four trained research physicians who had been trained by an experienced urogynaecologist.	Outcomes: primary outcome measure was PFDI-20 at 24 months. Secondary outcomes included prolapse, urinary, and anorectal symptoms; quality of life; costs; sexual functioning; prolapse stage; PFM function; and participants' perceived symptom improvement Key findings*: Bugge reported no significant difference between groups on the PFDI-20 or POPDI-6 scores at 12 or 24 months. The number of women self-reporting an improvement in symptoms was also not significantly different between groups at 12 or 24 months. There was also no significant difference on PQoL measures between the groups at 12 or 24-month follow-up.	Baseline, 3, 12 and 24 months after starting PFMT or having a successful pessary fitting	Publication: FT and also reported in the updated Cochrane review (218) Dropouts: 4/80 women in the PFMT group did not attend any PFMT appointments and another 10 discontinued; pessary fitting was successful in 47/82 women; 34 women did not receive pessary treatment mostly due to an unsuccessful fitting. AE: none in the PFMT group; 21/35 women in the pessary group reported one or more side effects at 24 months. These were: increased vaginal discharge in 14 women, increased UI in 10 women, and irritation/ erosions of the vaginal wall in 10 women.
Propst (2018) (249)	RCT Extended pessary care vs routine pessary care	130	Women who were existing pessary users who used the pessary to treat prolapse, UI or both USA	Routine pessary care (appointment scheduled at 12 weeks) Extended pessary care (appointment extended to 24 weeks) Pessary care in both groups included pessary removal and cleaning	Outcomes: primary outcome was incidence of vaginal epithelial abnormalities. Secondary outcomes included rates of vaginal epithelial abnormalities, patient satisfaction, degree of bother due to vaginal discharge, number of unscheduled visits Key findings: rate of epithelial was not significantly different between the two groups: 1.7% in the extended arm and 7.4% in the routine pessary group, which met the criteria for noninferiority. There was no difference in the rates of vaginal epithelial abnormalities between the groups at any time.	Baseline, and follow-up to 48 weeks	Publication: FT Dropouts: 9/66 women discontinued the intervention in the extended arm; 10/64 withdrew from the routine pessary arm. AE: none reported other than the epithelial abnormalities that were described.

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes
Taege (2017) (250)	RCT Application of anaesthetic cream at time of pessary change vs placebo cream at time of pessary change	54	Postmenopausal women who were existing pessary users USA	IG: 4g topical EMLA cream applied at the time of pessary change on patient discomfort. CG: placebo cream of equal volume applied	Outcomes: satisfaction score for pessary use and a VAS pain score. Physicians were also asked to mark their perception of women's pain using the same VAS score. Key findings: women in the EMLA cream group had significantly lower pain at pessary removal when compared with those assigned to placebo (p=0.015)	Baseline (immediately before pessary change) and immediately post-intervention	Publication: FT Dropouts: one woman dropped out from the EMLA group as she had issues with vaginal erosion which prevented reinsertion of the pessary AE: none reported and no issues with irritation
Tam (2019) (251)	RCT Pessary replacement at 3 months vs pessary replacement at 6 months	60	Women with stage I-IV prolapse using vaginal ring pessary Hong Kong, PRC	Vaginal ring pessary was replaced at either 3 or 6 months.	Outcomes: Primary outcome was complication rates as a result of using the pessary. Other outcomes included satisfaction with the pessary, change in self-reported symptoms, change in prolapse stage. Key findings: higher complication rate in the 6-monthly group than the 3-monthly group at month 9 but not statistically significant (p = 0.061). No statistically significant differences between groups in patient satisfaction scores, other prolapse-related symptoms or staging of prolapse.	Baseline and FU at 3 and 6 months	Publication: FT Dropouts: accounted for. One woman lost to FU in the 3-month FU group. AE or unintended events: no harms or unintended effects in each group
Tontivuthikul (2016) (252)	RCT Local oestrogen cream vs discontinued oestrogen cream	40	Postmenopausal women with prolapse who had successfully used a pessary for 6 weeks and who were using vaginal conjugated equine oestrogen cream Thailand	During the first six weeks, women were advised to remove their pessary every evening and reinsert in the morning. Women were then randomised: IG: continuing to use the oestrogen cream (0.5 g) once a week CG: asked to discontinue (control group) for 24 weeks.	Outcomes: primary outcome was a vaginal health assessment which included a vaginal symptom score, vaginal pH, and vaginal maturation. Secondary outcomes comprised difficulty in using the pessary and endometrial thickness Key findings: no statistically significant differences between groups for all vaginal health assessment at 12- and 24-weeks post-intervention. There was also no significant difference between groups about the difficulty to insert and remove the pessary or the endometrial thickness.	Baseline, 12 and 24 weeks	Publication: FT Dropouts: none AE: one woman in the CG with vaginal ulcer which resolved with treatment

Author, year	Study design/ Comparator	N	Study population / Country	Modality details or parameters	Outcomes / Key findings	Data collection and follow up time-points	Notes
Ziv (2019) (253, 269, 270)	Cross-over RCT Effect of a new disposable vaginal device for prolapse vs CARP	58	Limited detail. Pre-treatment POP-Q stages included 49 cases (32.2%) of stage I prolapse, 101 cases (66.4%) with stage II, and 2 cases (1.3%) with stage II prolapse. Israel / USA	IG: ND inserted for up to 7 days. Allowed to use as many devices as they wish (1-7 days) CG: CARP remained in situ for whole usage phase. First usage phase of 30±2 days began after a 14-16-day washout period. Followed by another 14-16-day washout period and then a second usage cross-over phase, where each group used the alternate device also for 30±2 days.	Outcomes: Vaginal swabs and cultures for microfora analysis. Women completed a daily diary, documenting length of use, functionality and AE. Key findings: While using the ND, 139 cases (95.3%) had complete reduction of their prolapse (stage 0), 5 cases (3.4%) had stage I prolapse, and 2 cases (1.3%) had stage II prolapse. In 98.7% of the cases prolapse during device usage was of either stage 0 or II. Low prevalence for SA. Following usage, 7 ND users (12%) and 5 CARP users (8.6%) had various SA counts detected in the vagina. Rate of fluctuation in SA counts (increase/decrease) while using either device was 13.8% (8/58).	Baseline, after first FU phase and after second FU phase	Publication: AB Dropouts: Unclear; 58 women completed the study per-protocol, using both vaginal devices AE: No vaginal infections, bothersome vaginal symptoms, or urinary infections in the ND group. In the CARP group there was one case of overt vaginal infection, two cases of UTI, and 2 cases of bothersome vaginal complaints.

Abbreviations: AB: abstract; AE: adverse events; CARP: commercially available ring pessary; CG: control group; CRADI-8: Colorectal-Anal Distress Inventory; CRAIQ-7: Colorectal-Anal Impact Questionnaire; EMLA: eutectic mixture of lidocaine 2.5% and prilocaine 2.5 %; FI: faecal incontinence; FT: full-text; FU: follow-up; IG: intervention group; IIQ-7: Incontinence Impact Questionnaire; ND: new vaginal device; NR: not reported; PA: physical activity; PFD: pelvic floor disease; PFDI-20: Pelvic Floor Distress Inventory; PFH: pelvic floor health; PFIQ-7: Pelvic Floor Impact Questionnaire; PFM: pelvic floor muscle; PFMT: pelvic floor muscle therapy; PGI-I: Patient Global Impression of Improvement-Incontinence; PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire; POP: pelvic organ prolapse; POPDI-6: Pelvic Organ Prolapse Distress Inventory; POPIQ-7: Pelvic Organ Prolapse Impact Questionnaire; PP: postpartum; PRC: Peoples Republic of China; PUS: perineal ultrasound; QoL: quality of life; RCT: Randomised controlled trial; SA: Staphylococcus aureus; UDI-6: Urinary Distress Inventory; UI: urinary incontinence; UTI: urinary infection; VAS: visual analogue scale.

4. SUMMARY CONSERVATIVE MANAGEMENT FOR POP

4.1. Educational and lifestyle intervention

Prevention

- Improving pelvic floor knowledge in healthy women could be recommended as it may reduce PFD symptoms **(Grade of recommendation: C New)**
- An enhanced educational intervention may be recommended to improve healthy women's knowledge of their pelvic floor. **(Grade of recommendation: D New)**
- A weight loss programme in overweight women with UI could be considered for improved prolapse symptoms and severity. **(Grade of recommendation: C New)**

Treatment

Liberal post-operative instructions could be recommended rather that restricted activities for reducing post-operative prolapse symptoms. **(Grade of recommendation: C New)**

4.2. Physical Interventions

Prevention

Antenatal PFMT cannot be routinely offered for prevention of postnatal prolapse**. (Grade of Recommendation: B)**

Postnatal PFMT +/- EStim could be recommended as beneficial in preventing prolapse in women in the post-partum period. (**Grade of recommendation: C New)**

Treatment

PFMT can be offered to women with symptomatic prolapse as this is associated with a reduction in prolapse symptoms and pelvic floor symptoms. (**Grade of recommendation: B)**

PFMT plus biofeedback may be recommended as this combination improves prolapse symptoms and pelvic floor symptoms compared with standard care**. (Grade of recommendation: C New)**

PFMT plus biofeedback does not offer benefit compared to PFMT alone for treatment of prolapse and may not be routinely recommended**. (Grade of recommendation: D New)**

An educational session including lifestyle and PFMT instruction may be considered as it appears to offer benefits over verbal PFMT instruction alone when treating prolapse. **(Grade of recommendation: D New)**

Postural exercises in addition to PFMT may be considered as they offer benefit over PFMT alone in treating prolapse. **(Grade of recommendation: D New)**

Adding a physical intervention to prolapse surgery, pre-, peri- or post-operatively did not improve prolapse symptoms or severity and cannot be recommended routinely. **(Grade of recommendation: B New)**

4.3. Pessary interventions

Prevention

Vaginal ring pessary cannot be recommended in women early after delivery to prevent or improve prolapse. (**Grade of recommendation: B)**

Treatment

Pessary and PFMT could both be recommended as treatment for prolapse, but cost and adverse events need to be taken into consideration. **(Grade of recommendation: C New)**

The combined use of a vaginal pessary plus PFMT, rather than PFMT alone, can be recommended for treatment of prolapse. **(Grade of recommendation: B New)**

A longer follow up interval for pessary users (e.g., 24 weeks, or 6 months) compared to a shorter interval (e.g., 12 weeks, or 3 months) could be recommended. **(Grade of recommendation: C New).**

The use of an oestrogen plus lactobacillus acidophilus vaginal tablet could not be recommended routinely as there is no evidence of benefit. **(Grade of recommendation: C New)**

Use of an anaesthetic cream over placebo could be considered to reduce pain on pessary removal. **(Grade of recommendation: C New)**

IV. URINARY INCONTINENCE IN MEN

UI in men remains under-reported and under-studied in comparison to studies in women. Pooled prevalence of UI in community-based men ranges from 4.81-32.17% (276). UI and other LUTS in men increase with age, with variations in prevalence rates reflecting different study populations, definitions of incontinence and methods (277). Despite the prevalence of UI and LUTS in older men, the aspect which continues to receive the most consideration with respect to conservative management is post-prostatectomy UI after radical prostatectomy (RP).

1. LIFESTYLE MODIFICATION INTERVENTIONS

Lifestyle recommendations are part of the primary care approach to prevention of chronic disease. Smoking cessation, healthy eating and weight loss, and caffeine and alcohol reduction are intended to be preventative in the onset of diabetes, obesity and cardiovascular disease. Little attention is placed on prevention of UI in men and few new trials were found to add to this edition.

1.1. Weight loss by obese or overweight Men

No new trials were found on weight loss.

1.2. Smoking

No new trials were found on smoking cessation in men.

1.3. Dietary modification in men

There were no RCT assessing impact of diet for preventing the development or worsening of LUTS in men. Four longitudinal cohort studies were identified that provided some evidence of the impact of diet on LUTS and UI scores (278-281). For more details, see Table 41.

Bauer *et al.* (278) followed 2,960 men diagnosed with non-metastatic prostate cancer for a median of 8.3 years with validated dietary questionnaires and the Expanded Prostate Cancer Index Composite SF domain (EPIC-SF), every four years to evaluate the impact diet has on urinary scores. They found that the Mediterranean Diet Score and other individual score components or dietary fat subtypes were not associated with UI scores. However, higher vegetable intake was associated with modestly higher UI scores (indicative of better urinary function) (P-trend=0.003). Conversely, men who consumed more monosaturated and polysaturated fats had worse urinary function with lower UI scores (P-trend=0.04) especially on the irritation/obstruction sub scores.

In a study examining the association between vitamin C intake and LUTS, 1,100 men aged 30-79 were randomly selected to take part in a larger study including 3,201 women (279). The authors found that men with a higher vitamin C intake at follow-up had lower scores on the American Urological Association (AUA) Symptom Index, with voiding and storage sub scores ranging from 0.6 to 2.0 points lower, compared to men with inadequate vitamin C intake (P<0.05).

Holton *et al.* (280) evaluated a subgroup of 1,670 men from an initial cohort of 5,994 men aged 67-100. This subgroup included men without severe LUTS at baseline and no prostate cancer diagnosis, who did not receive treatment for LUTS during the study. The study compared the dietary antioxidant intake of these men, some of whom developed LUTS while others did not. The authors found no significant association between antioxidant intake and LUTS progression or remission over seven years.

Fruit and vegetable intake was correlated with LUTS in a four-year study of 1,564 men by Liu (2016) (281). Using the international prostate scoring system (IPSS), they found that men over age 65 who had a higher intake of fruit and vegetables, had significantly reduced LUTS when compared to those who did not. The difference was stronger in those who ate more dark, green leafy vegetables (p= 0.006). Development of benign prostatic hyperplasia (BPH) and progression of LUTS was also lower in this group.

Summary

There is some evidence that dietary factors such as dark green leafy vegetables and vitamin C may reduce LUTS and incontinence prevalence. **(Level of evidence: 3)**

Recommendations

Weight loss: Weight loss through lifestyle changes can be recommended to obese and overweight men with UI, particularly those with type 2 diabetes. **(Grade of recommendation: B)**

Smoking abstinence could be recommended for men with UI. **(Grade of recommendation: C)**

A reduction in caffeine intake could be recommended for men with incontinence symptoms; evidence suggests that the equivalent of two cups of coffee per day (250mg) is associated with UI in men. **(Level of evidence 3: Grade of recommendation: C)**

High vegetable, fruit and vitamin C intake could be recommended to men in the primary and secondary prevention of LUTS, UI and BPH. **(Grade of recommendation: C New)**

Larger RCTs are needed to assess effect of lifestyle modification interventions on the prevention of incontinence and LUTS in men.

Table 41. Table of included studies of lifestyle interventions for UI in men

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Bauer (2018) (278)	Cohort	2960	Men diagnosed with non-metastatic prostate cancer	Participants after diagnosis of prostate cancer were assessed by the usual consumption of food items and supplements. Based on intake of specific food items the participants were categorized by the Mediterranean Diet Score, as follow: 0-3: low n=1039 4-5: moderate n=1015 6-9: high n=906	Mediterranean Diet Score and other individual score components or dietary fat subtypes were not associated with UI scores. However, higher vegetable intake was associated with lower rates of self-reported UI.	26 years	Adverse events: NR
Curto (2015) (279)	Cohort	1100	Participants from Boston area between 30-79 years old and balanced in number of Hispanic, black and non-Hispanic white race/ethnicity* *Data stratified for men and women	Using a food frequency questionnaire, dietary and supplemental vitamin C intake was assessed.	AUA Symptom Index (AUASI) to evaluate LUTS showed significant associations were found between dietary and supplemental vitamin C and progression of total LUTS or voiding symptoms.	5 years	Adverse events: NR
Holton (2016) (280)	Cohort	1670	Community-dwelling men aged 65-100 enrolled from US sites with no history of prostate cancer and treatment for LUTS	Participants were assessed using 69-item block food frequency questionnaire for dietary antioxidants intake (vitamin C, vitamin E, β-carotene, α-carotene, β-cryptoxanthin, lycopene, lutein/zeaxanthin) and analysis were stratified by LUTS symptoms at baseline as follow: Mild: n=1193 Moderate: n=477	AUA Symptom Index (AUASI) to evaluate LUTS showed that none of the dietary antioxidants was associated with a lower probability of LUTS progression or remission.	6.9 ±0.4 years	Adverse events: NR

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Liu (2016) (281)	Cohort	1564	Men aged 65 years and older who were able to walk independently were recruited on voluntary basis from local community of Hong Kong	Using a 289-item validated semi-quantitative food frequency questionnaire the dietary intake was assessed. The participants were categorized according to the fruits or vegetable intake, as follow: low moderate high	LUTS symptoms were assessed using IPSS. Compared to moderate group, high levels of fruits and vegetables intake significantly reduced LUTS symptoms, especially high intake of fruits, vegetables, dark and leafy vegetables. Associations of fruits and vegetables intake and progression of LUTS showed that compared to moderate group, high intake of dark and leafy vegetables reduced the risk of LUTS progression. Total FV consumption was not significantly associated with the overall LUTS progression.	4 years	Adverse events: NR

Abbreviations: UI: urinary incontinence; NR: not reported; AUA: American Urological Association; LUTS: lower urinary tract symptoms.

2. PELVIC FLOOR MUSCLE TRAINING

Post Prostatectomy Incontinence (PPI) is still the main focus of studies on PFMT for the management of UI in men. Different PFMT protocols are being assessed, and PFMT has been compared to other modalities including Pilates and EStim. Heterogeneity and varying outcome measures affected the ability to compare trial findings. More detail needs to be included on the specifics of PFMT exercise prescription and protocol (282) (283). Due to the changes in the types of trials being undertaken, the format of this section has changed slightly from previous editions. Studies have been separated into eight groups of interventions:

2.1. Pre- and peri-operative PFMT for management of PPI

2.2. Pre and post radical prostatectomy PFMT for management of PPI

2.3. PFMT for management of PPI compared to other modalities

2.4. PFMT compared to or plus alternative interventions for management of PPI

2.5. TURP (transurethral resection of the prostate)

2.6. PFMT for management of UI after radiation therapy

2.7. PFMT effect on erectile dysfunction and climacturia

2.8. PFMT for Other LUTS

A total of 28 new RCTs were found that assessed PFMT as a standalone treatment or combined with other conservative treatments to manage PPI. These were added to the 58 studies from the previous ICI reports (2). Twenty-two of the trials involved men pre or post RP (N=2,065 randomised), one trial involved men post TURP (N=72 randomised), two trials assessed PFMT after radiation therapy (N=227 randomised) and one used PFMT to manage climacturia and erectile dysfunction (ED) (N=33). Studies were of varying quality and blinding of participants to group allocation was not possible. Recommendations are found at the end of each section.

2.1. Pre- and peri-operative PFMT for management of PPI

Only two new trials were found assessing the effect of pre-operative PFMT (284, 285), and one trial examined the effect of starting PFMT while the catheter was still in place (286). These trials were added to the five previously included trials. The two pre-operative trials looked at the type of PFM training done. Sayner (2019) (abstract only) compared functional PFMT (n=15) twice daily to standard PFMT (n=15) three times daily. There was no description of the difference between a PFMT programme and a functional PFMT programme, other than that the latter had functional integration of the PFM (285). The main outcome measure was the ICIQ-SF measures at four, 12 and 26 weeks post-operatively. Santa Mina compared a prehabilitation programme (n=44) to usual care (n=42). Prehabilitation consisted of whole-body exercise plus PFMT, while the usual care group were given a written manual with PFMT to be completed before surgery. Whole body exercise was described as home-based moderate-intensity exercise prior to surgery (60 minutes, 3-4 days week plus daily PFMT preoperatively). The primary outcomes were the FACG and IPSS measured pre-operatively, at four,12 and 26 weeks (284). Filocamo (286) (abstract only) compared starting PFMT on day three post-operatively while the catheter was still in place (n=20) to a group who started after the catheter was removed on day 10 (n=19). Outcome measures were a bladder diary, QoL and ICIQ-male scores, and a 24-hour pad test at one, three, six, nine and 12 months. The primary outcome was no pad use and negative 24-hour pad test.

There was no indication of what PFMT consisted other than tightening around the catheter with the PFMs (286). In this chapter, we report on UI cure, improvement, symptoms and QoL, and if these outcomes were not available, the pad test.

Quality of the data
Sayner (285) described an un-blinded prospective, single-centre, pilot randomised controlled trial. Allocation concealment and ITT analysis was not reported. There were six participants lost to follow-up (three in each group). The study by Santa Mina (284) did not mention concealment of allocation nor of any blinding. The author acknowledged that this trial was not powered to reliability to detect between group differences. Filocamo and colleagues (286) used a randomised approach but no information was provided on sample size analysis or *post-hoc* power analyses. There were four dropouts (two in each group) due to post-operative complications.

Results
Sayner and colleagues (285) reported no adverse events and the ICIQ-SF showed a statistically significant difference in favour of the functional PFMT group at 26 weeks (mean difference: 3.67, p=0.02). Santa Mina (284) described good participation in this trial and general outcomes were improved in the prehabilitation group, but there was no statistically significant difference in outcome between groups. Twenty-nine percent of participants were lost to follow-up and there were five non-serious adverse events related to the general exercise programme: self-resolving haematuria (n=1), self-resolving atrial fibrillation while jogging during home-based exercise (n=1), leg pain (n=1), aggravation of lower arm muscle strain/lateral epicondylitis (n=1). In Filocamo's study (286), 4/18 (22%) participants in the PFMT group with the catheter *in situ* were completely continent at one month, 11/18 (61%) were continent at 3 months, 15/18 (83%) at six and nine months, and 16/18 (89%) at 12 months. In the group starting PFMT after the catheter was removed, 2/17 (11%) participants were completely continent at one month, 4/17 (23%) at three months, 7/17 (41%) at six months, 8/17 (47%) at nine months and 14/17 (82%) at 12 months. The difference was statistically significant at three, six and nine months but not at one and 12 months. Continence was attained earlier if PFMT was started earlier, but the effect wore off at 12 months.

Summary

When participants start PFMT before surgery, they become continent more quickly than when they start after surgery. Men attain continence up to three months earlier, but at 12 months, this difference is no longer apparent. **(Level of Evidence: 2)**

The new studies have the same issues as previously stated. They are small, vary in design and quality and have different outcome measures. Research is needed to clarify if early attainment of continence is economically viable and psychologically necessary.

Recommendation

Pre-operative instruction in PFMT can be recommended to facilitate earlier recovery of continence in men undergoing RP. **(Grade of recommendation: B)**

2.2. Pre and post radical prostatectomy PFMT for management of PPI

Five new trials were added to the existing nine which examined PFMT starting preoperatively and continuing post operatively for the management of post prostatectomy incontinence. Bassi (287) (abstract only) looked at pre and post PFMT (n=22) versus usual care (n=14), without giving any detail on training protocol. They used a 24-hour pad test, the ICIQ-UI SF, SF 36; IPSS and International Index of Erectile Function (IIEF-5), which were measured at baseline (pre-op) and at four, 12 and 26 weeks postoperatively. De Lira *et al*. (288) evaluated a protocol in an RCT after open RP. Looking at a usual care control group (n=15) versus treatment group (n=16) consisting of PFMT given over two physiotherapist-guided pre-operative sessions, which continued after surgery. PFMT took place three times per day with increasing intensity. The outcome measures were IIEF-5 and ICIQ-SF at baseline and three months post-surgery. Jalalina and colleagues (289) aimed to determine the effect of three months of PFM strengthening exercises on UI and QoL in participants after a suprapubic prostatectomy. Participants were asked to perform up to 100 PFM contractions per day. There were few details about the PFMT programme other than it was done in various positions and was prescriptive rather than individualised. The paper does not describe what the control group did. Outcome measures were ICIQ-UI SF and I-QOL obtained on admission, on day two post-operatively, and at seven days, and at two and three months. Participants kept a record of the frequency of exercises, and researchers phoned daily to increase motivation.

Millios (290) compared usual care (n=47) consisting of PFMT versus a high-intensity training routine. A very detailed protocol was described in this study. Usual care instructions were delivered by a physiotherapist pre-operatively in two 30-minute sessions, which encouraged three sets of daily PFMT consisting of 10 contractions of 10 second hold (30 per day) in different positions: supine, sitting and standing. The high-intensity PFMT group (n=50) were taught to do six sets, including 10 fast contractions and 10 slow contractions while standing only (120 per day). All received written and verbal instructions to "stop the flow of urine and shorten the penis while continuing to breathe". After surgery, all participants were followed-up every two weeks by a physiotherapist for the duration of the study. The primary outcome measure was pad weight measured at two, six and 12 weeks. Sayilan (291) studied the effect of post-robotic prostatectomy incontinence pelvic floor exercises (n=30) versus no exercises (n=30). The control group was given breathing exercises and had the opportunity to ask questions about the surgery. For the treatment group, training started one week before surgery with a PFMT programme and general physical activity. There were few details on the programme, which included supervised physiotherapy starting one week before surgery. The training then took place on the day of surgery, one and two days after surgery, as well as on the day the catheter was removed. Participants also participated in an unsupervised functional training programme, which included feedback with verbal and tactile pointers with transabdominal real-time ultrasound measures at baseline, and at one, three, and six months. Outcome measures were the ICIQ-SF, indwelling catheter (IDC), pad use, with the primary outcome being self-reported continence at six months using the ICIQ-UI.

Quality of the data
The study by Bassi was a small pilot study, which was reported only in abstract form. Recruited men were randomised, but blinding, allocation, ITT and loss to follow-up were not described (287). De Lira used computer-generated randomisation, the assessors were blinded, and there was no loss to follow-up. A small sample size (n=31) reduced the generalisability of this study (288). In a study with a larger sample size, Jalalina *et al*. recruited 60 men from a convenience sample and randomly allocated them to treatment or control groups. Four participants dropped out per group but there was no ITT analysis nor any mention of sample size analysis or *post-*

hoc power analysis. Millios (290) used a minimisation approach to randomisation. The study performed sample size calculations, and loss to follow-up included three participants in usual care and one in the high intensity group, but there was no ITT analysis. Lastly, Sayilan (2018) used randomisation and had detailed sample size calculations with no loss to follow-up, but did not describe blinding, allocation concealment, or ITT, risking bias in the study (291).

Results

The newer studies continue to report variable results. Some studies reported no differences in UI or the ICIQ-SF at three months and concluded that PFMT taught pre-operatively was not useful compared to usual care (287, 288). Three studies (289-291) found that there were significant differences favouring the PFMT group and there were improvements in UI at all time points. The study by Jalanina found statistically significant differences at one, two and three months on both the ICIQ-UI SF and I-QOL in favour of the PFMT group (289). Milios (290) found that high-intensity PFMT improved results and more men were continent at all time points compared to usual care (two weeks: 14% versus 4%, 6/52; six weeks: 32% versus 11%, 12/52; 12 weeks: 74% versus 43%). The weight of the 24-hour pad showed similar statistically significant results. Sayilan reported statistically significantly fewer pads used by the PFMT group at one and six months, and higher incontinence scores on the ICIQ-SF in the control group at three and six months (291).

Summary

There were five new trials added to the previous nine examining a variety of pre- and post-operative PFM training. Most new studies started pre-operatively and continued post operatively, and were compared to usual care. Different regimes of training were assessed and there was a wide variety of outcome measures used (287-291). There is significant heterogeneity in the protocols on how PFMT is taught to men and about the effectiveness of PFMT for post-prostatectomy incontinence. Many studies did not provide a detailed description on how the exercises were taught, and how they progressed or were assessed.

As in previous consultations, these trials found that short- to medium-term benefits to continence as reported in pad tests and self-reported symptoms. None of the new trials reported differences between groups at or after 12 months. Starting PFMT before, or shortly after, surgery continues to be supported if the aim is to attain continence earlier. Studies had small sample sizes, inconsistent outcome measures and varied in method and quality. Discussion is needed on the significance of an earlier return to continence, including benefits for QoL, which has not been studied.

Many studies did not describe the type of PFMT programmes that were studied, and the majority focused on training posterior PFMs (with cues to retain gas). The largest study in this section (290) focused on the anterior PFM and showed that using PFMT produced significant improvement at all time points. Most of the studies included in this update, and previous consultations, assessed or trained the pelvic floor of men via the anus. Prostatectomy destroys the smooth muscle of the prostatic urethra and possibly causes damage to the extrinsic urethral sphincter (292). Assessing the PFM anally or applying strength training protocols to the posterior PFM may not target the muscles that cause post-prostatectomy incontinence as much as a more anterior PFM protocol (cues to stop the flow of urine and shorten the penis) (282). A recent meta-analysis comparing protocols, favouring posterior pelvic floor versus anterior PFM, show that the risk of incontinence is reduced at three months (RR 0.85, 95% CI 0.75 to 0.95) when an anterior PFM approach is used (293). A large randomised clinical trial assessing personalised PFMT programmes is currently underway (294).

Recommendation

Early PFMT either pre-operatively or early post-operatively can be recommended to reduce time to continence after surgery. **(Grade of recommendation: B)**

2.3. PFMT for management of PPI compared to other modalities

2.3.1. PFMT plus or minus PFMT with EStim after radical prostatectomy

Three new trials (295-297) were added to the 11 previously included in this section. Full papers for two of the abstracts reported are available in the previous ICI edition (298, 299). Studies had heterogenous samples. Two studies had three arms: EStim, PFMT and Pilates (295, 299). The data discussed here compare EStim to control treatments. Studies assessing Pilates versus control or PFMT will be discussed in Section IV.2.3.3.

Gomes' 2018 (295) study compared PFMT with anal EStim (n=38) to a group undergoing anal EStim only (n=36) over a 10-week period. Outcome measures included the ICIQ-SF and pad tests, measured at baseline and after four months. Pedrali (299) compared PFMT combined with EStim versus no treatment. The first group (n=31) received 10 weekly individualised PFMT sessions with EStim and a home PFMT programme. The second group (n=31) had no treatment. Outcome measures were pad weight and use and the ICIQ-SF, which were measured at baseline (four weeks post-operatively) and repeated after four months.

Gonzales (296) recruited men to receive physiotherapy consisting of EStim and biofeedback, three days per week for three months (n=30), while the control group (n=30) received no specific treatment. Both groups received a printed guide about PFM exercises. Pad tests and the ICIQ-SF were measured at one, two, three and six months. Laurienzo (298) recruited men who were still incontinent one month after a RP. Three groups were used to assess the effect of EStim and PFMT combined with home exercises (n=42) versus PFMT with three specific exercises (n= 41), versus a control group (n=40), who were given usual post-operative information. Follow-ups assessed the 1-hour pad test, PFM strength, ICIQ-SF and IPSS and took place pre-operatively and after one, three and six months. Wang (297) (abstract only) looked at the efficacy of electrical pudendal nerve stimulation (EPNS) (n=64) versus PFMT with biofeedback and trans anal EStim (n=32). The EPNS group received 60 minutes of stimulation three times per week for eight weeks via long needles inserted near the pudendal nerve. The main outcome measure was the ICIQ-UI SF and secondary measures were pad use and leakage.

Quality of the data

Gomes (2018) (295) developed a study with careful attention to risks of bias, which were reduced with randomisation, allocation concealment and blinding. Four participants were lost to follow-up (three in the EStim group, one in the control group) and ITT analysis was not mentioned. Pedrali's study failed to discuss blinding of participants and ITT analysis. Three participants dropped out of the EStim group, two due to non-attendance and one due to discomfort

caused by the treatment (299). There were no control group dropouts. Gonzales' (2020) (296) study was well powered, but there was no ITT analysis and a dropout rate of 13/60 (five in the electrotherapy group, eight in the control). There was no blinding, concealment of allocation and randomisation was not described. In the Laurienzo trial (2018) (298), participants were blinded and randomised by computer, but ITT was not discussed. Only three participants dropped out per group in this otherwise high-quality study. The study by Wang (2018) had low ROB due to randomisation, blinding of assessors and ITT analysis. Allocation concealment was not discussed. Loss to follow-up was zero (297).

Results

Gomes *et al.* found statistically significant differences in the reduction of the number of pads used between groups (Group 2: 0.77±1v Group 3: 1.48±1.31) and the number of men who achieved continence between the treatment and no treatment groups (Group 2: 67.4±131.88 versus Group 3: 72.88±97.28 p=0.01) (295) favouring the PFMT plus EStim group. Gonzales *et al.* reported statistically significant differences in favour of the EStim and biofeedback group in the one-hour pad test with 64% recovering continence compared to 9%. Wang (297) found no difference between groups for the ICIQ-SF and leakage frequency (p=0.68). However, there was a statistically significant difference comparing baseline to study end within groups (p<0.05). The other two trials reported no benefit of PFMT with EStim compared to no treatment (298, 299), or of EStim compared to PFMT (298). Laurienzo concluded that there was no benefit of adding EStim to PFMT as there were no differences for the one-hour pad test or the QoL score between groups at any time points. However, within group changes were significant over time. Pedrali, similarly found no significant differences in pad weight or use, and ICIQ-SF scores between the EStim and control groups (299).

Summary

The use of EStim with or without PFMT is better than no treatment, but there is no benefit in adding EStim to other types of treatments. **(Level of evidence: 2)**

Recommendation

Adding EStim to a PFMT programme for men with persistent PPI cannot be routinely offered. **(Grade of recommendation: B)**

2.3.2. PFMT with biofeedback after radical prostatectomy

Three new trials were found assessing biofeedback after RP and added to the six previously included trials (300-302). All trials used anal probes to provide the biofeedback. Oh (2020) (300) investigated the effect of a novel biofeedback device for training PFMs. The biofeedback device has a pressure sensor under the perineum and anus that reportedly provides biofeedback to the pelvic floor, which helps strengthen the muscles. There was no description of the PFMT programme that was used, and there was no mention of verifying that participants were able to perform a correct PFM contraction. The intervention group (n=42) used the device with verbal and written instructions on PFMT, and the control group (n=42) received only the verbal and written instructions. Outcome measures were the 24-hour pad test, IPSS and IIEF-5 measured one, two and three months after surgery. Santos (2017) (301) recruited participants up to three months after surgery and compared PFMT to PFMT with biofeedback. This study aimed to assess the impact of adding anal biofeedback (n=8) to PFMT (n=8) using a one-hour pad test. Continence was deemed to be achieved if urine leakage was less than 2g, which was measured at baseline, and after five and nine weeks. Lin (302) compared the effect of PFMT with biofeedback (n=44) to no treatment (n=31) for six months. PFMT was done four times per day, where participants performed 20 PFM contractions and relaxations per session with the aid of a DVD and pamphlet. Biofeedback was provided via an anal probe. The main outcome measure was the one-hour pad test.

Quality of the data

In the study by Oh, randomisation, ITT and loss to follow-up were all detailed. Blinding and concealment of allocation was not described (300). Two participants dropped out from the biofeedback group. In the study by Santos *et al.,* there were no details on randomisation, concealment of allocation or blinding (301). Three participants were excluded due to post-operative complications (two from the intervention group and one from the control group). ITT was not discussed. Lin (302) conducted a quasi-experimental trial with no indication of how participants were randomised. Five were lost to follow-up in the biofeedback group and three in the control group. Blinding, allocation concealment and ITT analysis were not discussed.

Results

Oh (2020) found no statistically significant differences between groups, except in the one-month IPSS scores favouring the biofeedback group (p=0.028) (300). By the end of the study 27 (67.5%) participants in the biofeedback group and 26 (61.9%) participants in the control group achieved continence. In the study by Santos (301), 69% (n=9) of participants attained continence with the other four participants still reporting mild UI. While both groups showed significant improvement, there were no statistically significant differences between groups. Lin (302) also found a reduction in leakage in the second and third months in both groups. There was statisticaly significantly less leakage on the one-hour pad test in the PFMT with biofeedback group for both the two- and three-month follow-ups (two-month PFMT group: 27.68±51.84, control group: 79.44±71.94, three-month PFMT group: 9.27±25.23 control group: 27.11±40.88).

Summary

The three new trials and the six previously reported trials show that adding anal biofeedback to PFMT does not significantly improve outcomes, regardless of the type of biofeedback used. **(Level of evidence: 2)**

Recommendations

The addition of biofeedback to a PFMT programme cannot be routinely offered to men with persistent post-prostatectomy incontinence as it does not seem to add any clear benefit. However, biofeedback may be considered for subgroups of men presenting reduced proprioception **(Grade of recommendation: B)**

PFMT plus or minus Pilates

There were three trials that assessed the effect of Pilates (295, 299, 303): Two were three-armed trials assessing PFMT versus Pilates versus EStim (295, 299). Data on EStim have been separated and are reported in section IV.2.3.1. Au (303) conducted a feasibility RCT to study Pilates combined with PFM exercises and hypopressive exercises (n=25) versus PFM exercises (n=25) alone. 'Pelvic Floor Pilates' employed synergistic contractions of the pelvic floor

with the core. Outcome measures included a 24-hour pad test, QoL score and IPSS measured before surgery and after two, six, 12 and 26 weeks. Pedrali (2016) (299) compared Pilates versus PFMT with EStim versus no treatment. Pilates (n=28) was described as mat Pilates, which was done once per week for 45 minutes in addition to a home Pilates programme. Outcome measures were pad weight and use, ICIQ-SF, measured at baseline (four weeks after surgery) and repeated after four months. In another three-armed trial by Gomes *et al.* (295), Pilates (G1) (n=36) was compared to PFMT plus EStim (G2) (n=38) and a control group (G3). Outcome measures included the ICIQ-SF and pad tests, measured at baseline and after four months.

Quality of the data

In the study by Pedrali (299), participants were carefully randomised, and assessors were blinded, but authors failed to discuss the blinding of participants and ITT analysis. Two participants dropped out of the Pilates group due to attendance issues and none from the control group (299). The study by Au *et al.* reported high dropout rates with six in the Pilates plus group and seven in the PFMT group. Neither the participants nor the assessors were blinded, nor did they use ITT analysis (303). In the trial by Gomes (295), there was concealment of allocation and blinding of evaluators but no mention of ITT analysis. Four participants were lost to follow-up, two from the Pilates group and one from the control group.

Results

The only differences found in the study by Au (303) were between the Pilates group and the PFMT group at 26 weeks with statistically significantly reduced participant-reported leakages on the bladder diaries (RR 0.45 (0.22 to 0.98) favouring PFMT. In the study by Pedrali (299), all groups improved for the main outcome measures from baseline to four months. The only statistically significant between-group differences occurred between the Pilates and the no treatment group in daily pad use and ICIQ-SF in favour of the Pilates group (p=0.01). There were no statistically significant differences between the Pilates arm and the PFMT plus EStim arm in the study conducted by Gomes *et al.* (295). They concluded that Pilates was better than no treatment when looking at the proportion of men not needing to use pads (p<0.05).

Summary

Research does not currently support the use of Pilates over the use of PFMT for men with persistent post-prostatectomy incontinence. However, emerging evidence suggests that Pilates may be more effective than no treatment (295, 299). The use of Pilates in addition to PFMT or as a progression to PFMT requires more research. **(Level of evidence: 2)**

Recommendations

Pilates cannot be recommend over a PFMT programme for men with persistent post-prostatectomy incontinence as there is no evidence of superiority. **(Grade of recommendation: B New)**

Pilates to manage persistent post-prostatectomy incontinence in men may be considered over no treatment **(Grade of recommendation: D New)**

2.4. PFMT compared to or plus alternative interventions for management of PPI

With PFMT becoming the gold standard as first line treatment for PPI, other conservative treatments are being investigated for effectiveness in addition or compared to PFMT. Seven new trials were identified that combined post-operative PFMT with other conservative treatments. Techniques being used to treat PPI vary significantly and are often presented in small studies.

The effectiveness of using an oscillation rod (a flexible pole, which can be set into oscillation, resulting in tuneable, rapidly alternating forces) (304) to train the pelvic floor post RP was the focus of a study by HeyDenreich *et al.* (305). They compared sensorimotor training with an oscillating rod (n=93) to standard PFMT (n=91). The PFMT used was based on a protocol using the external anal sphincter as its focus. Outcome measures were one-hour and 24-hour pad tests and the FACT-PHRQoL, evaluated before and after three weeks of treatment. This is a concealed allocation randomised study, but neither the participants nor the assessors were blinded. There were no dropouts in this study. Both pad tests showed statistically significant differences favouring the novel treatment (one-hour pad test: p=0.008 24-hour pad test p=0.012) as did the Functional Assessment of Cancer Therapy (FACT-P) scores (p=0.017 between groups) (305).

Tanawy added whole-body vibration (n=32) to PFMT (n=32) to manage mild SUI after RP (306). PFMT was taught to both groups with an anterior focus to the exercises. Using the I-VAS, ICIQ-UI-SF and a 24-hour pad test, blinded assessors evaluated continence before treatment, after four weeks of treatment and at the two-month follow-up. This study was randomised but it is unclear if there was concealment of allocation or blinding of the assessors. Two participants dopped out in the vibration group and one in the control group. ITT analysis was not mentioned. At both time points, post-treatment results statistically significantly favoured the treatment group (p<0.001).

Zachovajeviene *et al*. evaluated the effect of postoperative diaphragm muscle training (n=49) and abdominal muscle training (n=49) to PFMT (n=50) on PFM strength and endurance and incontinence after RP (307). Details of the exercise protocols were missing. There was no information on the blinding of assessors and participants, but ITT analysis, randomisation and allocation concealment were included. The dropout rate of 14% (21/148) was equally divided at seven per group. Results of the eight-hour pad test showed a significant reduction in leakage after six months but no difference between the groups (307).

Crowe (308) evaluated the effectiveness of using a video to teach PFM exercises. Only an abstract was available for this study. Both groups (n=60) were provided PFMT by a physiotherapist, and one group was given additional education using an animated video. The Expanded Prostate Index Composite (EPIC-26) score was used to evaluate continence at one and three months. Details of randomisation, allocation concealment or ITT analysis were unavailable, and it is unclear how many of the 9 dropouts were in each group. No differences in the EPIC-26 scores were found between groups (308).

Novick (2014) added BT to PFMT to evaluate if there was any additional supportive value (309). PFMT was not described in this study. The BT group (n=36) was provided a handout and oral explanations on bladder irritants and advice on bowel health. The usual care group (n=32) doing Kegel exercises were given a handout. There was no discussion of allocation concealment and blinding

and ITT analysis were not described. The main outcome measure is the EPIC collected at six and 12 weeks. While both groups improved between weeks six and 12, and no differences were found between the two groups at any time point (309).

Chen *et al.* (310) compared usual care to a protocol that combined several other modalities. PFMT, 'urinary reflex training', BT, EStim and biofeedback were all offered to the training group (n=13) while usual nursing care was described as perineal and urination care (n=12). The main outcome was time to recovery of full continence. The study did not include details on randomisation, allocation concealment and blinding of assessors. There were no participants lost to follow-up and the authors used ITT analysis. Statistically significantly more men were continent at six months in the treatment group than in the usual care group (9/13 versus 3/12). There was no difference in the number of participants who were continent at 12 months.

A study by Zhang *et al.* (311) included men that were still incontinent six months after completing any treatment for prostate cancer. They were provided with either a support group (n=81) or telephone support (n=81) plus PFMT with biofeedback, which was compared to usual care (n=82). It was unclear if the usual care group received PFMT and if the participants were blinded or allocation was concealed. The outcome measure was frequency and volume of leakage on a bladder diary as well the I-PSS. There were 36 dropouts, spread evenly amongst the three groups and data included ITT analysis. After three months, men allocated to either of the PFMT plus biofeedback groups had improved more than the usual care group. This difference was not statistically significant at six months. Both treatment groups rated their UI as less problematic than the usual care group at three and six months.

Summary and recommendations

Using an oscillating rod (305), or whole-body vibration (306) may assist in improving post prostatectomy incontinence**.** More studies are needed. **(Level of evidence 3)**

Using a video in addition to physiotherapy-led PFMT (308) did not add value to treatment. However, research is needed to assess if it is effective for men who cannot access pelvic health physiotherapists. **(Level of evidence 3)** More research is needed on costs and benefits before treatments can be recommended for other LUTS such as urgency in men after prostatectomy.

Finally, there is some early evidence that novel interventions, which activate the PFM or involve support groups, may be beneficial after RP and therefore could be recommended; but data are very limited. **(Level of evidence; 3: Grade of recommendation C New)**

More high-quality studies are needed to determine the costs and benefits of adjunct treatments to PFMT.

2.5. TURP

2.5.1. Pre-operative TURP PFMT

No new studies were found. Little research has been dedicated to UI after TURP as the incidence of UI after TURP is reported to be very low.

2.5.2. Pre-operative versus post-operative TURP PFMT

The study by Anan *et al.* (312) was the only one that assessed the effect of pre- and post-operative pelvic floor exercises to improve continence after holmium laser enucleation of the prostate. Men were randomised to start PFMT one month before surgery (n=36) or to only start PFMT after surgery (n=36); both groups continued PFMT after surgery. PFMT consisted of three minutes of PFM contractions, three times per day. Self-reported continence was the main outcome measure with "fully continent" defined as no pad use. The ICIQ-SF was used to gauge QoL. Both were assessed at one, three and six months. This study only had two participants (one per group) lost to follow-up (312). The authors did not describe blinding, concealment of allocation or ITT analysis. At three months, there was a statistically significant difference in return of continence between the groups in favour of the group starting treatment pre-operatively. By six months there was no difference between the groups with all participants attaining continence, indicating that the pre-operative group attained continence earlier than the post-operative only group. There was no difference in QoL between the groups at any time point (312).

Summary

There continues to be limited evidence on the benefit of starting PFMT pre-TURP versus starting post TURP. Starting PFMT before holmium laser enucleation of the prostate may reduce the time to continence in this population. In the absence of sufficient data from rigorous and well-reported trials, it is unknown if PFMT reduces UI following TURP. **(No recommendation)**

2.5.3. Post-operative TURP PFMT for incontinent men

No new studies were found.

Summary

There is limited evidence on the benefit of PFMT post-TURP.

2.6. PFMT for management of UI after radiation therapy

A new section has been added for this edition on the management of long-term LUTS with PFMT in men who were treated with radiation therapy. There were two studies (313, 314) that assessed a multidisciplinary approach to manage these symptoms. Dieperink *et al.* (313) included PFMT in a programme that also supported men with counselling and whole-body exercises. The usual care offered was a consultation with a physician without further education or support. At the three-year follow-up, the PFMT group (n=72) and the usual care group (n=71) were compared using the EPIC and the SF-12. The abstract, presented by Faithfull *et al.* (314) reported on the impact of PFMT combined with psycho-educational instruction and peer support (n=35) versus usual care (n=31). Outcome measures were self-reported symptoms, QoL and self-efficacy scores.

Quality of the data

Dieperink *et al.* (313, 315) carefully designed their study, describing randomisation, concealment of allocation and blinding of the assessment. It was not possible to blind participants. The study used ITT analysis and 7/79 in the PFMT group and 11/82 in the control group were lost to follow-up in the original study three years earlier (313, 315). The abstract from Faithfull *et al.* (314) does not provide sufficient details to assess the quality of the study.

Results

Neither study found differences between the groups. Urinary scores (314) or the UI domain of the EPIC (313) were not statisticaly significantly different between groups. Dieperink suggested that this lack of long-term effect could be due to the absence of follow-up between the original study, which lasted three months, and the final evaluation at three years (313). Faithfull *et al.* found that coping mechanisms were better in the treatment group (314).

Summary

The effect of PFMT on LUTS in men undergoing radiation treatment requires more research.

2.7. PFMT effect on erectile dysfunction and climacturia

The long-term side effects of RP have been gaining more attention as more men survive longer after a prostate cancer diagnosis. Erectile dysfunction and climacturia or orgasm-associated incontinence can have major emotional and psychological influences.

In a study by Greaerts *et al.* (316), the effect of PFMT 12 months or more after RP was evaluated. Erectile function was assessed with the IIEF and a climacturia questionnaire, which was self-reported after three months of treatment. The treatment group (n=16) received PFMT assisted by EStim, and a home programme. The control group (n=17) did not receive any treatment. Allocation was not concealed, nor were participants analysed by ITT. Significant effects were attained in the treatment group (EF (4.1 (5.6) versus –0.2 (2.4), P= 0.025) climacturia (6/14 versus 0/17, P= 0.004)) (316).

Summary

Long-term side effects of RP, such as climacturia and erectile dysfunction appears to be reduced using PFMT. PFMT could be considered for the treatment of climacturia and erectile dysfunction in men post RP. More research in this area is needed. (**Level of evidence 2, Grade of recommendation: C (New))**

2.8. PFMT for Other LUTS

2.8.1. PFMT for post-micturition dribble (PMD)

No new trials were identified to add to the previously included trials.

Recommendation

Men with PMD could be instructed to perform a strong PFM contraction immediately after voiding or use urethral massage to empty the urethra. **(Level of evidence 3; Grade of recommendation: C)**

Table 42. Table of included RCTs of treatments for UI in men

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Anan (2020) (312)	RCT PFMT pre and postoperatively vs PFMT postoperatively	72	TURP Men with BHP undergoing holmium laser enucleation of the prostate	Participants were instructed to perform PFMT 3x/day for 3 minutes Group 1 (n=36): PFMT started 28 days preoperatively and on the second day after surgery and catheter removal instructions for PFMT Group 2 (n=36): PFMT on the second day after surgery and catheter removal	UI rate was significant lower in G1 when compared to G2 at 3 months follow up (p=0.01). No significant differences at 3 days, 1 and 6 months. 3 days G1: 14/35, G2: 19/35 (P=0.34) 1 month G1: 13/35, G2: 18/35 (P=0.34) 3 months G1: 1/35, G2: 9/35 (P=0.01) 6 months G1: 0/35, G2: 1/35 (P=1.00) ICIQ-SF score: no significant differences at 1, 3 and 6 months between groups. 1 month G1 (n=35): 5.4±4.9, G2 (n=35): 5.6±4.9 (P=0.89) 3 months G1 (n=35): 2.9±3.4, G2 (n=35): 3.8±4.6 (P=0.80) 6 months G1 (n=35): 1.5±2.0, G2 (n=35): 1.5±2.4 (P=0.83)	3 days, 1, 3 and 6 months after surgery	Adverse events: NR Loss of follow up: 2.77% (2/72) G 1: n=1; G2: n=1 Intention to treat: NR
Au (2019) (303)	RCT PFMT + Pfilates and hypopressives vs PFMT	50	Men undergoing radical prostatectomy	Participants were instructed to isolate and maximally contract the PFM with escalating repetition every 2 weeks (starting at 30 repetitions/day) G1 (n=25): PFMT G2 (n=25): PFMT + Pfilates and Hypopressive exercises	Severity of UI measured by 24-hour pad test weight no between-group differences. UI measured by 24-hour pad test no between-group differences. 3-day bladder diary was significant lower in G2 when compared to G1 at 26 weeks follow up (p<0.05) for Total leaks (24h) and Day leak. No significant differences at 2, 6 and 12 weeks for Total leaks (24h) and Day leak. No between-group differences for Night leaks 2, 6, 12 and 26 weeks. FACT-P total score no between-group differences. PORPUS HRQOL and total score were no observed between-group differences. HRQOL IPSS total score: no between-group differences.	2, 6, 12 and 26 weeks after surgery	Adverse events: none Loss of follow up: 26% (13/50) G1: n=6 G2: n=7 Intention to treat: Yes

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Bassi (2018) (Abstract) (287)	RCT PFMT pre and postoperatively vs Usual care	36	Men undergoing robot-assisted radical prostatectomy	G1 (n=22): Participants were instructed to perform PFMT G (n=14): usual care	Pad test, ICIQ-UI, IPSS-QoL and total scores no between-group differences. IPSS-QoL both groups showed significant within group comparison at 4 weeks when compared to baseline. UI no between-group differences at 4 and 12 weeks. Urinary incontinence 4 weeks G1: 19/22 G2: 12/14 12 weeks G 1: 3/22 G2: 2/14	1 week prior to surgery, 4 and 12 weeks after surgery	Adverse events: NR Loss of follow up: NR Intention to treat: NR
Chen (2013) (310)	quasi-RCT Nursing care vs Nursing care + PFMT + rehabilitation	25	Men after radical prostatectomy	G1 (n=13): Nursing care + PFMT (3x/day) + urinary reflex training + bladder training + EStim (daily, 30 minutes) + biofeedback (daily, 30 minutes) over 4 weeks G2 (n=12) conventional nursing care (perineal and urination care)	Urinary incontinence: UI cure significantly improve in G1 when compared to G2 at 6 months follow up (p=0.005). G1: 9/13, G2: 3/12 At 3 months follow-up, 10/13 of G1 recovered continence and at 6 months.13/13 were continent G2 recovered continence slower 4/12 by 3 months, 9/12 at 6 months and 12/12 by12 months.	1-3, 4-6, 7-9 and 10-12 months after radical prostatectomy	Adverse events: NR Loss of follow up: none Intention to treat: Yes
Crowe (2017) (Abstract) (308)	RCT Animated PF model and usual care vs Usual care	60	Men schedule for radical prostatectomy	G1: Usual care + animated PF model G2: Usual care + a prostate cancer DVD Usual care: verbal and written instruction followed by appointment with Pelvic Health Physiotherapist instruction	EPIC-26 for UI assessment: no significant difference between groups at 3 months.	1 and 3 months post-operatively	Adverse events: NR Loss of follow up: 15% (9/60) Intention to treat: NR
Dieperink (2020) (313)	RCT Multidisciplinary rehabilitation vs Usual care	161	Men who underwent radiotherapy and androgen deprivation therapy	G1 (n=79): Multidisciplinary rehabilitation sessions 1 hour each (2 nursing counselling + 2 physical therapy including instructions for home PFMT daily, 3 sessions of 10 repetitions for 8 seconds and if necessary, biofeedback; and exercises for major muscle groups) + usual care 4 and 12 weeks after radiotherapy. G2 (n=82): Usual care (physician consult after radiotherapy).	EPIC-26 UI domain no difference between groups (p=0.242) G1: 7.3(14.9), G2: 4.9(15.8) EPIC-26 disease-specific QoL no difference between groups (p=0.418) G1: 88.61(16.1), G2 86.45(17.1) Moderate-severe urinary problems no difference between groups (p=0.835) G1: 7/72, G2: 6/71	6 months and 3 years after radiotherapy	Adverse events: NR* (adverse events reported are related to ADT or radiotherapy) Loss of follow up: 8% (6/161) Intention to treat: Yes

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Faithfull (2015) (Abstract) (314)	RCT Self-management intervention vs Usual care	66	Men treated with radiotherapy for prostate cancer	G1 (n=35): Self-management (psycho educational instruction, problem solving and goal setting, PFMT instruction, support film provided within a small group over 4 sessions + one-to-one with a nurse specialist + 2 motivational telephone calls) G2 (n=31): Usual care	Urinary symptom scores not statistically significant between groups (p>0.09). QoL no statistically significant differences between groups (p>0.8).	6 months	Adverse events: NR Loss of follow up: NR Intention to treat: NR
Filocamo (2019) (Abstract) (286)	RCT PFMT + indwelling catheter vs PFMT after catheter removal	39	Men post radical prostatectomy	G1 (n=20): supervised PFMT with indwelling catheter in the 3rd post-operative day. Patients instructed to daily PFMT, including after catheter removal. G2 (n=19): supervised PFMT after catheter removal in the 10th post-operative day.	Cured (continent) The difference between the two groups was statistical relevant at 3, 6 and 9 months (p<0.05), was not statistically significant at 1 and 12 months. 1 month: G1: 4/18, G2: 2/17 3 months: G1: 11/18, G2: 4/17 6 months: G1: 15/18, G2: 7/17 9 months: G1: 15/18, G2: 8/17 12 months: G1: 16/18, G2: 14/17 QoL ICS male questionnaire total score The difference between the two groups was statistical relevant at 3, 6, 9 and 12 months (p<0.05). 1 month: G1: 25, G2: 28.57 3 months: G1: 15.41, G2: 19.92 6 months: G1: 13.58, G2: 16.57 9 months: G1: 13.05, G2: 14.75 12 months: G1: 12.09, G2: 14	1, 3, 6, 9 and 12 months after surgery	Adverse events: NR Loss of follow up: 10.25% (4/39) (G1: n=2; G2: n=2) Intention to treat: NR
Geraerts (2016) (316)	RCT PFMT 12 months after RP vs PFMT 15 months after RP	33	Men post radical prostatectomy	G1 (n=16): supervised PFMT 12 months after radical prostatectomy G2 (n=17): supervised PFMT 15 months after radical prostatectomy PFMT performed with electrostimulation (10 min) weekly (6 weeks) and 1x/fortnight (6 weeks) for both groups	Climacturia assessed 15 months after RP showed significant improvement in G1 G1: 6/14, G2: 0/1 7(p=0.004). 3 months after treatment the whole group (n=33) showed significant decrease within group comparison (p=0.001). Pre-treatment: 17/33 Post-treatment: 5/30	15, 18 and 21 months after RP	Adverse events: NR Loss of follow up: 12.12% (4/33) Intention to treat: NR

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Gomes (2018) (295)	RCT Pilates vs electrical stimulation + PFMT vs home PFMT	110	Men post radical prostatectomy	G1 (n=36): mat Pilates (1x/week, 45 minutes) for 10 weeks. G 2 (n=38): PFMT with anal electrical stimulation (1x/week, 45 minutes) for 10 weeks. G3 (n=36): instructions for home PFMT.	Pad usage demonstrated statistically significant reduction in pad usage in all groups. Between group comparison showed statistical difference in G1 vs G3 and G2 vs G3 comparison (p=0.01) G1: 0.73±1.26 (within group p<0.001) G2: 0.77±1 (within group p<0.001) G3: 1.48±1.31 (within group p<0.01) Pad test demonstrated significant improvement in all groups. G1: 85.85±180.6 (within group p<0.001) G2: 67.4±131.88 (within group p<0.001) G3: 72.88±97.28 (within group p<0.001) There was no statistically significant difference between G1 and G2, but G1 and G2 had a higher proportion of continents (no pads/day) than G3 after treatment (P < 0.05) ICIQ-SF scores demonstrated significant improvement in all groups. Between group comparison showed significant difference in QoL scores in G1 vs G3 (p<0.05). G1: 4.41±4.95 (within group p<0.001) G2: 5.77±4.54 (within group p<0.001) G3: 8.2±3.87 (within group p<0.001)	4 months after radical prostatectomy	Adverse events: NR Loss of follow up: 5.45% (6/110) Intention to treat: NR
Gonzalez (2020) (296)	RCT EStim + biofeedback vs education	60	Men who underwent radical prostatectomy due to prostate cancer	G1 (n=30): electrotherapy (15 minutes) + biofeedback (30 minutes) (3x/week, 45 minutes) + home PFMT (3x/day) s + PFMT printed guide education for 3 months G2 (n=30): PFMT printed guide education	1h Pad Test showed statistically significant differences between groups at 3 and 6 months (p=0.001) favoring treatment. 24h Pad Test showed statistically significant differences between groups at 3 and 6 months (p<0.003) favoring treatment ICIQ-SF score showed statistically significant differences between groups at 2, 3 and 6 months (p<0.014) favoring treatment.	1, 2, 3 and 6 months after treatment	Adverse events: NR Loss of follow up: 31.66% (19/60) G1:7; G2:12 Intention to treat: NR

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Heydenreich (2020) (305)	RCT PFMT + oscillating rod therapy vs PFMT + relaxation therapy	184	Men after radical prostatectomy	G1 (n=93): supervised PFMT + PFMT using oscillating rod (daily, 30 minutes) for 3 weeks G2 (n=91): supervised PFMT + daily relaxation All patients completed a standard treatment program consisted of PFMT, general endurance, and moderate strength training with exercised performed daily for 30 minutes over 3 weeks	The 1h Pad Test showed significant difference between groups (p=0.008) favoring G1. The 24h Pad Test showed significant difference between groups (p=0.012) favoring G1. The FACT-P HRQOL showed significant difference between groups (p=0.017) favoring G1. UI severity measured by 1h Pad Test showed reduction of urine loss significant different for high level (p=0.003) favoring G1. No significant difference in mild level. Mild G1: 0.8±1.9, G2: 1.6±3.2; p=0.051 Moderate G1: 15.4±13.3, G2: 21.8±20.1; p=0.094 High G1: 23±17.6, G2: 62.6±49.9; p=0.003	3 weeks after treatment	Adverse events: NR Loss of follow up: none (0/184) Intention to treat: Yes
Jalalinia (2020) (289)	RCT PFM vs usual care	68	Men undergoing suprapubic prostatectomy	G1 (n=34): preoperatively supervised PFMT+ PFMT postoperatively (3x/day) for 12 weeks G2 (n=34): education trainings	UI measured by ICIQ-SF showed significant difference between groups at 1-, 2- and 3-months favoring G1 (p=0.001). QoL measured by IQoL showed significant difference between groups at 1-, 2- and 3-months favoring G1 (p=0.001).	7 days, 1, 2 and 3 months after surgery	Adverse events: NR Loss of follow up: 11% (8/68) Intention to treat: NR
Laurienzo (2018) (298)	RCT PFMT vs PFMT + EStim vs no treatment	132	Men who underwent radical prostatectomy	G1 (n=40): No treatment (routine instructions) G2 (n=41): PFMT (3x/day) until complete 6 months follow-up G3 (n=42): PFMT (3x/day) + anal EStim (2x/week for 7 weeks)	1h Pad Test showed significant difference in the within group comparison. However, no statistical difference between groups in all follow-up periods. ICIQ-SF score showed significant difference in the within group comparison. However, no statistical difference between groups in all follow-up periods. IPSS score showed significant difference in the within group comparison. However, no statistical difference between groups in all follow-up periods.	1, 3 and 6 months follow-up after radical prostatectomy	Adverse events: NR Loss of follow up: 6.81% (9/132) G1: 3 G2: 3 G3: 3 Intention to treat: NR

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Lin (2011) (302)	quasi-RCT PFM vs no treatment	75	Men who undergo radical prostatectomy	G1 (n=44): PFMT with biofeedback (4x/day) G2 (n=31): no intervention	UI measured by 1h Pad test showed significant difference within group and between group favoring Group 1 (p<0.01). 1 month G1: 76.7±53.03, G2: 109.56±85.81 2 months G1: 27.68±51.84, G2: 79.44±71.94 3 months G1: 9.27±25.23, G2: 27.11±40.88	1, 2 and 3 months after catheter removed	Adverse events: NR Loss of follow up: 13.3% (8/75) G1: 5, G2:3 Intention to treat: NR
Lira (2019) (288)	RCT Preoperatively PFMT vs usual care	31	Men undergoing open retropubic radical prostatectomy for localized prostate cancer	G1 (n=15): usual care G2 (n=16): supervised preoperatively PFMT + biofeedback and after removal of the urethral catheter (3x/day)	UI measured rate showed no difference in both groups at 3 months follow-up (p>0.05). G1: 72.7%, G2: 70% ICIQ-SF scores showed no difference between groups (p=0.97). G1: 6.9±6.26, G2: 7±5.12	3 months after surgery	Adverse events: NR Loss of follow up: none Intention to treat: Yes

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Milios (2019) (290)	RCT High intensity PFMT vs usual PFMT	101	Men undergoing radical prostatectomy	Participants in both groups received physiotherapy-directed PFMT (2 sessions, 30 minutes) approximately 5 weeks prior to RP surgery, with both groups then following removal of the catheter prescribed a daily PFMT that differed in mode and intensity. G1 (n=47): Usual PFMT (3 sets daily, 10 contractions/set holding for 10 seconds totaling 30 contractions/day) G2 (n=50): High intensity PFMT (6 sets daily, each set comprising: 10 fast-1 second duration; and 10 slow- 10 seconds totaling 120 contractions/day)	UI measured by 24h Pad Test at 2-, 6- and 12-weeks post-surgery, the percentage of dry participants was greater across all time points in G2 demonstrating a faster return to continence. % Dry 2 weeks G1: 4%, G2: 14% 6 weeks G1: 11%, G2: 32% 12 weeks G1: 43%, G2: 74% 24h Pad Test 2 weeks (P<0.05) G1: 112.24±21.05, G2: 192.60±24.84 6 weeks G1: 50.38±11.48, G2: 103.31±15.31 12 weeks G1: 20.40±7.66, G2: 46.55±10.84 IPSS score measuring urinary symptoms and QoL showed no differences at 2 and 12 weeks, however a significant difference between groups at 6 weeks with better scores in Group 2. IPSS 6 weeks (P<0.05) G1: 4.93±0.44, G2: 6.81±0.75 EPIC-CP score measuring urinary score showed no differences at 6 and 12 weeks, however a significant difference between groups at 2 weeks with better scores in Group 2. 2 weeks (P<0.05) G1: 3.55±0.4, G2: 5.49±0.48	2-, 6-, and 12-weeks post-surgery	Adverse events: NR Loss of follow up: 3.96% (4/101) Intention to treat: NR

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Novick (2014) (309)	RCT Intensive bladder control education vs usual care	71	Men who undergo robot-assisted radical prostatectomy	All participants received usual care content: wearing pads as needed and instructions for PFMT. G1 (n= 36): Intensive bladder control education via verbal instructions on content and education handouts (for PFMT, bladder irritants and dietary suggestions) G2 (n= 32): no treatment	Bladder function measured by EPIC showed no difference between groups at 6 and 12 weeks. However, they improved at 12 weeks when compared to 6 weeks in the withing group comparison in both groups (G1: p=0.0003; G2: p=0.0008). 6 weeks G1: 58.89±17.54, G2: 66.30±16.27 12 weeks G1: 71.56±18.85, G2: 75.24±16.57 p=0.47 Intensity of bladder problems reflecting lack of urinary control showed no difference between groups at 6 and 12 weeks. However, they improved at 12 weeks when compared to 6 weeks in the withing group comparison in G1 (p=0.02). 6 weeks G1: 55.92±17.02 G2: 60.60±15.03 12 weeks G1: 62.82±17.19 (withing group p=0.08) G2: 65.44±14.85 (withing group p=0.02)	6 and 12 weeks after surgery	Adverse events: NR Loss of follow up: 4.22% (3/71) Intention to treat: NR
Oh (2019) (300)	RCT PFMT with biofeedback vs PFMT	84	Men with prostate cancer who undergo robot-assisted radical prostatectomy	G1 (n=42): PFMT with extracorporeal biofeedback device + usual care G2 (n= 42): usual care Usual care: Verbal and written instructions for PFMT after catheter removal and on an outpatient basis at least 1x/month. Instructions were a) 4x/day. b) 10 minutes per session of exercise. c) maximum of 10 seconds of tension with maximal tension intensity. Participants were advised to continue the PFMT as long as any degree of UI persisted.	24h Pad Test showed significant difference at 1 month follow-up favouring G1. However, 2 and 3 months follow up showed no difference. UI incidence defined by Pad Test weight showed no difference between groups at any follow ups. Average urine loss 1 month (p=0.028) G1: 71±48, G2: 120.8±132.7 P=0.028 IPSS showed significant difference in total score at 1 month follow-up favouring G1. However, 2 and 3 months follow up showed no difference. IPSS total score 1 month (p=0.046) G1: 0.25±9.15, G2: -3.81±8.98 QoL score showed no difference between groups at all follow ups.	1, 2 and 3 months after surgery	Adverse events: NR Loss of follow up: 2.38% (2/84) G1: 2; G2: 0 Intention to treat: Yes

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Pedriali (2016) (The abstract version was included in the previous ICI) (299)	RCT Pilates vs PFMT + EStim vs no treatment	90	Men who underwent radical prostatectomy	G1 (n=28): mat Pilates (1x/ week, 45 minutes) for 10 weeks G2 (n=31): PFMT with anal electrical stimulation (1x/week, 40-50 minutes) for 10 weeks G3 (n=31): no treatment	Pad weight demonstrated significant improvement in all groups (within group), however, between group comparison showed no difference (p=0.1). Number of pads/day G1: 97.65±20.35 (within group p<0.001) G2: 67.14±12.67 (within group p<0.001) G3: 80.25±20.86 (within group p<0.01) Pad test usage demonstrated significant improvement in all groups (within group). There was statistical difference between G1 and G3 (P=0.01) favouring G1. Number of pads/day G1: 0.84±1.4 (within group p<0.001) G2: 0.82±0.98 (within group p<0.001) G3: 1.58±1.33 (within group p<0.01) ICIQ-SF QoL scores demonstrated significant improvement in all groups (within group). Between group comparison showed significant difference in QoL scores in G1 and G3 (p=0.007) favouring G1. G1: 4.61±5.3 (within group p<0.001) G2: 5.6±4.39 (within group p<0.001) G3: 8.09±4 (within group p<0.01)	4 months after radical prostatectomy	Adverse events: NR Loss of follow up: 5,55% (5/90); Group 1: 2 Group 2: 3 Group 3: 0 Intention to treat: No
Santa Mina (2018) (284)	RCT Exercises + PFMT vs usual care	86	Men undergoing radical prostatectomy	Both groups received a prostate cancer support book and preoperative PFMT G1 (n=44): Home-based moderate intensity exercise prior to surgery (60 minutes, 3-4 days week + daily PFMT preoperative G2 (n= 42): manual of PFMT	No statistical difference between groups for FACT-P, FACT-G and IPSS at any time points.	Pre-operatively, 4, 12 and 26 weeks after surgery	Adverse events: 5 non-serious adverse events: self-resolving hematuria (1), self-resolving atrial fibrillation with jogging during home-based exercise (1), leg pain (1), aggravation of lower arm muscle strain/ lateral epicondylitis (1) Loss of follow up: 29.06% (25/86) G1: 11; G2: 14 Intention to treat: NR

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Santos (2017) (301)	RCT PFMT with biofeedback vs PFMT	16	Men who underwent retropubic or laparoscopy prostatectomy	All participants received oral and written instructions on home PFMT G1 (n=8): supervised PFMT with biofeedback (1x/week, 20 minutes) for 8 weeks + home PFMT G 2 (n=8): supervised PFMT	UI measured by 1h Pad Test showed no difference within groups in G1 (p=0.07). However, there was a significant difference within group in G2 (p=0.015). Continence G1: 4/7, G2: 5/6 Mild UI G1: 3/7, G2: 1/6 Moderate UI G1: 0/7, G2: 0/6 Moderate UI G1: 0/7, G2: 0/6 Number of patients using pads showed that in both groups all patients were not using pads after treatment (within group comparison; G1: p=0.021; G2: p=0.002).	After intervention	Adverse events: NR Loss of follow up: 18.75% (3/16) G1: 1; G2: 2 Intention to treat: NR
Sayilan (2018) (291)	RCT PFMT vs no treatment	60	Men post radical prostatectomy diagnosed with prostate cancer	G1 (n=30): preoperative supervised PFMT (1-4 sessions, 1 hour) + home PFMT (3x/day) for 6 months + written information G2 (n=30): Breathing exercises	ICIQ-SF scores in between group comparison showed that G2 scored significantly higher at 3 months (p=0.001) and 6 months (p=0.001). 1 month G1: 11.1±5.04, G2: 11.57±3.2 (p=0.911) 3 months G1: 9.03±3.55, G2: 14.27±3.25 (p=0.001) 6 months G1: 6.17±2.85, G2: 14.63±3.02 (p=0.001) The numbers of pads used showed between group significant difference in the 1 (p=0.008) and 6 months (p=0.001) follow-up.	1, 3 and 6 months after catheter removal	Adverse events: NR Loss of follow up: none Intention to treat: Yes
Sayner (2019) (Abstract) (285)	RCT Preoperative functional PFMT vs standard PFMT	30	Men scheduled or undergoing radical prostatectomy	G1 (n=15): Preoperative functional PFMT (2x/day) G2 (n=15): Preoperative standard PFMT (3x/day)	ICIQ-SF showed significant difference at 26 weeks in between group comparison favouring G1 (MD: 3.67, p=0.02).	4, 12 and 26 weeks post-operatively	Adverse events: none Loss of follow up: 20% (6/30) G1: 3; G2: 3 Intention to treat: NR

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Tantawy (2019) (306)	RCT PFMT + whole body vibration vs PFMT	64	Men post radical prostatectomy	Participants in both groups were advised to conduct home PFMT and illustrated handouts for exercise training G1 (n=32): Whole-body vibration training (3x/week, 45 minutes) for 4 weeks G 2 (n=32): no treatment	I-VAS, ICIQ-SF and 24h Pad Test showed statistical difference withing group comparison (p<0.001) and between group (p<0.001) at 4 weeks and 2 months follow-up favouring G1. I-VAS score (IQR) 4 weeks G1: 4 (3.5 to 4.2) (within group p<0.001) G2: 7.8 (7.3 to 8.6) (within group p<0.001) 2 months G1: 2 (1.9 to 2.4) (within group p<0.001) G2: 6.8 (6.3 to 7.5) (within group p<0.001) ICIQ-SF score (IQR) 4 weeks G1: 9 (6.8 to 10.3) (within group p<0.001) G2: 15 (12 to 17.3) (within group p<0.001) 2 months G1: 5 (4 to 6) (within group p<0.001) G2: 12 (10.8 to 14) (within group p<0.001) 24h Pad Test Mean ± SD 4 weeks G1: 44.1±7.6 (within group p<0.001) G2: 61.1±5.3 (within group p<0.001) 2 months G1: 29.6±10.5 (within group p<0.001) G2: 52.7±5.3 (within group p<0.001)	4 weeks of treatment and 2 months follow-up	Adverse events: NR Loss of follow up: 4.68% (3/64) G1: 2; G2: 1 Intention to treat: NR

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Wang (2018) (Abstract) (297)	RCT EStim vs EStim + PFMT with biofeedback	96	Men who underwent radical prostatectomy	G1 (n=64): Electrical pudendal nerve stimulation (60 minutes, 3x/week) during 8 weeks. G2 (n=32): Transanal electrical stimulation + PFMT with biofeedback (20 minutes, 3x/week) during 8 weeks.	ICIQ-SF analysis of total score, QoL, incontinence diapers and amount of leakage showed significant difference within group (p<0.05) and between group comparison (p<0.05). ICIQ-SF analysis for leakage frequency showed no significant difference between group comparison (p=0.68), however there was significant difference within group (p<0.05). ICIQ-SF score G1: 11 (7-14) (within group p<0.01) G2: 15 (9-17) (within group p<0.01); P<0.05 Leakage frequency subscore G1: 4 (3-4) (within group p<0.05) G2: 4 (4-4) (within group p<0.05); p=0.68 Leakage amount subscore G1: 4 (2-6) (within group p<0.05) G2: 6 (2-6) (within group p<0.05); p<0.05 QoL subscore G1: 3 (2-5) (within group p<0.05) G2: 5 (2.25-7) (within group p<0.05); p<0.05 Number of incontinence diapers score G1: 3 (1-3) (within group p<0.01) G2: 3 (3-4) (within group p<0.01); P<0.05	After treatment 8 weeks	Adverse events: NR Loss of follow up: none (0/96) Intention to treat: Yes
Zachovajeviene (2019) (307)	RCT PFMT vs Diaphragm muscle training vs abdominal muscle training	148	Men after radical prostatectomy	All participants performed supervised therapeutic exercises for 16 days. G1 (n=50): PFMT (2x/day, 30 minutes) G2 (n=49): diaphragm muscle training (2x/day, 30 minutes) G3 (n=49) abdominal muscle training (2x/day, 30 minutes)	UI measured by 8h Pad Test showed no difference in between group comparison (p>0.75), however, within group comparison showed significant decrease UI levels in all groups during each follow-up (p<0.001). 6 months: p>0.75 G1: 32.9 (17.9 to 47.9) (within group p<0.001) G2: 38.9 (22.6 to 55.3) (within group p<0.001) G3: 31.7 (19.5 to 43.9) (within group p<0.001)	14 days, 1, 3 and 6 months after surgery	Adverse events: none Loss of follow up: 14.18% (21/148) Intention to treat: Yes

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Zhang (2015) (311)	RCT PFMT with biofeedback + support group vs PFMT with biofeedback + telephone contact vs usual care	279	Men with early stage (I, II or III) prostate cancer who completed cancer treatment for at least 6 months.	G1 (n=91): PFMT with biofeedback (60 minutes) + support group (60-75 minutes, 3-5 subjects) for 3 months G2 (n=94): PFMT with biofeedback (60 minutes) + telephone contact (45 minutes) for 3 months G3 (n=94): no treatment	3-days diary showed decrease daily urinary leakage frequency at 3 months in G1 and G2 (p=0.019 and p<0.001) but no difference at 6 months. Daily urinary leakage 3 months G1: 1.6±2.5; G2: 1.9±2.5; G3: 2.7±3.3 6 months G1: 1.9±3.1; G2: 1.6±3.1; G3: 2.5±2.9 1h Pad test showed G3 showed a significant decrease compared to G2 (p=0.009). No difference was found at 6 months follow-up 3 months G1: 17.9±43.3; G2: 22.6±72.4; G3: 11±24.2 6 months G1: 18.1±49.2; G2: 7.5±21.8; G3: 13.8±36.7 UI severity measured by 7 item I-PSS showed that G1 presented less severe UI at 3 and 6 months (p<0.001) when compared to G3. G2 showed significant decrease at 6 months only (p<0.001). Urinary function assessed by UCLA-PCI showed that G2 reported significant better urinary function (p=0.049) and less bother (p=0.009) at 6 months when compared to G3. UI rated by VAS G1 and G2 rated UI less problematic than G3 at 6 months.	3 and 6 months after treatment	Adverse events: NR Loss of follow up: 12.54% (35/279) G1: 10; G2: 13; G3: 12 Intention to treat: Yes

Abbreviations: RCT: randomised controlled trial; NR: not reported; PFMT: pelvic floor muscle training; UI: urinary incontinence; VAS: visual analogue scale; ICS: International Continence Society; ICIQ-SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form; QoL: quality of life; IQR: interquartile range; HRQoL: Health-Related Quality of Life; FACT-P: Functional Assessment of Cancer Therapy-Prostate; PORPUS HRQOL: Patient-oriented Prostate Utility Scale – Quality of Life; IPSS: International Prostate Symptom Score; EPIC-26: Expanded Prostate Cancer Index Composite-26; IQoL: Urinary Incontinence Quality of Life Scale; UCLA-PCI: UCLA Prostate Cancer Index.

3. ELECTRICAL STIMULATION

Electrical stimulation (EStim) works by activating the motor fibres of the pudendal nerve, which can result in contraction of the PFMs or the striated peri-urethral musculature, supporting the intrinsic part of the urethral sphincter closing mechanism. For male SUI, EStim could be used to enhance contraction of the PFMs in the same way as female SUI.

EStim can also be helpful in men with detrusor overactivity (DO) or UUI because it can stimulate afferent fibres of the pudendal nerve, decreasing the sensation of urgency and inhibiting parasympathetic activity, which results in a decrease in involuntary detrusor contractions (317, 318). As a stand-alone therapy it is unclear whether EStim enhances continence recovery. It has been postulated that continence is regained more rapidly and the duration of the application of EStim is reduced when PFMT is augmented with EStim (318). EStim is also believed to be more effective in participants who are initially unable to identify and correctly contract their PFMs (317). EStim should be avoided for patients with carcinoma of the bladder or prostate, as EStim may increase abnormal cell activity (319). A previous relevant Cochrane systematic review was updated and contributed to this section (320).

Two types of non-invasive EStim, i.e., anal EStim or transcutaneous electrical nerve stimulation (TENS) are commonly used. The surface electrodes are positioned over the perineal region.

Questions addressed are:
- Is EStim effective in the prevention of UI?
- Is EStim better than no active treatment (placebo, sham, control, or no treatment) for treatment of UI?
- Is one type of EStim better than another in the treatment of UI?
- Is EStim better than other treatments in the treatment of UI?
- Does the addition of EStim to other treatments add any benefit in the treatment of UI?

Despite the prevalence of incontinence and LUTS in older men, the only area which has received systematic consideration with respect to EStim is associated with postprostatectomy incontinence (PPI). All prostatectomy types and approaches were considered, including RP (open, laparoscopic, or robotic) for prostatic cancer, or surgery for benign prostatic enlargement (TURP, laser prostatectomy, or less invasive surgeries). Other studies for LUTS such as UUI included men and women.

This section presents the evidence for the use of EStim in the prevention and treatment of PPI in men.

Eligible interventions were non-invasive EStim without implanted electrodes (PTNS and MStim are described in section IV.4). A literature search of relevant systematic reviews and reports of RCTs and quasi-RCTs was performed, and no participants with UI due to neurological or cognitive impairment were included.

The primary outcomes were cure rates and improvement rates (the number of men improved, including cure). There was considerable variability in the way these outcomes were measured. Data on health related QoL and adverse effects were also extracted.

The Cochrane review (317) found six RCTs (five full papers and one abstract) on PPI. There was considerable variation in the interventions used, study protocols, types of EStim parameters and devices, study populations and outcome measures. Frequencies of 5 to 20 Hz are usually used for UUI, 20 to 50 Hz for SUI, and for mixed UI around 20 Hz or high and low frequency alternately. The trials were mostly small and generally there was insufficient information to assess ROB. Four trials evaluated the effect of adding PFMT to EStim versus PFMT alone or with biofeedback. There was some evidence that EStim enhanced the effect of PFMT in the short term but not after six months (317, 318). There were, however, more adverse effects (pain or discomfort) with EStim.

Five studies of EStim in men and women, four with UUI and one with SUI, and eleven studies of men with PPI were summarized in the 6th ICI report.

Two new trials were identified for this update and included in this section. The new trials were targeted for PPI.

The EStim parameters and protocols in this section are summarised in Table 43. There was considerable variation in the intervention protocol.

Table 43. Summary of EStim protocols (EStim for men)

Author, year	Current	Current Intensity	Pulse Shape Duration	Frequency	Duty cycle	Electrodes	Treatment duration	Target UI
Laurienzo (2018) (298)	NR	NR Max tolerable intensity	1ms	35 Hz	Rise time 2 sec; on – 6 sec; off 2 sec; standing time 12 sec	anal	20 min, 2x per week for 7 weeks	PPI
Gomes (2018) (295)	NR	NR	1ms	(SUI) 50 Hz (UUI) 4 Hz	NR	anal	20 min	PPI
Gonzalez (2020) (296)	Square wave pulse	Maximum 24mA Max tolerable intensity	300µ	20 Hz	NR	NR	15 min, 3x per week for 3 months	PPI

Abbreviations: EStim: Electrical stimulation; NR: not reported; PPI: post-prostatectomy urinary incontinence; SUI: stress urinary incontinence; UUI: urge urinary incontinence; UI: urinary incontinence

3.1. Prevention

No new trials were identified. There remain no studies on the effect of EStim for prevention of non-post prostatectomy UUI or SUI in men.

3.2. Treatment

Two new trials were added to the 16 RCTs, included in the 6th ICI (295, 296).

3.2.1. Is EStim better than no treatment, placebo, or control for treatment of UI?

Two earlier placebo-controlled trials (one for UUI and one for SUI) did not separate male and female results.

No new trials were identified to add to the sixth ICI reports.

Summary

In the continued absence of sufficient data from rigorous and well-reported trials, it is not known if EStim, as a stand-alone treatment for male UUI or SUI, is better than no treatment, placebo, or control treatments.

3.2.2. Is one EStim approach better than another?

No new trial was identified. No studies comparing EStim protocols were included in previous consultations.

Recommendation

In the absence of data, it is not known if one EStim protocol is better than another for the treatment of UI in men. **(No recommendation)**

3.2.3. Is EStim better than other treatments?

The sixth ICI report summarized three studies: one study compared EStim to magnetic stimulation (Mstim), another study compared EStim to verbal/written instruction on PFMT, and a crossover trial compared EStim to oxybutynin. These studies included men and women with UUI, but there were few men in these three trials.

No new trials were identified.

Summary

A total of three studies were assessed in the sixth ICI report. Due to insufficient data, it is unknown whether EStim is better than another treatment for UI in men. **(Level of evidence 2/3)**

Recommendations

No recommendation can be made.

3.2.4. Does the addition of EStim to other treatments add benefit?

Two new studies (Table 44) were added to the previous 11 studies on EStim plus PFMT in men with PPI, for a total of 13 included studies (295, 296).

One study by Gomes *et al.* (295) compared Pilates (which included PFMT) to PFMT plus EStim, and control (no therapy) in 120 patients with PPI. This was a similar study to that previously reported in the sixth ICI (321). The other study by Gonzalez *et al*. compared EStim plus biofeedback versus control (no treatment) in 60 patients with PPI (296).

Quality of data

Randomisation was achieved using sealed envelopes in one study (295) but was not defined in the other (296). Participants and evaluators were not blinded in either study (296). Statistical analysis was conducted on patients completing the trial for both studies (295, 296). Loss to follow-up was between 5-10% in the Gomez trial (295) and more than 10% in the Gonzalez trial (296). Adverse events were not reported in any studies.

Results

Gomez *et al.* reported that Pilates and the PFMT plus EStim treatment groups achieved a ststistically significantly higher number of fully continent patients than the control group ($P<0.05$). Continence (no pads) rates were 59% in Pilates, 54% in PFMT plus EStim, and statistically significantly greater than the control group (26%) after treatment (295, 322).

Gonzales *et al*. reported statistically significant differences in the 1-hour and 24-hour pad tests between EStim plus biofeedback versus control at three months ($p=0.01$ and $p=0.001$). The continence rates in the 1-hour and 24-hour pad tests were 64% and 44%, respectively, in the EStim plus biofeedback group at three months, and 9.1% and 4.5%, respectively, in the control group at three months. The ICIQ showed statistically significant differences between the two groups at three months ($P=0.001$) and six months ($P=0.0001$), again favouring the intervention group (296).

Summary

Thirteen studies investigated the addition of EStim plus PFMT or biofeedback in men with PPI. The new data did not change the Level of evidence or Grade of recommendation. Data suggest that EStim plus PFMT or biofeedback is superior to no treatment. However, there is no further benefit of EStim when added to PFMT compared to PFMT or Pilates training alone. The safety of using EStim in an area with cancer cannot be guaranteed (319). **(Level of evidence: 2)**

Recommendations

Although a combined intervention including EStim plus PFMT or biofeedback appears to be superior to no treatment, adding EStim to PFMT for men with PPI cannot be routinely offered. **(Grade of recommendation: B)**

Table 44. Summary of data on EStim + another treatment vs the other treatment

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow up…)
Gomes (2018) (295)	Group 1: Pilates (including PFMT) for 10 weeks Group 2: PFMT+EStim for 10 weeks Group 3 instructions to perform PFMT at home	120	PPI (SUI, UUI, MUI)	Continence (Number of pads/day) (QoL) ICIQ-UI SF	G1(59%). G2(54%) >G3(26%), P<0.05 P<0.01 between Group 1 and Group 3 NS between Group 2 and Group 3	10 weeks after the intervention	104 participants completed the RCT
Gonzalez (2020) (296)	EStim+BF 3 days/week for 3 months vs control (no treatment)	60	PPI 3 months post-surgery	Continence rate in 1-h pad test at 3M Continence rate in 24-h pad test at 3M Results of 1-h pad test at 3M and 6M Results of 24-h pad test at 3M and 6M ICIQ	Estim+BF > control (64% vs 9.1%) at 3 months Estim+BF > control (44% vs 4.5%) Estim+BF > control (P=0.01 and 0.01) Estim+BF > control (P=0.03 and 0.01) Estim+BF > control (P=0.01)	6 months after the 3-month intervention	47 participants completed the study Loss to follow-up: 5 in EStim+BF group 8 in control group

Abbreviations: PFMT: pelvic floor muscle training; EStim: Electrical stimulation; BF: biofeedback; PPI: post-prostatectomy urinary incontinence; SUI: stress urinary incontinence; UUI: urge urinary incontinence; MUI: mixed urinary incontinence; QoL: quality of life; ICIQ-UI SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form; NS: non-significant; PFMS: pelvic floor muscle strength

4. MAGNETIC STIMULATION (MSTIM)

MStim is a novel noninvasive approach which has been used to manage a number of neurological and psychiatric disorders. In terms of the therapeutic mechanism for male UI, MStim can generate a pulsed magnetic field through an electrified coil, which induces a flow of ions to form eddy currents when the excitable tissue is exposed to the magnetic field. Consequently, human motor nerves are depolarized and produce an action triggering external sphincter contraction (323, 324). Additionally, detrusor relaxation induced by MStim also contributes to male continence (325). Although MStim has been widely used to treat all types of UI in women, there are only limited studies exploring the effect of MStim on male UI secondary to RP. No new studies were identified.

4.1. Prevention

No trials investigating the primary or secondary prevention effects of MStim for men with UI were found.

4.2. Treatment

A total of three trials (two published, one abstract without data) were identified and only the two published trials were included in the 5th & 6th ICI. No new studies were identified based on current available evidence.

4.2.1. Is MStim better than no treatment, placebo, or control for treatment of UI?

No studies were found addressing this question.

4.2.2. Is one MStim approach better than another?

No studies were found addressing this question.

4.2.3. Is MStim better than other treatments?

No new studies were identified.

4.2.4. Does the addition of MStim to other treatments add benefit?

No new studies were identified.

5. PENILE VIBRATORY STIMULATION

This conservative treatment was included in the 5th edition. Penile vibratory stimulation (PVS) stimulates the pudendal nerve to treat SUI in men post prostatectomy. It has previously been shown to increase the external sphincter pressure in men with spinal cord injury (326, 327) and vibratory stimulation applied to the perineum in healthy women was related to increased external urethral pressure (328). No new trials have been found to add to the small pilot study (329) found in the last edition. No recommendations can be made.

6. SCHEDULED VOIDING REGIMENS

Scheduled voiding regimens include BT, timed voiding, habit training and prompted voiding. They are frequently combined to achieve maximum benefits. Although there is evidence to suggest that

scheduled voiding regimens, especially BT and timed voiding, are commonly used in the treatment of men with UI and other LUTS, there has been substantially less research that addresses their use in men compared to women, leaving insufficient evidence to comment on effectiveness.

For this edition there were no new trials to add to the 6th edition. In men, behavioural treatment may be just as effective for some LUTS, including UI, as pharmacological therapy. Further studies of high quality are needed before a recommendation for practice can be supported.

7. COMPLEMENTARY AND ALTERNATIVES MEDICINES

There is increasing evidence for the use of CAMs in management of chronic diseases. Basically, CAMs therapy including acupuncture, herbal therapy, massage, yoga, Tai Chi, Qi Gong, meditation, Ayurveda and homeopathy. In the 6th ICI, only a few low-quality trials were identified. Small sample size, absence of objective assessment, and lack of long term follow up were the main limitations. In the 7th ICI, these limitations remain. Three low quality, small sample studies were added to this section.

7.1. Prevention

One RCT examined the effect that participating in a structured yoga programme (n=35) during radiation therapy for prostate cancer had on urinary symptoms versus control (n=33) (330). Unfortunately, there were several ROB in this study with no blinding, allocation concealment or ITT analysis. There was also a large loss to follow up. While the IPSS increased over time in both groups, there was no difference between the groups after 6-9 weeks of yoga (330).

Another RCT looked at a pre-RP exercise programme (n=10) versus usual physical activity (n=10) using the IPSS (331). There were not sufficient details available in this abstract only to assess the ROB. No differences were reported between groups on the IPSS at 6 months after RP (331).

Summary

Yoga and generalised exercise programmes do not appear to impact urinary symptoms after treatment for prostate cancer as measured on the IPSS. **(Level of evidence 3)** Therefore, Yoga may not be routinely offered to all men with urinary symptoms after treatment for prostate cancer. More studies are needed. **(Grade of Recommendation D).**

7.2. Treatment

7.2.1. Acupuncture vs no treatment, sham acupuncture or any other treatment?

7.2.1.1. SUI

No new trials were identified.

7.2.1.2. OAB, UUI, MUI

One non blinded, moderate ROB trial was found observing the application of two weeks of Chinese medicine on the umbilicus + electroacupuncture (n=-42) versus tolterodine (n=41) in the management of OAB after TURP (332). On both outcome measures of UI and OABSS the Chinese traditional medicine group did statistically significantly better. Emerging translated literature suggest that traditional medicine may be of interest in male UI. More research in this field is warranted. **(Level of evidence 3).**

7.2.2. What is the most effective acupuncture protocol?

No new trials were identified.

7.2.3. Other approaches?

No trials were identified.

Table 45. Table of included RCTs for complementary and alternatives medicines in men.

Author, year	Study type/ Comparator	N	Study population	Modality details or parameters	Outcomes/results	Follow up	Notes (side effects, loss of follow-up…)
Exercise							
Ben-Josef (2017) (330)	RCT Yoga vs no yoga	68	Men undergoing 6-9 weeks of external beam radiation therapy	Group 1 (n=35): Yoga during radiation therapy (75 minutes, 2x per week) for 6-9 weeks. Group 1 (n=33): no yoga	IPSS was used to determine the severity of urinary symptoms and urinary QoL, and between-group differences at all follow-ups (p=0.1022) Week 4 Group 1 (n=22): 11.14±5.01 Group 2 (n=28): 13.34±6.82 Final Group 1 (n=22): 10.79±6.7 Group 2 (n=28): 15.04±6.5	4th week of radiotherapy and 1 week after the last treatment session/ external beam radiation therapy	Adverse events: NR Loss of follow up: 26.47% (19/68); Group 1: n=13 Group 2: n=5 Intention to treat: No
Flannigan (2020) (331) Abstract	RCT Aerobic and resistance exercise vs usual physical activity	20	Men diagnosed with prostate cancer and scheduled for a radical prostatectomy	Group 1: combined supervised aerobic and resistance exercise program for 8-12 weeks. Group 1: usual physical activity	There were no significant differences between the start and 6 months after RP regarding IPSS and FACT-P scores.	6 months after radical prostatectomy	Adverse events: NR Loss of follow up: 5% (1/20); Group 1: n=1 Intention to treat: NR
Acupuncture							
Jia (2014) (332)	RCT Electroacupuncture + Chinese medicine vs medication	83	Men who underwent transurethral resection of the prostate	Group 1 (n=42): Chinese medicine on umbilicus (3x per day, 30 minutes) + electroacupuncture (daily, 30 minutes) for 2 weeks Group 2 (n=41): tolterodine 2mg (2x/day) for 2 weeks	UI and OABSS significantly decreased in Group 1 when compared to Group 2 (p<0.05). UI: Group 1 (n=42): 0.8±0.5 Group 2 (n=41): 1.3±0.8 Between group comparison p<0.05 OABSS Group 1 (n=42): 6.6±1.2 Group 2 (n=41): 8.9±2.1 Between group comparison p<0.05	2 weeks after transurethral resection of prostate	Adverse events: NR Loss of follow-up: 0/83 Intention to treat: Yes

Abbreviations: RCT: randomized controlled trial; IPSS: International Prostate Symptom Score; QoL: quality of life; NR: not reported; UI: urinary incontinence; OABSS: Overactive Bladder Symptom Score

8. SUMMARY CONSERVATIVE MANAGEMENT FOR MALE UI

8.1. Lifestyle modification interventions

Prevention

Weight loss through lifestyle changes can be recommended to obese and overweight men with UI, particularly those with type 2 diabetes. **(Grade of recommendation: B)**

Smoking abstinence could be recommended for men with UI. **(Grade of recommendation: C)**

A reduction in caffeine intake could be recommended for men with incontinence symptoms; evidence suggests that the equivalent of two cups of coffee per day (250mg) is associated with UI in men. **(Level of evidence 3: Grade of recommendation: C)**

High vegetable, fruit and vitamin C intake could be recommended to men in the primary and secondary prevention of LUTS, UI and BPH. **(Grade of recommendation: C New)**

8.2. PFMT

Pre-operative instruction in PFMT can be recommended as it facilitate earlier recovery of continence in men undergoing RP **(Grade of recommendation: B)**

Early PFMT either pre-operatively or early post-operatively can be recommended to reduce time to continence after surgery. **(Grade of recommendation: B)**

There does not seem to be any benefit of adding EStim to a PFMT programme for men with persistent PPI and therefore it cannot be recommended routinely. **(Grade of recommendation: B)**

The use of biofeedback does not seem to add any benefit to a PFMT programme for men with persistent post-prostatectomy incontinence and therefore it cannot be recommended routinely. However, biofeedback may be considered for subgroups of men presenting reduced proprioception **(Grade of recommendation: B)**

The use of Pilates does not seem to be superior to a PFMT programme for men with persistent post-prostatectomy incontinence and therefore cannot be recommended for men with persistent post-prostatectomy incontinence. **(Grade of recommendation: B New)**

Pilates may be considered over no treatment to manage persistent post-prostatectomy incontinence in men. **(Grade of recommendation: D New)**

Novel interventions, which activate the PFM or involve support groups, could be beneficial after RP, but data is very limited **(Grade of recommendation C New)**

Long-term side effects of RP, such as climacturia and erectile dysfunction appears to. Be reduced using PFMT. PFMT could be considered for the treatment of climacturia and erectile dysfunction in men post RP. More research in this area is needed. **(Grade of recommendation: C (New).**

Men with PMD could be instructed to perform a strong PFM contraction immediately after voiding,or use urethral massage to empty the urethra. **(Grade of recommendation: C)**

8.3. EStim

Treatment

Although a combined intervention including EStim plus PFMT or biofeedback appears to be superior to no treatment, adding EStim to PFMT for men with PPI cannot be recommended routinely. **(Grade of recommendation: B)**.

8.4. MStim

No recommendation

8.5. Penile vibratory stimulation

No recommendation

8.6. Schedule voiding regimens

No recommendation

8.7. Complementary and alternative medicine

Yoga and generalised exercise programmes do not appear to impact urinary symptoms after treatment for prostate cancer as measured on the IPSS and therefore may not be routinely offered to all men with urinary symptoms after treatment for prostate cancer. More studies are needed. **(Level of evidence 3, Grade of recommendation D)**

V. URINARY INCONTINENCE IN MEN AND WOMEN

1. TIBIAL NERVE STIMULATION

Tibial nerve stimulation (TNS) is a form of peripheral neuromodulation targeted towards symptom relief of OAB and UUI.

Evidence for the use of TNS for the prevention and treatment of UI in adults (study with men and women with results combined) is presented below. Evidence for the use of TNS for the prevention and treatment of neurogenic UI is presented in the section VI.

Questions addressed are:
- Can TNS prevent UI?
- Is TNS better than no treatment, placebo, or control treatments for UI?
- Is TNS better than other treatments for UI?
- Does the addition of TNS to other treatments add any benefit?
- What is the best programme of TNS for UI in adults?
- What is the effect of TNS on LUTS other than UI?
- What factors might affect the outcome of TNS?

A literature search for reports of relevant systematic reviews and reports of RCTs and quasi-RCTs was performed (see Appendix 1). Trial data reported in conference abstracts as well as full text papers were included. Search dates were from 9th September 2015 to December 31st, 2020.

Eligibility criteria:

1. Reports of RCTs or quasi-randomised trials of TNS, percutaneous or transcutaneous.
2. Adult men and women with UI and/or OAB (with or without urgency incontinence) presentation of data combined for men and women. Trials including women only are presented in section II.6.

Evidence overview
This section was included for the first time in the 6th ICI with no date restrictions on searches applied. A total of 7 RCTs of tibial nerve stimulation (TNS) in adults were identified and one Cochrane systematic review of anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults (133), in which TNS trials with adults of both sexes only were included. Since then, a further eleven trials and a full report on a previously presented abstract (333) have been added.

Overall, five randomised trials compared TNS with a sham intervention (334-338). Four trials compared TNS with other active treatments for UI: two trials compared percutaneous TNS with different anticholinergics (339, 340), one trial compared percutaneous TNS with injected onabotulinumtoxin-A (341) and one trial compared transcutaneous TNS with transcutaneous electrical nerve stimulation (TENS) of the sacral foramina (342). Three trials compared different stimulation protocols (333, 343, 344). Percutaneous TNS was used in 7 randomised trials (335, 337-341, 344). Transcutaneous TNS was used in 4 trials (333, 334, 336, 342, 343). A direct comparison of transcutaneous and percutaneous TNS for treatment of UI has been undertaken in an adult population (343).

1.1. Prevention
There have been no studies on the effect of TNS for prevention of UUI/OAB in adults.

1.2. Treatment

1.2.1. Is TNS better than no treatment, placebo, or control for treatment of UI?
Five randomised controlled trials in adult men and women address this question. Two RCTs (334, 337) were adequately powered whereas Vohra (2002) (338) and Booth (2013) (336) are both pilot RCTs and Lashin 2020 (335) is an abstract of a small trial and reports no power calculation. See Table 46.

Quality of data
Computerised randomisation was used in four studies (334, 336-338) and not reported in Lashin 2020 (335). Adequate allocation concealment was reported in three (334, 336, 337) and unclear in two (335, 338). Subjects and outcome assessors were blinded throughout in three studies (334, 336, 337), with blinding unclear in two (335, 338). Three studies reported ITT analysis (334, 336, 337); the type of analysis was not reported in two (335, 338). There was no apparent inequality in loss to follow-up across the groups: In the ELECTRIC care home trial (334) 30 transcutaneous TNS and 31 sham residents were lost to follow up at 6 weeks (7 and 4 died from unrelated causes, respectively): 197 transcutaneous TNS and 178 sham resident data was analysed. In the SUmiT trial (337) seven subjects were lost to follow-up in the percutaneous TNS and 5 in the sham group thus 94% and 95% respectively were analysed. Two of the 30 subjects (6.6%), both from the sham group, discontinued in one trial (336), one subject (4.5%) from the control group dis-continued in one trial (338) and no attrition was reported by Lashin (335). Mild or moderate treatment relat-ed adverse events were reported by 2 sham subjects who complained of a heavy sensation/leg pain in ELECTRIC (334) and 6 percutaneous TNS subjects in SUmiT (337). They included ankle bruising (1 of 110, 0.9%) discomfort at needle site (2 of 110, 1.8%) bleeding at the needle site (3 of 110, 2.7%) and tingling in the leg (1 of 110, 0.9%). The Lashin (2020) (335) trial reported pain/discomfort at the needle site in 4 (16%) percutaneous TNS subjects and 2 (8%) sham; bleeding at the needle site in 1 (4%) percutaneous TNS subject and 2(8%) sham; tingling in the leg and ankle bruising in 1 (4%) percutaneous TNS subject and 0 (0%) in sham. No subjects in the transcutaneous TNS trial (336) reported adverse events and presence of adverse events was unclear in one study (338). Two trials were reported as pilots with no sample size calculation (336, 338), in one trial (335) no sample size calculation was provided and two trials were ade-quately powered (334, 337), however the payment of subjects for time and expenses in the SUmiT trial was a potential limitation and the efficacy achieved may not be equivalently reflected in translating to real world practice. ROB of bias was low in three trials (334, 336, 337) and high in two (335, 338).

Results
No study reported cure rates for UI. Four trials reported UI improvements and one trial reported no effect of transcutaneous TNS on UI in residents of care/nursing homes (334). In the SUmiT trial (337) 37.9% percutaneous TNS subjects reported moderate or markedly improved urgency incontinence compared to 22.1% sham subjects (p=0.02). Voiding diary analysis showed percutaneous TNS to be statistically significantly superior to sham in reducing urge incontinence episodes (p=0.002) from a median of 3.0 episodes accompanied by moderate to severe urgency per day at baseline, to a median of 0.3 episodes at 13 weeks (p<0.0001). Lashin (2020) (335) reported statistically significantly improved scores on the

OAB symptom scale in the percutaneous TNS group compared to the sham group at 7 weeks (Homma: 5.9±3.2 PTNS group, 9.6±1.4 sham, p<0.001; Blavais 16.6±3.4 PTNS group, 20.8±2.3 sham, p=0.007); 3months (Homma: 5.8±3.3 PTNS group, 9.2±1.1 sham, p<0.001; Blavais 18.2±4.3 PTNS group, 21.9±2.1 sham, p<0.001) and 6 months (Homma: 5.7±3.0 PTNS group, 9.8±1.8 sham, p=0.001; Blavais 19.2±4.2 PTNS group, 22.0±3.1 sham, p=0.005). In the two pilot trials Booth (2013) reported improved ICIQ-UI SF in 10 of 15 (67%) transcutaneous TNS group and 6 of 13 (46%) sham group (p=0.132, NS); Vohra reported statistically significantly reduced UI in 7 of 11 percutaneous TNS subjects but provided no estimates of effect size. There were no significant differences reported between transcutaneous TNS and sham groups in the ELECTRIC trial (334) in adjusted mean differences (95% confidence interval) of 24-hour volume of UI on pad test at 6 weeks (53ml; CI-22 to 128ml, p=0.164), 12 weeks (70ml; CI-9 to 148ml, p=0.081) or 18 weeks (21ml; CI -60 to 102ml, p=0.605). Data were not reported separately by sex in any of the trials.

In one large trial (337), percutaneous TNS subjects reported statistically significant improvements in over-all bladder symptoms with 54.5% reporting moderate or markedly improved Global Response Assessment (GRA) from baseline compared to 20.9% of sham subjects (p<0.001). A statistically significant difference between the groups in favour of percutaneous TNS was found for the OAB-q quality of life scores (p=0.006) and the SF36 general health survey quality of life scores significantly improved between baseline and 13 weeks for the percutaneous TNS group in the physical (p=0.002) and mental (p=0.049) domain scales. Voiding diaries were improved in 13 of 25 (52%) subjects who received percutaneous TNS (p<0.001) in the Lashin trial (335) but the authors did not specify the measurement time point. One pilot trial (338) reported significant improvements in quality of life (QoL questionnaires not specified and SF-36) but provided no data or figures to support this.

A prospective study to assess long-term outcomes and determine frequency of top-up stimulation sessions required was reported (337). Fifty responders to the original trial underwent a fixed 14-week tapered stimulation protocol, followed by a personal treatment plan aimed at maintaining improvements. Twenty-nine of 50 (58%) completed the outcomes. 77% of these maintained moderate or marked improvement in OAB symptoms at three years with a median 1.1 treatments each month.

Summary

The results of three trials, one rigorous, well-reported trial and two low quality trials, showed that percutaneous TNS is safe and more effective than a sham treatment for improving urgency incontinence in adults with OAB/UUI. There is evidence that effects are sustained for up to 3 years with regular treatment. **(Level of evidence: 1)**

One rigorous, well-reported trial showed that transcutaneous TNS is safe but has no effect on UI (of unspecified type) in older adults living in nursing or care homes. **(Level of evidence: 2)**

Further studies are needed to determine the effectiveness of transcutaneous TNS on OAB/UUI in frail older adults and in other adult populations.

Recommendation

Percutaneous TNS can be offered to men and women (adults) with UUI/OAB who do not achieve satisfactory results from first line lifestyle and behavioural intervention and pharmacological therapy. **(Grade of recommendation: B)**

Transcutaneous TNS cannot be offered to frail older adults as a treatment for UI as there is evidence of no effect **(Grade of recommendation: B New)**

In the adult population with UUI/OAB, Transcutaneous TNS may be a useful option to test earlier in the treatment algorithm, following lifestyle and behavioural interventions and before more invasive therapies are considered.

Table 46. Characteristics of studies comparing tibial nerve stimulation (TNS) with no treatment, placebo or control treatments for UI

Author, year	Comparator groups	N	Study population	Modality details or parameters	Outcomes	Follow up
Vohra (2002) (338)	Treatment group: Percutaneous TNS Active electrode: 34-gauge needle provides sensation. Inactive electrode: calcaneal surface electrode. Control group: Sham TNS Described as 'TNS treatment without nerve stimulation'	22	Adults with urgency frequency syndrome of > 6 months and urodynamic detrusor overactivity Males: not reported Females: not reported Results reported together	Pulse width: not reported Frequency: 20 Hz Intensity: 0.5-10mA according to sensory & motor response. Duration: 30 minutes Number sessions: 12 Programme length: 12 weeks	Micturition diary QOL questionnaires Repeat urodynamics SF-36 .	12 weeks

Author, year	Comparator groups	N	Study population	Modality details or parameters	Outcomes	Follow up
Peters (2010) (337)	Treatment group: Percutaneous TNS Active electrode: 34-gauge needle provides sensation. Inactive electrode: calcaneal surface electrode. Control group: Sham TNS Placebo needle with sensation of insertion. Inactive	220	Adults (>18) with OAB symptoms Males: 46 Females: 174 Results reported together	Pulse width: not reported Frequency: 20 Hz Intensity: 0.5-9mA according to sensory & motor response. Duration: 30 minutes Number sessions: 12 Programme length: 12 weeks	Primary outcome: Moderate/marked improvement in 7 level GRA at week 13 Secondary outcomes: Change in individual GRA symptoms 3-day voiding diary parameters OABq scores SF-36 QoL scores	13 Weeks
Booth (2013) (336)	Treatment group: Transcutaneous TNS Active: Surface electrode medial malleolus provides sensation. Inactive: surface electrode 10cm proximal to medial malleolus, Control group: Sham Transcutaneous TNS Surface electrodes X2 positioned below lateral malleolus and 10cm proximal to avoid tibial nerve current applied 2 mA	30	Older adults (>65) resident in care homes with urinary symptoms and/or incontinence Males: 6 Females: 24 Results reported together	Pulse width: 200 μS Frequency: 10 Hz Intensity: 1-50mA according to sensory & motor threshold and subject comfort. Duration: 30 minutes Number sessions: 12 Programme length: 6 weeks	AUASI ICIQ-UI SF PVR	6 Weeks
Booth (2020) (334)	Treatment group: Transcutaneous TNS Active: Surface electrode medial malleolus provides sensation. Inactive: surface electrode 10cm proximal to medial malleolus, Control group: Sham Transcutaneous TNS Surface electrodes X2 positioned below lateral malleolus and 10cm proximal to avoid tibial nerve current applied 4 mA	406	Older adults resident in care/ nursing homes with UI managed by pads and toilet programme. Males: 91 Females: 315 Results reported together	Pulse width: 200 μS Frequency: 10 Hz Intensity: 1-50mA according to sensory & motor threshold and subject comfort. Duration: 30 minutes Number sessions: 12 Programme length: 6 weeks	Primary outcome: 24-hour pad weight test for volume of urine leaked Secondary outcomes: number pads used, PPBC DEMqol	6, 12, 18 weeks
Lashin (2020) (335)	Treatment group: Percutaneous TNS Active electrode: 34-gauge needle provides sensation. Inactive electrode: calcaneal surface electrode. Control group: Sham TNS 34-gauge needle in medial gastrocnemius muscle. Inactive	50	OAB adult patients Males: 13 Females: 37 Results reported together	Pulse width: not reported Frequency: 20 Hz Intensity: 0.5-9mA according to sensory & motor response. Duration: 30 minutes Number sessions: 6 Programme length: 2 weeks	Homma OABSS Blavais OABSS 3-day voiding diary parameters	7 weeks, 3, 6 months

Abbreviations: GRA: Global Response Assessment; UUI: urinary urge incontinence; OABq: Overactive Bladder Questionnaire; SF-36: 36-Item Short Form Health Survey; AUASI: American Urological Association Symptom Index; ICIQ-UI SF: International Consultation on Incontinence Questionnaire on Urinary Incontinence Short Form; PVR: post-void residual urine volume; PPBC: Patient Perception of Bladder condition; DEMqol: Dementia Quality of Life; OABSS: Overactive Bladder Symptom Scores.

1.2.2. Is TNS better than another treatment for UI?

Two trials compared percutaneous TNS with another treatment for UI (Table 47). The other treatment was an oral drug – extended release tolterodine 4mg daily (339) or intra-detrusor injections of botulinum toxin type A [BTX-A] (341). There are no trials comparing transcutaneous TNS with other treatments in the adult population.

Quality of data

In Peters (2009) (339) 1:1 randomisation to percutaneous TNS or tolterodine was implemented using a random block design stratified by investigational site, however the success of allocation concealment was unclear. Sherif (2017) (341) provided no information about randomisation or allocation concealment. Blinding of subjects and clinicians was not possible given the different nature of the interventions with the comparator to percutaneous TNS being an oral medication (339) or intra-detrusor injection of BTX (341). Outcomes were subject reported in both trials and no indication of any assessor blinding was provided. An ITT analysis was not undertaken in either study. No reasons for withdrawal were provided for the 3 participants who dropped out in the Sherif trial (341). In the Peters trial (339), seven subjects (14%) with-drew from the drug group and nine (18%) from the percutaneous TNS group; none due to adverse effects; Adverse effects were mild or moderate in both groups with 14.3% (7 subjects) from the tolterodine arm reporting moderate adverse effects and 16.3% (8 subjects) from the percutaneous TNS group. Percutane-ous TNS related adverse events included leg cramps, intermittent foot/toe pain, generalised swelling, headache, haematuria, inability to tolerate stimulation, worsening incontinence and vasovagal response to needle placement (339). Sherif (341) reported adverse events of post-void residual urine >200ml requiring clean intermittent catheterisation in two patients (6.6%), early postoperative haematuria in three patients (10%) and UTI in two patients (6.6%). Minor localised bleeding and temporary pain were reported by an unspecified number in the percutaneous TNS group. The Peters trial (339) was adequately powered for a non-inferiority margin of 20% in number of voids per 24 hours based on the sample size calculation. No sample size calculation was reported by Sherif (341). Long-term follow-up of percutaneous TNS subjects for nine months after initial treatment completion was reported by both studies (341, 345). The overall ROB for both studies is high.

Results

Data were reported for the whole group with no differentiation by sex in both trials. Peters (2009) (339) reported that the global response assessment (GRA) demonstrated statistically significant subjective as-sessment of bladder symptom change compared to baseline, with 79.5% (35) of the percutaneous TNS group reporting cure (1) or improvement (34) and 54.8% (23) of the tolterodine group reporting cure (2) or improvement (21) (p=0.01). Both groups had improved significantly but there was a statistically significant difference between the groups in favour of the percutaneous TNS. Symptoms of UUI, reported in the void-ing diaries, improved significantly in both groups however there were no between-group differences for these measures. Similarly, quality of life scores showed statistically significant improvements for both treatment groups (P<0.001) but no between-group differences. The percutaneous TNS group reported statistically significantly less dry mouth than the tolterodine group (p=0.01) and a non-significant lower rate of constipation.

Follow-up to determine duration of effect up to 12 months from baseline was offered to percutaneous TNS responders (those who reported a successful response to GRA after 12 weeks) (345). Thirty-three of the 35 responders chose to continue. The GRA showed sustained improvements in 96% at 12 months, with a mean of 21 days between treatment sessions.

Sherif (2017) (341) reported statistically significant improvements in UI episodes, based on 3-day bladder diaries, for those treated with percutaneous TNS at 6 weeks, 3 and 6 months post-treatment (baseline UI episodes 4.7 + 1.01; 6 weeks UI episodes 2.2 + 0.7 P<0.05; 3 months UI episodes 2.6 + 0.7 P<0.05; 6 months UI episodes 3.3 + 0.6 P<0.05; 9 months UI episodes 4.2 + 1.04 NS) and those treated with BTX-A (baseline UI episodes 4.3 + 1.1; 6 weeks UI episodes 1.8 + 0.7 P<0.05; 3 months UI episodes 2.4 + 0.7 P<0.05; 6 months UI episodes 3.1 + 0.5 P<0.05; 9 months UI episodes 3.5 + 1.2; P< 0.05) but statistically significant improvements only extended to 9 months in the BTX-A group . Quality of life, measured by a single ques-tion on the OABSS, was significantly improved in both percutaneous TNS and BTX-A groups at all time points however the improvement was greater in the BTX-A group and the difference between the two groups was statistically significant at 6 weeks and 9 months.

Summary

Two trials compare percutaneous TNS with another treatment for UI. Evidence from a single RCT indicates that percutaneous TNS may be as effective as tolterodine, for urgency UI with an improved side effect pro-file; evidence from a single study comparing percutaneous TNS with BTX-A in the treatment of refractory idiopathic OAB indicates a significant reduction in UI episodes up to 6 months following treatment with percutaneous TNS but that it may be less effective than BTX-A in the management of refractory OAB, alt-hough associated with fewer side-effects. However, study design limitations in both trials suggest caution and further studies are recommended to establish the effects of percutaneous TNS in comparison to other pharmacological treatments. **(Level of Evidence: 2)**

As there were no trials comparing transcutaneous TNS with another active treatment, trials are needed to determine the effects of transcutaneous TNS compared to common anticholinergic drugs used to treat UUI/OAB in adults.

Recommendation

TNS can be considered as an alternative to tolterodine anticholinergic medication for OAB/UUI. (Grade of recommendation: B) There is insufficient evidence available to make further recommendations about TNS in comparison to other treatments for UI.

Table 47. Characteristics of studies of tibial nerve stimulation (TNS) added to other active treatment

Author, year	Comparator groups	N	Study population	Modality details or parameters	Outcomes/results	Follow up
Peters (2009) (339)	Treatment group: Percutaneous TNS Active electrode: 34-gauge needle provides sensation. Inactive electrode: calcaneal surface electrode. Comparator treatment group: Daily tolterodine ER 4mg	100	Adults with urinary frequency of at least 8 voids/24 hours Males: 6 Females: 94 Results reported together.	Pulse width: not reported Frequency: 20 Hz Intensity: 0.5-9mA according to sensory & motor response. Duration: 30 minutes Number sessions: 12 Programme length: 12 weeks	Primary outcome: mean reduction in number of urinary voids in 24 hours Secondary outcomes: change in 24 hour UUI episodes, number of voids causing waking, daily voided volume, episodes of urgency. OABq Investigator & subject OAB ratings using GRA.	12 weeks
Sherif (2017) (341)	Parallel group randomised clinical trial: 2 arms. Treatment group: Percutaneous TNS Active electrode: 0.22mm needle inserted 5cm above medial malleolus. Inactive electrode: calcaneal surface electrode. Comparator treatment group: Intradetrusor injection of botulinum toxin type-A (BTX-A) 100U	60	Adults (>18 years) with refractory idiopathic OAB symptoms. Males: 9 Females: 51 Results reported together	Percutaneous TNS Pulse width: NR Frequency: 20Hz Intensity:0.5-9mA Duration: 30 minutes Number sessions: 12 Programme length: 12 weeks Single BTX-A injection by cystoscopy in 20 sites (0.5 ml each site) under spinal anaesthesia with antibiotic prophylaxis. If PVR > 200ml ISC started	Outcomes: OABSS, urgency scale, QoL at 6 weeks, 3, 6 and 9 months. Frequency, nocturia, leaking episodes, PVR urine at 6 weeks, 3, 6 and 9 months. Urodynamic studies at 3, 9 months	6 weeks, 3, 6, 9 months

Abbreviations: GRA: Global Response Assessment; UUI: urinary urge incontinence; OABq: Overactive Bladder Questionnaire; ER: extended release; OABSS: Overactive Bladder Symptom Score; QoL: Quality of Life; PVR: Post Void Residual.

1.2.3. Does the addition of TNS to other UI treatment add any benefit?

One RCT was identified (340) that compared percutaneous TNS with percutaneous TNS plus oxybutynin, for treatment of patients with urodynamically diagnosed detrusor overactivity (DO). One new RCT was identified (342) comparing transcutaneous TNS plus transcutaneous electrical nerve stimulation (TENS) of the sacral foramina (SF) with transcutaneous TNS alone, for first-line treatment of idiopathic OAB (Table 48).

Quality of data

Karademir (2005) (340) reported randomisation following urodynamic studies into percutaneous TNS group or percutaneous TNS plus 5mg daily oxybutynin hydrochloride but no description of method of randomisation or adequacy of allocation concealment, blinding of subjects, clinicians or assessors or type of analysis. Surbala (2014) (342) used computer-generated randomisation and reported on allocation concealment, blinding of assessors and ITT analysis. No subject dropped out in either study. There were no adverse events in Surbala (2014) (342) and in Karademir (2005) (340) adverse events were mild: percutaneous TNS plus drug group - seven reported dry mouth, one blurred vision; percutaneous TNS group – one reported a small haematoma, one local tenderness. There was no sample size calculation in either study, no long-term follow-up and overall ROB was high.

Results

In Karademir (2005) (340) four of five subjects receiving percutaneous TNS only and all five subjects receiving percutaneous TNS and oxybutynin, with urgency UI reported cure on voiding diary. The numbers were too small for statistical analysis. Overall treatment response was defined as patient reported improvement in OAB symptoms of frequency, urgency and urge incontinence by > 35% and occurred in 61.6% percutaneous TNS group and 83.2% percutaneous TNS plus oxybutynin group. The between group difference was not statistically significant. Surbala (2014) (342) reported all stimulation resulted in statistically significantly improved OABSS, UDI-6 and IIQ-7 at 4 weeks. Large effect sizes (> 0.8) were shown for all outcomes, with combined transcutaneous TNS and SF TENS, compared to transcutaneous TNS alone. No UI-specific results were presented.

Summary

The evidence is limited to two small, low-quality trials **(Level of evidence: 2)** which indicate the possibility of additional effects from adding oxybutynin to a programme of percutaneous TNS or parasacral TENS to a programme of transcutaneous TNS.

Large, well-designed trials are needed to establish whether the addition of any anticholinergic drug or other type of EStim enhances the effectiveness of TNS in adults with UUI/OAB.

Recommendation

Based on current evidence on adding oxybutynin to percutaneous TNS and adding parasacral TENS to transcutaneous TNS could be considered for additional benefit, in adults with OAB. (**Grade of recommendation C)**

Further high-quality trials are needed.

Table 48. Characteristics of studies of tibial nerve stimulation (TNS) added to other active treatment

Author, year	Comparator groups	N	Study population	Modality details or parameters	Outcomes/results	Follow up
Karademir (2005) (340)	Treatment group: Percutaneous TNS plus oral oxybutynin hydrochloride 5mg daily. Percutaneous TNS plus oral oxybutynin hydrochloride 5mg daily Active electrode: 34-gauge needle provides sensation. Inactive electrode: calcaneal surface electrode. Comparator treatment group: Percutaneous TNS Active electrode: 34-gauge needle provides sensation. Inactive electrode: calcaneal surface electrode.	43	Adults with > 6 months history of OAB symptoms and DO on UDS Males: 5 Females: 38 Results reported together	Pulse width: 200 µS Frequency: 20 Hz Intensity: 0.5-9mA according to sensory & motor response. Duration: 60 minutes Number sessions: 8 Programme length: 8 weeks	Outcomes measured with Bristol Urinary Questionnaire and voiding diary. Improvements in symptoms by >70%, 35-70% and <35% represented complete remission, partial remission and no response.	8 weeks
Surbala (2014) (342)	Parallel group RCT, 3 arms Treatment group: Transcutaneous TNS: surface electrode proximal to medial malleolus and second 10cm cephalad plus sacral foramina (SF) TENS: surface electrodes placed over S2-3 parasacral region Comparator treatment group 1: SF TENS: surface electrodes placed over S2-3 parasacral region Comparator treatment group 2: Transcutaneous TNS surface electrode proximal to medial malleolus and second 10cm cephalad	44	Adults with idiopathic OAB Males:14 Females:30 Results reported together	Transcutaneous TNS Pulse width: 200µs Frequency: 10Hz Intensity: NR individually adjusted Duration: 20 minutes Number sessions: 24 Programme length: 4 weeks SF TENS Pulse width: 200µs Frequency: 10Hz Intensity: NR. Individually adjusted Duration: 20 minutes Number sessions: 24 Programme length: 4 weeks	Outcomes: OABSS UDI-6 IIQ-7	4 weeks

Abbreviations: OAB: overactive bladder; OABSS: Overactive Bladder Symptom Score; UDI-6: Urinary Distress Inventory 6; IIQ-7: Incontinence Impact Questionnaire 7; TENS: Transcutaneous Electrical Nerve Stimulation; SF: sacral foramina.

1.2.4. What is the best TNS protocol for UI in adults?

Three RCTs compared different stimulation protocols. Finazzi-Agro (2005) (344) compared weekly and thrice weekly percutaneous TNS, Seth (2018) (333) compared weekly and daily transcutaneous TNS using a novel device and Ramirez-Garcia (2018) (343) compared efficacy of percutaneous TNS and transcutane-ous TNS in adults with idiopathic OAB. Details are provided in Table 49.

Quality of data

Computer-generated online randomisation was used by Ramirez-Garcia (2018) (343) and Seth (2018) (333) with associated allocation concealment. Selection bias is possible in Finazzi-Agro (2005) (344) as random-isation methods were not described. Blinding of subjects or clinicians was not possible within these study designs. Type of analysis was not reported in two trials (333, 344) while ITT analysis was reported in Ramirez-Garcia (343). Outcomes were reported at the end of each treatment protocol but no long-term follow up was reported. Withdrawals were high (29.2 %) in the Seth pilot trial (333), with 8 of the 14 with-drawals being device related, although no significant adverse events occurred. There were no withdrawals in the Finazzi-Agro trial and no adverse events reported. Ramirez-Garcia (343) reported 7 drop-outs (10.3%) and no serious adverse events.

Results

In the Finazzi-Agro trial (344) 4 of 11 (36%) subjects with UI in the weekly percutaneous TNS group and 5 of 11 (45%) subjects with UI in the 3 X weekly percutaneous TNS group reported complete cure after treat-ment. Overall success of >50% reduction in micturition episodes/24 hours or (if incontinent) UI epi-sodes/24 hours was confirmed for 11 of 17 (63%) subjects in the weekly percutaneous TNS group and 12 of 18 (67%) subjects in the 3 times weekly percutaneous TNS group. Subjective improvement was reported after 6-8 sessions, regardless of frequency of delivery. In the Seth trial, 18 of 34 (53%) subjects who com-pleted the 12-week protocol were responders [daily treatment (n=9), weekly (n=9)], rating their improve-ment as moderate to significant on the General Response Assessment (GRA). Statistically significant improvements in ICIQ-OAB (p=0.001) and ICIQ LUTSqol were reported for both daily and weekly stimula-tion groups. There were no differences in ICIQ or bladder diary parameters between those with idiopathic and neuropathic OAB however the proportion of idiopathic OAB GRA responders was 36% (5/14) com-pared to 65% (13/20) in the neuropathic OAB group. Ramirez-Garcia showed non-inferiority of transcuta-neous TNS compared with percutaneous TNS in both urgency and leakage episodes, which reduced by similar amounts in both groups: 23% and 47% in transcutaneous TNS and 14.6% and 60% in percutaneous TNS. Both groups achieved statistically significant mean increases of 21.5 and 22.1 points (P<0.001) in I-QOL with no statistically significant between group difference.

Summary

One small well conducted RCT demonstrates non-inferiority of transcutaneous TNS compared to percuta-neous TNS for reducing urgency UI episodes and improving quality of life. **(Level of evidence: 1b)**

Two small trials indicate that no benefit on outcome is conferred by a more than once weekly stimulation protocol for percutaneous or transcutaneous TNS however it is possible that symptom improvement may be more rapid with a more frequent delivery protocol. **(Level of evidence: 2)**

Larger, rigorous and well-reported trials are needed to confirm the most effective type of TNS, timing and duration of protocols to treat UI.

Recommendation

Percutaneous or transcutaneous TNS can be delivered at least once weekly, and the protocol determined by patient preference. **(Grade of recommendation B New)**

Table 49. Characteristics of studies comparing one protocol of Tibial Nerve Stimulation (TNS) with another for UI

Author, year	Comparator	N	Study population	Modality details or parameters	Outcomes	Follow up
Finazzi-Agro (2005) (344)	Treatment group A: weekly percutaneous TNS Active electrode: 34-gauge needle provides sensation. Inactive electrode: calcaneal surface electrode. Comparator treatment group B: 3 x weekly percutaneous TNS Active electrode: 34-gauge needle provides sensation. Inactive electrode: calcaneal surface electrode.	35	Adults with refractory OAB syndrome Males: 7 Females: 28 Results reported together	Pulse width: not reported Frequency: 20 Hz Intensity: 0.5-9mA according to sensory & motor response. Duration: 30 minutes Number sessions: 12 Programme length: 12 weeks (Group A); 4 weeks (Group B)	24 hour BD I-QoL SF36 UDS Success defined as those who reported micturition epi-sodes/24hours or incontinence episodes/24 hours reduced by >50%	4 weeks (3X weekly TNS) 12 weeks (1 X weekly TNS)
Seth (2018) (333)	Parallel group randomised clinical trial, 2 arms. Treatment group Transcutaneous TNS using GekoTM device weekly Comparator treatment group Transcutaneous TNS using GekoTM device daily	48	Adults with idiopathic (24 subjects) or neuropathic (24 subjects) OAB Number with UI 38 Males 10 Females 38 Results reported together	Transcutaneous TNS delivered via the GekoTM device Pulse width: varied between 70 and 560 µs, increased as tolerated Frequency: 1Hz Intensity: 27mA Duration: 30 minutes Number sessions: 12 (weekly group), 84 (daily group) Programme length: 12 weeks	Outcomes: Respond-er defined as those rating moderate to sig-nificant improvement on GRA Change in individual GRA symptoms ICIQ-OAB, ICIQ-LUTSqol BD parameters	12 weeks
Ramirez-Garcia (2019) (343)	Parallel-group non-inferiority randomised clinical trial; 2 arms. Treatment group: Transcutane-ous TNS Active: Surface electrode 5cm above medial malleolus pro-vides sensation. Inactive electrode: calcaneal surface electrode. Comparator treatment group: Percutaneous TNS Active electrode: needle insert-ed 5cm above medial malleolus. Inactive electrode: calcaneal surface electrode.	68	Adults with clinical idiopathic OAB and urodynamic DO Males: 22 Females: 46 Results reported together	Transcutaneous TNS Pulse width: 200µs Frequency: 20Hz Intensity:0.5-20mA Duration: 30 minutes Number sessions: 12 Programme length: 12 weeks Percutaneous TNS Pulse width: 200µs Frequency: 20Hz Intensity:0.5-20mA Duration: 30 minutes Number sessions: 12 Programme length: 12 weeks	Primary outcome: Difference in number of daytime frequency voiding of at least two voids. Secondary outcomes: Reduction in nocturia, urgency episodes, leakage episodes and improved I-QOL	12 weeks

Abbreviations: GRA: Global Response Assessment; UDS: Urodynamic studies; SF-36: 36-Item Short Form Health Survey; ICIQ-OAB: International Consultation on Incontinence Questionnaire on Overactive Bladder; ICIQ-LUTSqol: International Consultation on Incontinence Quality of Life questionnaire; BD parameters: bladder diary parameters.

1.3. What is the effect of TNS on LUTS other than UI?

No trials were identified that analysed the effect of TNS in adults with other LUTS alone i.e., frequency of voiding, urgency, nocturia and integrated reporting of UI and other LUTS was a feature of all studies. In one RCT comparing efficacy of transcutaneous TNS and percutaneous TNS (343), the primary outcome was reduction in daytime frequency of voiding. This outcome significantly reduced in the transcutaneous TNS group by 1.3 episodes (95% CI 0.5,2.0) (P=0.002) compared to a non-statistically significant reduction in the percutaneous TNS group of 0.4 episodes (95% CI -0.3,1.1) (P=0.213). Similar results were found for number of urgency episodes in 24 hours, which reduced in the transcutaneous TNS group by 2.2 episodes (95% CI 1.1,3.1) (P<0.001) compared to 1.4 episodes in the percutaneous TNS group of (95% CI -0.3,3.1) (P=0.102). Voiding frequency in 24 hours was significantly reduced in the transcutaneous TNS group by 1.6 episodes (95% CI 0.8, 2.5) (P<0.001) compared to 0.8 episodes in the percutaneous TNS group (95% CI -0.1,1.6) (P=0.073). The adjusted analysis of the differences between transcutaneous TNS and percutaneous TNS showed no statistical significance for the primary outcome of daytime frequency of voiding in the per protocol (P = 0.089) or the ITT analysis (P = 0.064).

For percutaneous TNS, in the large, well reported SUmiT trial the percutaneous TNS group reported statis-tically significant improvements in voiding diary symptoms of frequency, night-time voids and voids with moderate to severe urgency, compared to the sham group (Peters 2010). A small pilot trial reported re-duced day and night-time frequency and urgency by 63% after 12 weekly 30-minute percutaneous TNS sessions, although no effect size estimates were provided. The elimination of detrusor overactivity on repeat urodynamic testing was also shown (338).

For transcutaneous TNS, compared with sham, one trial in care home residents (336) reported statistically significantly improved total AUASI scores for 87% of the transcutaneous TNS group compared to 31% sham group (p<0.001).

When comparing percutaneous TNS with 4 mg daily tolterodine, Peters (2009) reported a statistically significant reduction in bladder diary reports of voiding frequency, nocturia, moderate to severe urgency episodes in both groups and no between-group differences.

Self-reported urinary urgency was statistically significantly reduced at 6 weeks, 3 and 6 months by percutaneous TNS and BTX-A but at 9 months only by BTX-A (341).

One trial comparing two percutaneous TNS protocols (344) reported a statistically significant reduction in frequency (P=0.01) for both once and three times weekly treatment regimes. A similar result was reported by Seth (2018) (333) who showed a reduction in 24-hour frequency from 11.5 at baseline to 8.8 at week 12 for both the daily- and the weekly- transcutaneous TNS groups.

1.4. Factors affecting outcomes

None of the included TNS trials addressed the effect of age or any other factor on prediction of outcome of TNS. Effectiveness of transcutaneous TNS on UI in frail older adults resident in care homes was the focus of a large, rigorous trial (334) and a well-reported pilot trial (336) where the mean age was 85 and 84.2 years respectively. The adherence to the transcutaneous TNS was high (85-100%), with no serious adverse effects reported however transcutaneous TNS in the ELECTRIC trial conferred no benefit on volume of UI in this elderly, frail population, 75% of whom were dependent of staff for assistance to use the toilet. A prospective study (346) of prognostic factors for successful percutaneous TNS showed that sex, age, weight, body mass index, indication for percutaneous TNS, duration of symptoms, number and type of previous treatments, number of UI episodes/24 hours, voiding frequency/24 hours and total IQoL scores were all unrelated to the success or not of percutaneous TNS in men and women with OAB, non-obstructive urinary retention or chronic pelvic pain. A low Mental Component Summary Score on the SF-36 was a negative predictive factor for success of percutaneous TNS, both subjectively and objectively. Additionally, patients with OAB who had detrusor overactivity had poorer outcomes than those without, as did those with low bladder capacity at baseline (137). A retrospective chart review of 162 women to identify prognostic factors for successful TNS found that in women treated with percutaneous TNS for refractory OAB, a history of depression/anxiety and severe baseline urgency UI, were positive predictors of a successful percutaneous TNS outcome (347).

These results mean there is no reason to exclude older adults, those with a long symptom history, weight difficulties, anxiety/depression, severe symptoms, or failure of previous treatments and that they should be offered TNS where indicated, except where recognised contraindications to TNS, such as a cardiac pacemaker are present. Only in those patients with poor mental health overall and/or overactive and/or low-capacity bladders at baseline, or who are dependent on others to use a toilet, should the possibility of limited success be considered.

Summary

The evidence on which to base recommendations for best practice in the use of TNS to treat OAB/UUI in men and women remains sparse, for both percutaneous and transcutaneous TNS. However, it is sufficiently robust to support the use of percutaneous TNS when less intensive and invasive behavioural treatment options have **failed (Level of evidence: 1)** and there is the suggestion that percutaneous TNS may be as effective as some drug therapy, making it a viable alternative. **(Level of evidence: 2)**

Only four trials investigated transcutaneous TNS. One large trial showed no effect on UI of unspecified type in older people dependent on staff to use a toilet. **(Level of evidence: 2)** The other three trials showed promising results suggesting further well-designed and reported trials in different adult populations would allow decisions to be made about the place of transcutaneous TNS in the treatment algorithms for OAB/UUI in men and women. **(Level of Evidence: 2)**

A single RCT has demonstrated non-inferiority of transcutaneous TNS compared to percutaneous TNS in decreasing daytime frequency and UUI episodes in men and women with idiopathic OAB. **(Level of evidence: 1b)**

Health economic information is required to establish the cost effectiveness of the different forms of TNS, particularly in comparison to pharmacotherapy.

Based on the included studies percutaneous TNS continues to use a standard protocol regarding stimulation parameters of frequency and session duration. Most studies report using the Urgent PC™ stimulator however the study comparing transcutaneous and percutaneous TNS (343) used an alternative low voltage stimulator (URO STIM). The number of individual sessions, overall duration of programme and timing of delivery protocols remain varied. There is also variation between percutaneous and transcutaneous stimulation parameters This variability re-

flects the limited understanding of the mechanisms of TNS effect, which cannot be assumed to be identical for both percutaneous and transcutaneous routes of delivery. Further investigation is required, for both percutaneous and transcutaneous TNS, to determine the most effective type of stimulation and treatment protocols and further compare the modalities for superior intervention in different populations.

Recommendations for practice:

In adults with OAB/UUI percutaneous TNS is better for improving UUI than no treatment or sham and can be offered to adults with UUI/OAB who do not achieve satisfactory results from first-line lifestyle and behavioural interventions or drug therapy. **(Grade of recommendation: B)**

At least weekly TNS sessions can be offered during an active treatment programme with regular top-ups provided to sustain benefits for up to three years. **(Grade of recommendation: B)**

Transcutaneous TNS can be offered as an alternative to percutaneous TNS for treating adults with idiopathic OAB/UUI. Transcutaneous TNS can be the recommendation of choice and preferred by patients and clinicians as it is a less invasive approach, with reduced related adverse effects. **(Grade of recommendation: B New)**

Transcutaneous TNS cannot be offered to frail older adults with UI who are dependent on others to use a toilet as there is evidence of no effect **(Grade of recommendation: B New)**

Percutaneous TNS can be offered as an alternative to tolterodine for OAB/UUI in adult men and women. **(Grade of recommendation: B)**

Future research directions:

Currently available evidence compares percutaneous TNS with older antimuscarinics. Future rigorous trials should compare percutaneous TNS with other commonly used antimuscarinics and beta 3 adrenergic agonists for efficacy and adverse effect profiles, in men and women with OAB/UUI.

The effectiveness of adding drug therapy to percutaneous and transcutaneous TNS should be further investigated in high quality trials with adults with OAB/UUI.

Trials of new delivery systems for TNS, such as use of implanted tibial nerve stimulators are needed.

Further evidence of the effectiveness of transcutaneous TNS to treat OAB/UUI in adults is needed and its place in the treatment algorithm should be clarified, especially in relation to percutaneous TNS.

Research comparing transcutaneous TNS with all types of drug therapy is required.

Further rigorous and well-reported trials are needed to establish the most effective dose of percutaneous TNS and transcutaneous TNS, including the timing and duration of TNS protocols, stimulation parameters and maintenance regimes.

Cost-effectiveness of percutaneous and transcutaneous TNS needs to be established, especially in relation to other forms of treatment, including drug therapies and botulinum toxin.

Evidence on longer term outcomes of percutaneous and transcutaneous TNS is needed.

VI. NEUROLOGICAL CONDITIONS

Conservative Management of UI in Neurological Patients

UI is commonly reported by patients with neurological disorders and the pattern of lower urinary tract (LUT) dysfunction is influenced by the site of the neurological lesion in the neuraxis. Suprapontine lesions affect the cerebral cortex, subcortical white and grey matter and upper brainstem following stroke, neurodegeneration (e.g., Parkinson's disease (PD), Alzheimer's disease) and neuroinflammation (multiple sclerosis), resulting predominantly in urinary storage symptoms and UUI. The spinal cord is affected by neuroinflammation (multiple sclerosis (MS)), trauma and congenital anomalies (spinal bifida), typically resulting in mixed storage and voiding symptoms. Disorders affecting the conus, cauda equina and peripheral nerves result predominantly in voiding dysfunctions.

This new section reviews the evidence for the effects of conservative management on neurogenic UI. The interventions are grouped into PFMT, EStim (including tibial nerve stimulation and TENS performed in other regions), acupuncture, toilet assistance and multimodal rehabilitation intervention. Eligibility criteria for study participants and outcomes, as well as criteria used to assess ROB in the included studies, are identical to those described in the previous sections. Highest levels of evidence available were reviewed and they are summarized in the different tables in this section. Table 50 provides an overview of the included studies of conservative management for UI in neurological patients. As this is a new section, we limited the assessment of the literature and levels of recommendations to conservative management only.

Table 50. Studies of conservative management for UI in neurological patients

Intervention	Number of studies	Outcomes assessed
PFMT		
Multiple Sclerosis	8	OAB (2), urinary incontinence (4), OAB/ urinary incontinence (3), OAB/ urinary incontinence/nocturnal enuresis (1)
HTLV1 associated myelopathy	1	OAB (1)
Spinal Cord Injury	2	OAB/ urinary incontinence (1)
Alzheimer disease	1	urinary incontinence (1)
Stroke	5	urinary incontinence (5)
Parkinson's Disease	1	OAB/ urinary incontinence (1)
Electrical Stimulation		
Tibial nerve stimulation		
Transcutaneous (TTNS)		
Spinal Cord Injury	1	urinary incontinence (1)
Parkinson's Disease	2+1 (non RCT)	OAB/urgency incontinence, urinary incontinence (2)
Stroke	2	urinary incontinence (1), urgency urinary incontinence/nocturnal enuresis (1)
Multiple Sclerosis	2+1 (non RCT)	Urgency (1)
Mixed Neurological group	2	urinary incontinence (1), perception of bladder condition (1)
Percutaneous (PTNS)	9 (non RCT)	
Parkinson's Disease	3	
Multiple Sclerosis	4	
Mixed Neurological group	2	
TENS performed in other regions		
Stroke	2 -Positive electrode (second lumbar spinous process), Negative electrode (middle and lower third of junction between posterior superior iliac spine and ischial node) -Positive electrode (second sacral level), Negative electrode (middle and lower third of junction between posterior superior iliac spine and ischial node)	OAB (1), OAB/ urinary incontinence (1)
Mixed neurological group	1 (intravaginal/intra-anal electrical stimulation vs pudendal nerve)	LUTS (1)
Multiple Sclerosis	2	OAB (1), OAB/ urinary incontinence (1)
Acupuncture		
Stroke	Electroacupuncture (6), acupuncture (9)	urinary incontinence (10), LUTS (2), OAB (1), urinary functions (1)
Spinal Cord Injury	Electroacupuncture (1)	urinary incontinence (1), LUTS (1)
Parkinson's Disease	Electroacupuncture (1)	urinary incontinence (1)
Toilet assistance		
Stroke	Bladder training (2), timed voiding (2), systematic voiding programme (1)	urinary incontinence (3), urinary incontinence/ urgency incontinence (1)
Spinal Cord Injury	Bladder training (1)	urinary incontinence (1)
Parkinson's Disease	Bladder training (1)	urinary incontinence, OAB (1)
Multimodal rehabilitation intervention		
Multiple Sclerosis	Bladder management programme (1)	LUTS (1)
Spina bifida	High intensity rehabilitation programme including bladder/ bowel management programme (1)	LUTS (1)

1. PELVIC FLOOR MUSCLE TRAINING

1.1. Prevention

There were no studies identified.

1.2. Treatment

There were 17 RCTs that included PFMT in a study arm (348-367), and the characteristics of these studies are presented in Table 51. The interventions studied were highly variable and usually combined with other modalities of treatment. PFMT alone was only assessed in five studies (348, 350, 358, 361-364). PFMT with intravaginal or intra-anal EStim was evaluated in three studies (350, 351, 357, 365), and with biofeedback in five (350, 353, 355-357, 365). PFMT was combined with other interventions, such as education about pelvic anatomy and function (354, 359, 366), general rehabilitation (359, 360), surface electrical muscle stimulation (348, 360), exercises (i.e., breathing and relaxation exercises) (352), BT (354, 366), intermittent catheterisation (367) medication (349, 353), fluid management (366), and a video about behavioural management (349). The PFMT intervention was either supervised (351, 353-356, 358, 359, 361-364) or performed at home unsupervised (348, 350, 357, 358, 365, 366) (Table 51).

Quality of data

Randomisation was considered appropriate in 12 studies (348, 350, 351, 353, 355-359, 361-364, 366, 367) and could not be determined in the remaining studies. Allocation concealment could be assessed in only two studies and was considered adequate (357, 366). Two studies were double blinded (355-357) and evaluators alone were blinded in four studies (350, 351, 359, 364, 366). Information regarding an ITT analysis was obtainable in only four studies (350, 357, 366) and was performed in two (357, 366). Loss to follow-up was reported in only two studies (350, 355, 356).

Results

Table 51 summarizes the results of these studies. Studies evaluating PFMT in patients with MS and post-stroke demonstrated a significant improvement in UI symptoms when compared to no-treatment (i.e., not related to active LUTS treatment including general education or rehabilitation) or sham treatment (355, 356, 359, 361-363). However, in a cohort of post-stroke men, PFMT was associated with an improvement in PFM strength and function but not LUTS (364). Nonetheless, this study included (364) a small sample size with a long-term follow-up (six months), and although the attendance to weekly PFMT was high, the consistency of the training might not have been monitored. One study, in patients after stroke assessing supervised PFMT, demonstrated improvements in UI severity when compared to unsupervised PFMT at home (358). This finding is in line with PFMT results found in non-neurological female patients with UI (refer to section II.2.3.1).

Studies evaluating the addition of biofeedback to PFMT showed mixed results. Improvement in OAB and UI symptoms was noted in MS patients when the intervention was added to intravaginal or intra-anal EStim (351, 357, 365). However, in a study evaluating a cohort of MS patients (353), no significant improvement in incontinence episodes was observed in those receiving EMG biofeedback and medication. Likewise, in a cohort of women with incomplete spinal cord injury (SCI), no further benefit in continence was seen with the addition of intravaginal or intra-anal EStim, although both treatment groups improved after intervention (350). Other than differences in the population and the addition of intravaginal or intra-anal EStim to the intervention arm, studies that showed benefit presented a much larger sample size than the studies with no benefit.

PFMT as part of a multimodal behaviour therapy in a cohort of patients with PD was found to be more effective in reducing incontinence episodes compared to a control (366).

One of the studies primarily evaluated the addition of mirabegron to a PFMT intervention with behavioural management (349) and was therefore not considered when determining a recommendation. Another study (367) compared PFMT with intermittent urethral catheterisation to plum-blossom needle and was also not considered when determining a recommendation. One further study (352) analysed the efficacy of PFMT and exercises for UI on SCI patients, however, this study did provide information about the type and level of injury.

No serious adverse events were reported in any of these studies. However, one participant in the PFMT group reported soreness in the pelvic area. (350)

Summary

A total of 17 RCTs across different neurological groups, including MS, incomplete SCI, Parkinson's disease, Alzheimer disease and post-stroke, assessed the effects of PFMT on UI, OAB symptoms and/or LUTS against an active, no treatment or placebo comparator.

The interventions that were evaluated and the study designs adopted differed considerably between studies. Data from two well-designed high-quality studies in MS and PD patients (357, 366) (**Level of evidence: 2a)** and most of the other studies (**Level of evidence: 2**) demonstrated a significant improvement in UI symptoms, LUTS and QoL across different neurological groups following supervised or home PFMT combined with biofeedback and also with added active treatments such as intravaginal EStim, BT, and behavioural management. (**Level of evidence: 2**)

Recommendation

PFMT alone or combined with other active treatments is an effective and safe treatment, more effective than no active treatment for managing OAB and related UI symptoms. Therefore, PFMT can be recommended as first line treatment in patients with MS, incomplete SCI, PD, and post-stroke. **(Grade of recommendation: B New)**

These findings need to be investigated further with larger good-quality trials.

Table 51. RCT studies evaluating PFMT

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Bottini (2019) (348)	RCT	Multiple sclerosis and Myelopathy associated with HTLV-I Single centre Brazil	Group 1 (n=10): PFMT at home (2x/week) during 4 months Group 2 (n=10): PFMT at home + electrical stimulation (2x/week, 1 hour) during 4 months	-Overactive bladder version 8 (OABv8): Group 2 showed significant improvement when compared to baseline (p = 0.001) Statistical comparisons between groups are not reported - Qualiveen Instrument: NR	Adverse effects: NR Follow-up: post-intervention (4 months)
Brown (2020) (349) Abstract	RCT	Multiple Sclerosis USA	Group 1 (n=14): PFMT + Mirabegron (25 – 50 mg) + Behavioral management during 10 weeks Group 2 (n=14): PFMT + Placebo + Behavioral management during 10 weeks	- OAB Symptom Composite Score Group 1 was 0.47 (95% CI 0.047 to 0.893, p=0.031) higher than Group 2. Incontinence episodes: no significant difference between groups	Adverse effects: none Follow up: post-intervention (10 weeks)
Elmelund (2018) (350)	RCT	Incomplete spinal cord injury Single centre Denmark	Group 1 (n=17): PFMT (daily) during 12 weeks Group 2 (n=19): PFMT (daily) + intravaginal electrical stimulation (daily) during 12 weeks All participants were trained by a physiotherapist but the intervention was performed at home. The PFMT training included digital vaginal and rectal palpation and EMG biofeedback.	-ICIQ-UI-SF: between group comparison showed no significant difference at 12 and 24 weeks. The within-group analyses showed a significant improvement from baseline at 12 and 24 weeks in the PFMT group -3-day bladder diary/ Daily UI: between group comparison showed no significant difference at 12 and 24 weeks. Daily incontinence episodes showed improvement from baseline at 12 and 24 weeks in the PFMT group. -Pad Test 24h: between group comparison showed no significant difference at 12 and 24 weeks. The within group comparison showed improvement in the Group 2 at 12 weeks and Group 1 at 24 weeks follow-up. -ICIQ-OAB: between group comparison showed no significant difference at 12 and 24 weeks. The within group comparison showed improvement in the Group 2 at 24 weeks -Patient Global Impression of Improvement scale (PGI-I): between group comparison showed no significant difference at 12 and 24 weeks.	Adverse effects: Group 1: soreness in PF area (n=1) Group 2: none Follow up: post-intervention (12 weeks) and 24 weeks

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Ferreira (2019) (351)	RCT	Multiple Sclerosis Single centre Brazil	Group 1 (n=16): Supervised PFMT and intravaginal electrical stimulation (30 minutes 2x/week) during 6 months Group 2 (n=15): home PFMT during 6 months	Qualiveen questionnaire: For general QoL the within-group analyses showed a significant improvement from baseline to 6 months in Group 1. The between group comparison showed significant difference favoring the Group 1. OAB Assessment Questionnaire: The within-group analyses showed a significant improvement from baseline to 6 months in both groups. The between group comparison showed significant difference favoring the Group 1.	Adverse effects: NR Follow-up: post-intervention (6 months)
Gaikwad (2020) (352)	RCT	Spinal cord injury Single centre India	Group 1 (n=14): Conventional exercises (medication, electrical stimulation – 20 minutes and exercises training, timed voiding program and intermittent catheterization) (3x/week, 30-45 minutes) during 4 weeks Group 2 (n=14): PFMT + exercises (3x/week, 30-45 minutes) during 4 weeks	-King's Health Questionnaire significant within and between group difference on incontinence impact, severity measures and symptom severity. -1h Pad Test Significant improvement in Group 1 and 2 (p=0.0288). Group 2 had greater efficacious mean value when compared to Group 1.	Adverse effects: NR Follow-up: post-intervention (4 months)
Klarskov (1994) (353)	RCT	Multiple Sclerosis Denmark	Total patients randomized n=20 Group 1: biofeedback using bladder pressure and surface EMG + supervised PFMT (40 minutes, 2x/week) + medication Group 2: supervised PFMT (40 minutes, 2x/week) + medication	-Number of Incontinence Episodes and pad changes: not reported. -Pad test 60 minutes: not reported. -Visual Analogue Scales for Incontinence: not reported. No difference between groups. However, the authors presented the results from both groups as a whole with significant reduction on the visual analogue scale for UI and significant decrease in the daily number of UI episodes and use of pads on the dairy. There was no difference in the pad test.	Adverse effects: NR Follow up: NR
Lee (2017) (354)	RCT	Alzheimer disease or cognitive impairment Single centre Korea	Group 1 (n=52): supervised PFMT with vaginal palpation and verbal feedback (6 sessions, 60 minutes at 2 weeks intervals) + home exercises + PF Education + bladder training during 12 weeks Group 2 (n=46): PF Education + bladder training	-Frequency volume chart UI: Groups 1 and 2 showed significant within group improvement when compared to baseline ($p<0.05$) at 12 weeks. Significant reduction in Group 1 compared to Group 2 ($p<0.001$). -ICIQ-UI-SF: no significant difference between and within groups at 4 weeks. Group 1 showed significant within group improvement when compared to baseline ($p<0.01$) at 12 weeks. Significant reduction in Group 1 compared to Group 2 ($p<0.001$) at 12 weeks.	Adverse effects: NR Follow up: Follow up: Mid and post-intervention (4, and 12 weeks)

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Lucio (2011) (355, 356)	RCT	Multiple Sclerosis Single centre Brazil	Group 1 (n=18): supervised PFMT with assistance of vaginal perineometer (2x/week, 30 minutes) + home PFMT (3x/daily) during 12 weeks + home exercises Group 2 (n=17): Introduction of vaginal perineometer without contraction (2x/week, 30 minutes) during 12 weeks	-Pad Test 24h: Group 1 showed significant reduction when compared Group 2 (p = 0.001) -UUI: Group 1 showed significant reduction when compared Group 2 (p<0.0013). -Nocturnal enuresis: Group 1 showed significant reduction when compared Group 2 (p<0.0034). -Overactive bladder version 8 (OABv8): Group 1 showed significant reduction when compared Group 2 (p<0.0001). -ICIQ-UI-SF: Group 1 showed significant reduction when compared Group 2 (p=0.0003). -Qualiveen Instrument: 1) Specific Impact of Urinary Problems on Quality of Life (SIUP): Group 1 showed significant reduction when compared Group 2 (p=0.0001). 2) General Quality of Life: Group 1 showed significant reduction when compared Group 2 (p=0.0443).	Adverse effects: NR Follow up: post-intervention (12 weeks)
McClurg (2008) (357)	RCT	Multiple Sclerosis Multi centre UK	Group 1 (n=37): home PFMT (daily) + EMG biofeedback (1x/week, 15 min) + placebo neuromuscular electrical stimulation (daily, 30 minutes) during 9 weeks Group 2 (n=37): home PFMT (daily) + EMG biofeedback (1x/week, 15 min) + active neuromuscular electrical stimulation (2 parameters: a) correct use of PFM (1x/week, up to 30 min – supervised); and b) inhibition of detrusor overactivity (daily, up to 30 minutes) during 9 weeks	-Leakage episodes per 24h: Groups 1 and 2 showed significant within group improvement when compared to baseline (p≤0.001) at 9, 16 and 24 weeks. Significant reduction in Group 2 compared to Group 1 (p<0.001) at 9 weeks. No significant difference in between group comparison at 16 and 24 weeks. -24h Pad Test: Groups 1 and 2 showed significant within group improvement when compared to baseline (p=0.001) at 9, 16 and 24 weeks. Significant reduction in Group 2 compared to Group 1 (p≤0.005) in all time points. -Incontinence Impact Questionnaire (IIQ) and Urogenital Distress Inventory (UDI): There was a significant superior benefit in Group 2 in the irritative subscale of the UDI at weeks 16 and 24 (p≤0.043).	Adverse effects: none Follow up: post-intervention (9 weeks), 16 and 24 weeks.

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Perez (2020) (358)	RCT	Multiple Sclerosis Multi centre Spain	Group 1 (n=24): Unsupervised PFMT at home (3x/day) during 12 weeks Group 2 (n=24): Supervised PFMT at home (2-3x/day) + 30 min weekly physiotherapist appointment during 12 weeks	-Leakage reduction: Groups 1 and 2 showed significant within group improvement when compared to baseline (p≤0.001) at 12 weeks. No significant difference in between group comparison at 12 weeks. -ICIQ-UI – SF 1)UI severity both groups showed improvement when compared to baseline (p<0.05) at 4, 8 and 12 weeks. No significant difference in between group comparison at 4 weeks. Significant improvement in Group 2 when compared to Group 1 (p<0.05) at 8 and 12 weeks. 2)QoL: Groups 1 and 2 showed significant within group improvement when compared to baseline (p<0.05) at 4, 8 and 12 weeks. No significant difference in between group comparison at 4, 8 and 12 weeks. -OABQ-SF 1)LUTS: Groups 1 and 2 showed significant within group improvement when compared to baseline (p≤0.05) at 4, 8 and 12 weeks. No significant difference in between group comparison at 4, 8 and 12 weeks. 2)QoL: No significant difference in within group comparison at 4 weeks in both Groups and in Group 1 at 8 weeks. Groups 1 and 2 showed significant within group improvement when compared to baseline (p=0.001) at 12 weeks. No significant difference in between group comparison at 4, 8 and 12 weeks.	Adverse effects: NR Follow up: Mid and post-intervention (4, 8, and 12 weeks)
Shin (2016) (359)	RCT	Stroke Single centre Korea	Group 1 (n=18): Supervised PFMT (3x/week, 50 minutes) + PF Education + General rehabilitation – gaiting training and stretching (3x/week, 50 minutes) during 6 weeks Group 2 (n=17): PF Education + General rehabilitation – gaiting training and stretching (3x/week, 50 minutes) during 6 weeks	-Bristol Female Urinary Symptoms Questionnaire Inconvenience (activities of daily living): significant reduction in Group 1 when compared to Group 2 (p<0.01). -Urinary Symptoms: significant reduction in Group 1 when compared to Group 2 (p<0.01).	Adverse effects: NR Follow up: post-intervention (6 weeks)

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Smilskalne (2009) (360) Abstract	RCT	Stroke Latvia	Group 1: Conventional physiotherapy (5x/week, 1 hour) during 4 weeks Group 2: Conventional physiotherapy (5x/week, 1 hour) + PFMT (5x/week, 30 minutes) during 4 weeks Group 3: Conventional physiotherapy (5x/week, 1 hour) + PFMT (5x/week, 30 minutes) + functional electrical stimulation (5x/week, 15 minutes) during 4 weeks	-Urogenital distress inventory (UDI-6) Comparing results of the Group 1 and 2 the difference is not statistically significant	Adverse effects: NR Follow up: post-intervention (4 weeks)
Tibaek (2005) (361-363)	RCT	Stroke Multi centre Denmark	Group 1 (n=14): Supervised PFMT (1x/week, 1 hour) + home exercises (1-2x/day) during 3 months Group 2 (n=12): Standard program of general rehabilitation without UI treatment	-Number of urinary incontinence episodes 24h: no significant difference within and between groups. -Pads test 24h number and weight: no significant difference within groups. Significant reduction in weight on Group 1 when compared to Group 2 (p=0.013) at 12 weeks. -Incontinence Impact Questionnaire (IIQ): no significant difference within groups in all time points. No significant difference between groups at 6 months.	Adverse effects: NR Follow up: post-intervention (12 weeks) and 6 months
Tibaek (2017) (364)	RCT	Stroke Multi centre Denmark	Group 1 (n=16): Supervised PFMT (1x/week, 1 hour) + home exercises during 3 months Group 2 (n=15): Standard program of general rehabilitation without LUTS treatment	-Danish Prostatic Symptom Score (DAN-PSS-1) 1)Symptom score: Groups 1 and 2 showed significant within group improvement when compared to baseline (p<0.01) at 12 weeks and no significant difference at 6 months. No significant difference between group at 12 weeks and 6 months. 2)Bother score: Groups 1 and 2 showed significant within group improvement when compared to baseline (p=0.01) in both groups at 12 weeks and in Group 2 at 6 months. No significant difference between group at 12 weeks and 6 months. 3)Total score: Groups 1 and 2 showed significant within group improvement when compared to baseline (p<0.01; p=0.03) at 12 weeks and no difference at 6 months. No significant difference between group at 12 weeks and 6 months. -3-day voiding diary: not reported.	Adverse effects: none Follow up: post-intervention (12 weeks) and 6 months

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Vahtera (1997) (365)	RCT	Multiple Sclerosis Single centre Finland	Group 1 (n=40): Intravaginal and intra-anal electrical stimulation (6 sessions/2 weeks; during 10 minutes each frequency) + biofeedback PFMT (1or 2 sessions) + home PFMT (3-5x/week) during 6 months Group 2 (n=40): None	-Leakage of urine in the absence of effort: no significant between-group difference at week 3 and 2 months. Significant reduction in Group 1 compared to Group 2 at 6 months (p<0.05). -Leakage of urine on minimal effort: no significant between-group difference at 2 months. Significant reduction in Group 1 compared to Group 2 at week 3 (p<0.001) and 6 months (p<0.001). -Leakage of urine on heavy effort: Significant reduction in Group 1 compared to Group 2 at week 3 (p<0.001), 2 months (p<0.001), and 6 months (p<0.001). -Volume of urine loss: Significant reduction in Group 1 compared to Group 2 at week 3 (p<0.001), 2 months (p<0.001), and 6 months (p<0.001). -Severity of Lower Urinary Tract Symptoms: no significant between-group difference at week 3, 2 months, and in women at 6 months. Significant between-group difference in men at 6 months.	Adverse effects: none Follow up: Mid and post-intervention (3 weeks, 2 and 6 months)
Vaughan (2019) (366)	RCT	Parkinson's Disease Multi centre USA	Group 1 (n=26): Home PFMT (daily) + bladder training + fluid management + education during 8 weeks Group 2 (n=27): Practice mirrored-shape drawings (1x/day, 15 minutes) during 8 weeks	-Bladder diary UI: no significant difference between groups -ICIQ-OAB/Symptom score: no significant difference between groups -ICIQ-OAB/Bother Score: significant reduction in Group 1 compared to Group 2 (p=0.048) -ICIQ-OAB/Quality of life: significant reduction in Group 1 compared to Group 2 (p=0.037)	Adverse effects: NR Follow up: post-intervention (8 weeks)
Zhang (2019) (367)	RCT	Stroke China	Group 1 (n=30): PFMT + intermittent urethral catheterization during 2 months Group 2 (n=30): Plum-blossom needle (5x/week) + moxibustion (5x/week, 15 minutes) + intermittent urethral catheterization during 2 months	-Frequency of Urinary Incontinence: significantly decreased in both groups (p<0.05). Between group comparison showed a significant improvement in Group 2 (p<0.05).	Adverse effects: NR Follow up: post-intervention (2 months)

Abbreviations: RCT: randomized controlled trial; HTLV-I: Human T-lymphotropic virus type 1; PF: pelvic floor; PFMT: pelvic floor muscle training; NR: not reported; UI: urinary incontinence; QoL: quality of life; EMG: electromyography; OAB: overactive bladder; ICIQ-UI-SF International Consultation on Incontinence Questionnaire on Urinary Incontinence Short Form; ICIQ-OAB: International Consultation on Incontinence Questionnaire on Overactive Bladder; OABv8: Overactive bladder questionnaire - 8; PGI-I: Patient Global Impression of Improvement scale; NR: not reported

2. ELECTRICAL STIMULATION

This section assesses EStim on UI and is divided into tibial nerve EStim, under which transcutaneous TNS and percutaneous TNS will be discussed, and TENS performed in other regions.

2.1. Tibial Nerve Stimulation

2.1.1. Transcutaneous TNS

2.1.1.1. Prevention

There were no studies identified.

2.1.1.2. Treatment

Nine RCTs (146, 368-375) (Table 52) and two non-RCT open label studies (376, 377) (Table 53) were retrieved evaluating transcutaneous TNS in small numbers of participants (ranging from five (375) to 50 (370)). The study design varied considerably and transcutaneous TNS was evaluated alone. However, in one study, transcutaneous TNS was assessed when combined with education about pelvic anatomy and function (371). In another study (372), TTNS was combined with PFMT and biofeedback. Duration of stimulation was 20 minutes (368) or 30 minutes (146, 369-371, 373-375), and the treatment was performed daily (368), thrice weekly (146), twice weekly (369, 370, 372-375), or weekly (371). The length of the intervention lasted for four weeks (370), five weeks (374), six weeks (369, 373, 375), nine weeks (371) and twelve weeks (146, 368, 372). The comparator arm used sham treatment in most studies (146, 368, 369, 373-375), medication (370), general advice/stretching of the lower limbs (373), PFMT and biofeedback (371), or intravaginal EStim (372).

Quality of data

Randomisation was considered appropriate in five studies (146, 368, 369, 372, 374). Allocation concealment was considered adequate in two studies (146, 369). Five studies were double blinded (146, 368, 369, 374, 375), whereas only the assessor was blinded in two studies (371, 372). Information regarding blinding of participants was considered as high ROB in four studies given the nature of the intervention (370-373). Information regarding an ITT analysis was obtainable in only four studies (146, 371, 372, 374) and loss to follow-up was reported in two studies (371, 374) (Table 52).

Results

The results are presented in Tables 52 and 53. Different outcomes were measured in the studies. A significant improvement was reported in most studies, mainly in the intervention arm compared to baseline (368, 370-374). The between group comparisons showed that improvement in bladder-related symptoms (UI, OAB symptoms) and QoL was reported in some studies with PD and MS participants (368, 372). However, most studies showed no improvement compared to the control group (146, 369-371, 373, 374). One of the studies primarily assessed feasibility and did not evaluate efficacy (375). In studies where transcutaneous TNS was compared to sham stimulation (146, 368, 369, 374, 375), a significant improvement was observed only in one study (368) with PD patients. The study presented improvement in the bladder diary and 24-hour outcomes, including night-time urinary frequency, urinary urgency, UUI episodes, use of pads, and questionnaires such as the OAB-V8 and King's Health Questionnaire scores, which were reported three months after the intervention (368). The sample studied was small, although a rationale for powering the study was provided.

No serious adverse effects were reported in any of the studies in the transcutaneous TNS arm. However, one study (369) reported that one participant presented minor skin irritation and other reported ankle cramping. In the study that compared transcutaneous TNS with solifenacin (370), five participants that received the medication reported dry mouth, and two of these dropped out of the study because of this side effect.

Summary

A total of nine RCTs and two non-RCT open label studies assessed the effects of transcutaneous TNS on UI, OAB symptoms and/or UUI compared to an active or sham comparator across different neurological groups including PD, post-stroke, incomplete SCI, MS and mixed neurological participants.

The interventions evaluated and the study designs adopted differed considerably between studies.

Although data from the studies demonstrate a significant improvement in the symptoms of participants after treatment, only one study comparing transcutaneous TNS to a sham treatment (368) demonstrated efficacy in participants with PD. (**Level of evidence: 2**)

Recommendation

Based on the evidence available, TNS to reduce OAB and related UI symptoms in patients with PD MS, incomplete SCI, post-stroke and mixed neurological diseases could be considered. More studies are needed. **(Grade of recommendation: C New)**

Table 52. RCT studies evaluating TTNS

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Araujo (2021) (368)	RCT	Parkinson's Disease Single centre Brazil	Group 1 (n=18): Transcutaneous tibial nerve stimulation (daily, 20 minutes) during 12 weeks Group 2 (n=18): Sham transcutaneous tibial nerve stimulation (daily, 20 minutes) during 12 weeks	Relief of bladder symptoms showed significant between group difference at 12 weeks and 90 days follow-up. No significant difference at 30 days. Number of urgency incontinence episodes showed significant within and between group. Number of pads showed significant within and between group. Overactive bladder version 8 (OABv8) showed significant within and between group. King's Health Questionnaire: - Impact of incontinence showed significant within and between group at 12 weeks. -Severity of urinary symptoms significant within group difference and no between group difference (p=0.089) at 12 weeks.	Adverse effects: NR Follow up: post-intervention (12 weeks), 30- and 90-days follow-up (after intervention).
Booth (2016) (369)	RCT	Stroke UK	Group 1 (n=27): Transcutaneous tibial nerve stimulation (2x/week, 12 sessions, 30 minutes) during 6 weeks Group 2 (n=27): Sham stimulation (2x/week, 12 sessions, 30 minutes) during 6 weeks	The study did not detect any significant difference between groups for number of participants continent after treatment, number of incontinent episodes and health status and quality of life.	Adverse effects: Group 1 and 2: one participant (3.7%) each group had residual urine volume of more than 150ml at the 6-weeks bladder scan. One participant (group unclear) had minor skin irritation and other reported ankle cramping. Follow up: post-intervention (6 weeks) 12, and 26 weeks follow-up
Chen (2015) (370)	RCT	Spinal cord injury China	Group 1 (n=50): Transcutaneous tibial nerve stimulation (30 minutes, 2x/week) during 4 weeks Group 2 (n=50): Solifenacin succinate (5mg, 1x/day) during 4 weeks	Total leakage volume statistical difference within groups at 2 and 4 weeks ($p<0.05$). Incontinence Quality of Life (I-QoL) statistical difference within groups at 2 and 4 weeks ($p<0.05$). No significant improvements between groups	Adverse effects: Group 1: none Group 2: 5 participants had dry mouth (2 drop out because of the side effect) Follow-up: Mid and post-intervention (2 and 4 weeks)

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Gaspard (2014) (371)	RCT	Multiple sclerosis Single centre Belgium	Group 1 (n=15): Transcutaneous tibial nerve stimulation + PF education (9 sessions, 30 minutes/week) during 9 weeks Group 2 (n=16): PFMT with biofeedback (9 sessions, 30 minutes/week) + home exercises (2x/day) + PF education during 9 weeks	SF-Qualiveen questionnaire score significant difference within groups at 6 months. Frequency of urgency episodes significant difference within groups at 6 months. The study did not detect any significant difference between the 2 groups for quality of life (p = 0.197) and overactive bladder (p = 0.532). Only the Qualiveen fears score varied in favor of the PFMT group at 9 weeks (p = 0.040).	Adverse effects: none Follow up: post-intervention (9 weeks) and 6 months
Lucio (2016) (372)	RCT	Multiple Sclerosis Single centre Brazil	Group 1 (n=10): supervised PFMT with EMG biofeedback + sham sacral neuromuscular electrical stimulation (2x/week) during 12 weeks Group 2 (n=10): supervised PFMT with EMG biofeedback + intravaginal neuromuscular electrical stimulation (2x/week) during 12 weeks Group 3 (n=10): supervised PFMT with EMG biofeedback + transcutaneous tibial nerve stimulation (2x/week) during 12 weeks All participants were instructed to perform PF contractions at home.	24h Pad Test- all groups presented significant reductions in the post-intervention and no difference between group comparison. Overactive bladder version 8 (OABv8): all groups presented significant reductions in the post-intervention and between group: Group 2 improved more than Groups 1 and 3 (p<0.01). Urge urinary incontinence: all groups presented significant reductions in the post-intervention and no difference between group comparison (p=0.83). ICIQ-UI-SF: all groups decreased scores and no statistically significant differences were found among the 3 groups. Qualiveen Instrument Specific Impact of Urinary Problems on Quality of Life (SIUP): significant difference in the post-intervention in Group 2 and no difference in Groups 1 and 3. Between group comparison showed that Group 2 improved more than Groups 1 and 3 (p<0.01). Health Related Quality of Life Ns	Adverse effects: NR Follow up: post-intervention (12 weeks)
Monteiro (2014) (373)	RCT	Stroke Single centre Brazil	Group 1 (n=12): Transcutaneous electrical stimulation of tibial nerve (2x/week, 30 minutes, 12 sessions) during 6 weeks Group 2 (n=12): Stretching session of lower limbs (1-3x/month, 30 minutes, 12 sessions) + general advice during 6 weeks	Urge Urinary Incontinence: Group 1 presented significant difference in the post-intervention at 6 weeks. No between group difference at 6 and 12 weeks. Nocturnal enuresis: No within and between group differences at 6 and 12 weeks.	Adverse effects: none Follow up: post-intervention (6 weeks) and 12 months

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Perissinotto (2015) (374)	RCT	Parkinson's Disease Single centre Brazil	Group 1 (n=12): Transcutaneous tibial nerve stimulation (2x/week, 10 sessions, 30 minutes) during 5 weeks Group 2 (n=11): Sham transcutaneous tibial nerve stimulation (2x/week, 10 sessions, 30 minutes) during 5 weeks	Number of urge urinary incontinence episodes: Group 1 presented significant difference in the post-intervention. No between group difference. Overactive bladder version 8 (OABv8): Group 1 presented significant difference in the post-intervention ($p<0.05$). No between group difference. ICIQ-SF: Group 1 presented significant difference in the post-intervention ($p<0.05$). No between group difference.	Adverse effects: NR Follow up: post-intervention (5 weeks)
Tornic (2020) (375)	RCT	Mixed neurological patients Switzerland	Group 1 (n=5): Transcutaneous tibial nerve stimulation (2x/week, 12 sessions, 30 minutes) during 6 weeks Group 2 (n=4): Sham transcutaneous tibial nerve stimulation (2x/week, 12 sessions, 30 minutes) during 6 weeks	Bladder diary – Number of leakages per 24h* *Statistical comparisons between and within groups are not reported	Adverse effects: none Follow up: post-intervention (6 weeks)
Welk (2020) (146)	RCT	Mixed neurological patients Single centre Canada	Group 1 (n=26): Transcutaneous tibial nerve stimulation (30 minutes) during 12 weeks Group 2 (n=24): Sham transcutaneous tibial nerve stimulation (30 minutes) during 12 weeks	The study did not detect any significant difference between the 2 groups for perception of bladder condition, 24-hour pad weights, Neurogenic Bladder Symptom Score and Qualiveen Short Form.	Adverse effects: none Follow up: post-intervention (12 weeks)

Abbreviations: RCT: randomized controlled trial; PFMT: pelvic floor muscle training; NR: not reported; EMG: electromyography; ICIQ-UI-SF International Consultation on Incontinence Questionnaire on Urinary Incontinence Short Form.

Table 53. non-RCT studies evaluating TTNS

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Ohannessian (2013) (376)	Cohort	Parkinson's Disease Single centre France	n=6 Transcutaneous tibial nerve stimulation (20 minutes daily) during 6 weeks.	OABv8 no significantly difference after TTNS (p=0.2) Pre-TTNS: 21/40 Post-TTNS: 14/40	Adverse effects: NR Follow up: post-intervention (6 weeks)
Sèze (2011) (377)		Multiple Sclerosis Multi centre France	n=70 Transcutaneous tibial nerve stimulation (20 minutes daily) during 3 months.	Reduction of 2.7 leakages per week (p<0.001), complete continence in 44.9% of the patients and improvement in QoL (p<0.001). Leakages per week Day 30: 2.8 (5.4) Day 90: 3.1 (6.4) % continent Day 30: 44.9% Day 90: 47% QoL Day 30: 1.4 (0.8) Day 90: 1.4 (0.9)	Adverse effects: NR Follow up: post-intervention (day 30 and 90)

Abbreviations: NR: not reported; QoL: quality of life; OABv8: Overactive bladder version 8; TTNS: Transcutaneous tibial nerve stimulation.

2.1.2. Percutaneous TNS

2.1.2.1. Prevention

There were no studies identified.

2.1.2.2. Treatment

There were no RCT studies found, however nine single-arm cohort studies were identified (378-386), evaluating percutaneous TNS in a variable number of participants (ranging from 14-83). The characteristics of these studies are presented in Table 54. In all the studies, 20 Hz stimulation was delivered percutaneously for a duration of 30 minutes, once per week for 12 weeks.

Results

The results are presented in Table 54. Except for one study, most reported improvement of UI symptoms and OAB and/or QoL after percutaneous TNS (378-386). No adverse events were reported in any of these studies.

Summary

A total of nine single-arm cohort studies assessed the effects of percutaneous TNS on UI, OAB symptoms and/or UUI across different neurological groups including PD, MS and mixed neurological participants.

The data demonstrated a significant improvement in symptoms after percutaneous TNS.

However, these observations are based on studies without a comparison group. (**Level of evidence: 3**)

Recommendation

Percutaneous TNS could be considered for UI in neurological patients. Adequately powered well-designed RCTs are needed to confirm the effectiveness of PTNS for neurological patients. **(Grade of recommendation: C New)**

Table 54. Non-RCT studies evaluating PTNS

Author, year	Type of study	Population	Intervention	Outcome	Notes:
El-Senousy (2013) (378)	Cohort	Parkinson's Disease Single centre Egypt	n=33 PTNS: Unilateral needle 5 cm above the medial malleolus and posterior to the tibial edge. Electrical stimulation was performed with pulse width 200 msec frequency of 20 Hz and individualized amplitude equal to 1.5 threshold for evoking toes plantar flexion and/or fanning (1x/week, 30 minutes) during 12 weeks.	Leakage and urge incontinence episodes significantly decrease after PTNS (p=0.001; p=0.04) There was a significant improvement in total IPSS score among patients with moderate disability after PTNS. No statistical difference in patients with mild and severe stages of disability.	Adverse effects: none Follow up: post-intervention (12 weeks)
Finazzi-Agrò (2003) Abstract (379)	Cohort	Mixed neurological patients Italy	n=14 PTNS: A needle was inserted 5 cm cephalad to the medial malleolus. Electrical stimulation was performed with pulse width 200 msec frequency of 20 Hz and adjustable current 0-10mA (1x/week, 30 minutes) during 12 weeks.	Number of leakages per 24h was not statistically significant Effect size: -4.0 (-12.94 to 4.94)	Adverse effects: none Follow up: post-intervention (12 weeks)
Gobbi (2011) (380)	Cohort	Multiple sclerosis Multi centre	n=18 PTNS: Unilateral needle 5 cm above the medial malleolus and slightly posterior to the tibial. A surface electrode was placed on the ipsilateral calcaneus. Electrical stimulation was performed with a current level of 0.5-9 mA using charge-compensated 200 um with a pulse rate of 20 Hz based on each subject's footplantar motor and sensory responses (1x/week, 30 minutes) during 12 weeks.	No statistical differences in the number of patients with UI (p=0.6). Significant improvement in QoL in most domains of the Kings Health Questionnaire (p<0.05). Patient perception of bladder condition (PPBC) significant improvement of LUTS (p=0.003).	Adverse effects: none Follow up: post-intervention (12 weeks)
Kabay (2009) (381)	Cohort	Multiple sclerosis Turkey	n=19 PTNS: Unilateral needle 5 cm above the medial malleolus and posterior to the edge of the tibia. A ground electrode was placed on the ipsilateral extremity. Electrical stimulation was applied using charge-compensated 200 usec pulses with a pulse rate of 20 Hz. Intensity level was then chosen as the intensity immediately under the threshold determining motor contraction (1x/week, 30 minutes) during 12 weeks.	Mean OAB score was statistically significant when compared to before TTNS (p<0.05) Number of leakages per 24h was not statistically significant* Effect size: -3.1 (-12.04 to 5.84)	Adverse effects: none Follow up: 12 weeks

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Kabay (2016) (382)	Cohort	Parkinson's Disease Turkey	n=47 PTNS: Unilateral needle 5 cm above the medial malleolus and posterior to the edge of the tibia. Electrical stimulation was applied using charge-compensated 200 usec pulses with a pulse rate of 20 Hz. Intensity level was then chosen as the intensity immediately under the threshold determining motor contraction during 12 weeks.	Urge incontinence decreased by 3.1 episodes daily (p<0.001) The change from baseline on the ICIQ-SF, OABv8, and OAB-q at 12-week PTNS treatment demonstrated significant difference in symptom severity and health-related QoL (P <.001)	Adverse effects: none Follow up: 12 weeks
Kabay (2017) (383)	Cohort	Multiple sclerosis Turkey	n=21 PTNS: Unilateral needle 5 cm cephalad from the medial malleolus and posterior to the edge of the tibia, placing the ground electrode ipsilateral extremity. Electrical stimulation was applied using charge-compensated 200 usec pulses with a pulse rate of 20 Hz. Intensity level was then chosen as the intensity immediately under the threshold determining motor contraction (1x/week, 30 minutes) during 12 weeks. At the end of treatment, unsuccessful patients who did not respond to treatment received a tapering protocol for PTNS to 1 year treatment. The patients from tapering protocol underwent at 14-day intervals for 3 months, 21-day interval for 3 months, and 28-day intervals for 3 months.	Voiding diary parameters of urge incontinence decreased by 3.4 episodes daily (p<0.001) and were sustained for all results from 12 weeks through 12 months follow up. ICIQ-SF, OABv8 and OAB-q demonstrated significant improvement in symptom severity and health related quality of life (p<0.001), and improvement at all time points through 12 months (p<0.001).	Adverse effects: none Follow up: 3, 6, 9 and 12 months
Kabay (2021) (384)	Cohort	Parkinson's Disease Turkey	n=76 PTNS: Unilateral needle 5 cm cephalad from the medial malleolus and posterior to the edge of the tibia, placing the ground electrode ipsilateral extremity. Electrical stimulation was applied using charge-compensated 200 usec pulses with a pulse rate of 20 Hz. Intensity level was then chosen as the intensity immediately under the threshold determining motor contraction (1x/week, 30 minutes) during 12 weeks. At the end of treatment, unsuccessful patients who did not respond to treatment received a tapering protocol for PTNS to 1 year treatment. The patients from tapering protocol underwent at 14-day intervals for 3 months, 21-day interval for 3 months, and 28-day intervals for 3 months	Voiding diary parameters of urge incontinence decreased by 4.2 episodes daily (p<0.001) and were sustained for all results from 12 weeks through 24 months follow up. ICIQ-SF, OABv8 and OAB-q demonstrated significant improvement in symptom severity and health related quality of life at all time points through 24 months (p<0.001).	Adverse effects: NR Follow up: 3, 6, 9, 12 and 24 months

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Tudor (2020) (385)	Cohort	Mixed neurological group UK	N=49 12 once-weekly, 30-min sessions Tibial nerve stimulated with a 34-gauge needle inserted at a 60° angle approximately 5 cm cephalad to the medial malleo- lus and slightly posterior to the tibia at a frequency of 20 Hz and pulse width of 200 μs	Change in ICIQ-OAB total score; median (IQR) −4 (−9.3, 2.5) (p=0.04) Change in ICIQ-LUTSqol total score; median (IQR) − 34 (− 53, 4.8) (p = 0.05) Change in 24-h urinary frequency (BD); median (IQR) − 0.85 (− 2.8, 0.4) (p = 0.3) Change in mean bladder urge score (BD); median (IQR) 0 (− 0.4, 0.2) (p = 0.9) Change in mean number of incontinence episodes (BD); median (IQR) −0.2 (−1, 0.2) (p=0.8)	No significant side effects reported
Zecca (2014) (386)	Cohort	Multiple sclerosis Switzerland	n=83 PTNS: Unilateral needle 5 cm above the medial malleolus and slightly posterior to the tibia. A surface electrode was placed on the ipsilateral calcaneus. Electrical stimulation was applied using a current level between 0.5 and 9 mA with charge-compensated 200 μsec pulses with a pulse rate of 20 Hz based on each subject's foot/plantar motor and sensory responses (1x/week, 30 minutes) during 12 weeks. At the end of treatment, the patients who did not respond to treatment switched to receiving maintenance treatment every 3 weeks for the next 3 months. After, symptoms were evaluated again and those who did not respond to this protocol, received further maintenance therapy every 2 weeks for 3 months.	Bladder diary parameters significantly improved at 24 months (p<0.05).	Adverse effects: none Follow up: 24 months

Abbreviations: PTNS: percutaneous tibial nerve stimulation; LUTS: lower urinary tract symptoms; QoL: quality of life; OAB: overactive bladder; ICIQ-UI-SF International Consultation on Incontinence Questionnaire on Urinary Incontinence Short Form; OABv8: Overactive bladder version 8; ICIQ-OAB: International Consultation on Incontinence Questionnaire on Overactive Bladder; ICIQ-LUTS: International Consultation on Incontinence Questionnaire on Lower Urinary Tract Symptoms; BD: bladder diary; OABq: Overactive bladder questionnaire; IQR: interquartile range.

2.2. TENS performed in other regions

2.2.1. Prevention

There were no studies identified.

2.2.2. Treatment

There were five RCTs identified (387-391) and the characteristics of these studies are presented in Table 55. Electrodes were placed in different areas as indicated in Table 55, and essentially the sacral roots (388, 389, 391) or intravaginal/intra-anal regions (387, 390) were stimulated. The intervention consisted of TENS either daily for 30 (388, 389, 391) to 45 (390) minutes, twice (387), thrice weekly (390) or more (389). The length of the intervention varied: four weeks (390), 10 weeks (389), 60 days (388), 90 days (391) and 180 days (387). The comparator was either usual care (388), EPNS with a needle electrode (390), a differing frequency of stimulation (20 Hz versus 75 Hz) (391), home PFMT (387), sham (389) or no treatment (391).

Quality of data

Randomisation was considered appropriate in four studies (387, 389-391). Allocation concealment was considered adequate in three studies (389-391). Three studies confirmed that the evaluator was blinded (387, 389, 391). Information regarding an ITT analysis was available in two studies (389, 390), and low ROB for loss to follow-up was reported in four studies (387, 389-391). For one study (387), the authors were contacted to confirm possible biases.

Results

The results are presented in Table 55. In all the RCTs, a significant improvement in LUTS was reported after the intervention in participants with mixed neurological diseases, multiple sclerosis and post-stroke (388-391) when compared to usual care (388), PFMT alone (387), sham (389) and EPNS with a needle electrode (390). Improvement in symptoms was also observed following both 20 Hz and 75 Hz stimulation compared to no-treatment, however the 20 Hz group showed a greater benefit when compared to 75 Hz group (391).

No adverse effects were reported in any of the studies.

Summary

A total of five RCTs in stroke, multiple sclerosis and other different neurological populations assessed the effects of TENS on UI, OAB symptoms and/or LUTS. The interventions evaluated and the study designs adopted differed considerably between studies, most used Estim alone and one in combination with PFMT. However, data from all studies demonstrated a significant improvement in all outcomes assessed (**Level of evidence: 2**), when compared to an active treatment including a higher frequency (75 Hz) of EStim, PFMT alone, usual care or no treatment. Data from one well-designed high-quality study (389) in post-stroke patients demonstrated a significant improvement in OAB and UI symptoms when compared to sham,

Recommendation

TENS appears to be an effective and safe treatment for managing OAB and related UI in some neurological groups, including stroke and mixed neurological patients and can be recommended as a first line treatment option. **(Grade of recommendation: B New)**

However, large high-quality RCTs are needed for a definitive conclusion.

Table 55. RCT studies evaluating Transcutaneous electrical nerve stimulation (TENS) performed in other regions

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Ferreira (2016) (387)	RCT	Multiple sclerosis Single centre Brazil	Group 1: Surface electrostimulation - Frequency: 2 Hz with two electrodes positioned on the S4 dermatome-perineum region (2x/week) + PFMT (daily) during 6 months Group 2: home PFMT (2x/week) during 6 months	Qualiveen Questionnaire: The within-group analyses showed a significant improvement from baseline after 6 months in both groups. No difference between groups in general QoL. OAB-V8: The within-group analyses showed a significant improvement from baseline after 6 months in both groups. The between group comparison showed significant difference favoring the Group 1.	Adverse effects: NR Follow-up: post-intervention (6 months)
Guo (2014) (388)	RCT	Stroke Single centre China	Group 1 (n=32): Transcutaneous electrical nerve stimulation (30 minutes 1x/day) during 60 days Group 2 (n=29): Basic therapy during 60 days Positive electrode: second lumbar spinous process Negative electrode: middle and lower third of the junction between the posterior superior iliac spine and ischia node	Overactive bladder symptom score significant difference between group ($p<0.05$).	Adverse effects: None Follow-up: post-intervention (60 days)
Guo & Kang (2018) (389)	RCT	Stroke Multi centre China	Group 1 (n=41) Neuromuscular electrical stimulation (30 minutes, 5x/week) during 10 weeks Group 2 (n=41) Sham neuromuscular electrical stimulation (no active probe, 30 minutes, 5x/week) during 10 weeks Positive electrode: second sacral level on opposite sides of the vertebral column Negative electrode: inside of the middle and lower third of the junction between the posterior superior iliac spine and the ischial node	OABSS: Significant difference between group favoring Group 1. ICIQ-SF: Significant difference between group favoring Group 1.	Adverse effects: None Follow-up: post-intervention (10 weeks)

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Li (2018) (390)	RCT	Mixed neurological patients China	Group 1 (n=40): Electrical pudendal nerve stimulation with needles placed bilateral to the sacrococcygeal joint (3x/week, 45 minutes) during 4 weeks Group 2 (n=20): Intravaginal/intra-anal electrical stimulation (3x/week, 45 minutes) during 4 weeks	International Consultation on Incontinence Questionnaire - Lower Urinary Tract Symptoms score significant difference between group (p=0.005). International Consultation on Incontinence Questionnaire - Lower Urinary Tract Symptoms Quality of Life score (ICIQ-LUTSqol) significant difference between group (p<0.001).	Adverse effects: NR Follow-up: post-intervention (4 weeks)
Liu (2016) (391)	RCT	Stroke China	Group 1 (n=27): Transcutaneous electrical nerve stimulation – Frequency 20Hz (30 minutes 1x/day) during 90 days Group 2 (n=27): Transcutaneous electrical nerve stimulation – Frequency 75Hz (30 minutes 1x/day) during 90 days Group 3 (n=27): No treatment Positive electrode: second sacral level Negative electrode: middle and lower third of the junction between the posterior superior iliac spine and ischial node	Overactive Bladder Symptom Score (OABSS): Group 1 and 2 presented significant difference in the post-intervention (p<0.05). Significant between group difference in Group 1 vs 2, 1 vs 3 and 2 vs 3 comparison. Incontinence episodes: Group 1 and 2 presented significant difference in the post-intervention (p<0.05). Significant between group difference in Group 1 vs 2, 1 vs 3 and 2 vs 3 comparison.	Adverse effects: None Follow-up: post-intervention (90 days)

Abbreviations: RCT: randomized controlled trial; NR: not reported; OABSS: Overactive Bladder Symptom Score; OABv8: Overactive bladder questionnaire – 8; ICIQ-SF International Consultation on Incontinence Questionnaire on Urinary Incontinence Short Form, ICIQ-LUTS: International Consultation on Incontinence Questionnaire on Lower Urinary Tract Symptoms.

3. ACUPUNTURE

3.1. Prevention

There were no studies identified.

3.2. Treatment

There were fifteen RCTs identified (392-406) and the characteristics of these studies are presented in Table 56. The intervention was highly variable and usually consisted of acupuncture (394, 397, 405, 406) or electroacupuncture alone (393, 399, 401), combined with medication (392, 395, 400, 404), or moxibustion (396, 398), or usual care (402). One study (403) evaluated the addition of ginger-salt-separated moxibustion and medication to the acupuncture protocol and another study evaluated the addition of electroacupuncture to a transperineal urethral sphincter injection of botulinum toxin protocol (400). A sham comparator was used in only one study (399), whereas in the remaining studies an active comparator was used: usual rehabilitation including standard physiotherapy, BT and general advice on fluids intake (393, 394), different types of acupuncture (395, 398, 405), medication (392, 396, 400, 404, 406) or catheterization (397, 401, 402). Two studies evaluated the addition of ginger-salt-partitioned moxibustion to acupuncture (398, 403).

Quality of data

Randomisation was considered appropriate in eight studies (392, 393, 395-397, 400, 401, 403), high-risk in one (398) and could not be determined in the remaining studies. Allocation concealment could be assessed in only two studies and considered adequate (393, 403). Blinding of evaluators could be assessed in only two studies (393, 399) and was double blinded in one (399). Information regarding an ITT analysis was obtainable in only one study (393) and loss to follow up was rated low ROB in twelve studies (393, 395-400, 402-406).

Results

Table 56 summarizes the results of these studies. A significant improvement in UI symptoms was reported in most studies (392-406) but not all reported improvement in symptoms or cure rates (393, 398, 402). Overall, studies that added active treatments to electroacupuncture in participants with PD, SCI and post-stroke(392, 396, 400), and acupuncture in post-stroke participants (398, 402-404) were effective when compared to medication added to other treatment or medication alone, acupuncture alone, and indwelling catheterisation. Furthermore, electroacupuncture (393, 399, 401) and acupuncture (394, 397, 406) alone in post-stroke participants is more effective compared to usual care including standard physiotherapy, BT and general advice on fluids intake, medication, sham, and indwelling catheterization. Two studies (395, 405) comparing different modalities of acupuncture showed that electroacupuncture was superior to acupuncture (395) and acupuncture with elongated needle was superior to acupuncture with filiform needle (405) in post-stroke participants.

No serious adverse effects were reported in any of the studies. However, in three studies (393, 401, 403) reported minor adverse events such as numbness, cramping, vomiting, skin burn, bruises on arms and torso, abdominal pain and low back pain. In one study (393), drop-out was reported due to pain at the needling sites.

Summary

A total of fifteen RCTs across participants with PD, SCI and post-stroke assessed the effects of acupuncture or electroacupuncture on UI, OAB symptoms and/or LUTS against an active or placebo comparator.

The interventions evaluated, and the study designs adopted, differed considerably. The quality of most studies could not be determined and the only study where quality parameters could be assessed (393) did not show a significant improvement in UI symptoms after the intervention.

However, data from the remaining studies demonstrated a significant improvement in symptoms following intervention. (**Level of evidence: 3**)

Recommendation

There is uncertainty regarding acupuncture as an alternative to medication and usual care for managing OAB and related UI in post-stroke, PD and SCI patients.

No recommendation can be made

High quality RCTs with clear reporting and outcome assessment would be beneficial for the recommendation.

Table 56. RCT studies evaluating acupuncture.

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Chen (2012) (392)	RCT	Parkinson's Disease China	Group 1 (n=30): electroacupuncture (1x/day) + Tolterodine orally (1mg 2x/day) with one day break per week during 6 weeks Group 2 (n=30): Tolterodine orally (2mg 2x/day) during 6 weeks	Frequency of UI of 24h: after treatment improved in both groups. Between group comparison showed that Group 1 was superior to the Group 2 ($p < 0.05$)	The adverse reactions in Group 1 were less than those in Group 2. Follow-up: post-intervention (6 weeks)
Chen (2020) (393)	RCT	Stroke Multi centre China	Group 1 (n=16): Electroacupuncture (20 minutes, 1-2x/week) during 4 weeks Group 2 (n=18): Usual rehabilitation (standard physiotherapy, bladder training and general advice on fluids intake) during 4 weeks	OABSS: significant difference between group comparison at week 5 and 8. No significant difference between group comparison at weeks 1, 2, 3, and 4. Number of incontinence episodes: no significant difference between group comparison at week 5 and 8.	Adverse effects: numbness (n=1), pain at the needling sites (n=1 – drop out), cramping (n=1), vomiting (n=1) and low back pain (n=1) Follow-up: week 1, 2 and 3 (during intervention); post-treatment (4 weeks); 1- and 4-weeks follow-up (week 5 and 8)
Chu (1997) (394)	RCT	Stroke China	Group 1 (n=30): Scalp needle embedding acupuncture during 1-2 weeks Group 2 (n=30): Usual care (no acupuncture)	2-week follow-up reported that 16 patients in the intervention group totally regaining normal urine and 12 patients in the intervention group partially regaining normal urine and the number of patients no regaining is 2. Between group comparison showed significant difference (p=0.001).	Adverse effects: NR Follow-up: 2 weeks
Chu (2011) (395)	RCT	Stroke China	Group 1 (n=56): Electroacupuncture (1x/day with one day break per week, 30 minutes) + calcium ion antagon, angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist, compound thromb-clearing agent (i.v.) during 4 weeks Group 2 (n=55): Acupuncture (1x/day) + Calcium ion antagon, angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist, compound thromb-clearing agent (i.v.) during 4 weeks	Severity of UI and symptom scores: Within group comparison statistically significant. Number of participants continent after treatment (cured): Between-group comparison statistically significant favoring Group 1.	Adverse effects: The infection rate of the electroacupuncture group was lower than control group Follow-up: post-intervention (4 weeks)

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Jiang (2020) (396)	RCT	Stroke China	Group 1 (n=30): Jingui Shenqi pills + Suoquan capsules (orally) during 2 weeks Group 2 (n=30): Electroacupuncture (30 minutes) + moxibustion (daily, 6x/week) during 2 weeks	Urinary incontinence (day/night) The two groups showed significant reduction ($p<0.01$). Between group comparison showed decrease in Group 2 ($p<0.05$). Urinary incontinence degree Increase number of cases with UI degree I and II ($p<0.05$). Between group comparison showed increase UI degree I and II in Group 2 ($p<0.05$). Clinical symptoms of urinary incontinence Reduce score of clinical symptoms ($p<0.05$). Between group comparison showed reduction of UI symptoms score in Group 2 ($p<0.05$). Effective rate showed significant difference between group comparison.	Adverse effects: NR Follow-up: post-intervention (2 weeks)
Li (2015) (397)	RCT	Stroke China	Group 1 (n=24): Acupuncture 1x/day with one day break per week, 30 minutes) during 3 weeks Group 2 (n=20): Indwelling catheterization during 3 weeks	American Urological Association Symptom Index (AUASI) significant difference between group comparison favoring Group 1.	Adverse effects: NR Follow-up: post-intervention (3 weeks)
Liu (2006) (398)	Quasi-RCT	Stroke China	Group 1 (n=41): Ginger-salt-partitioned moxibustion + acupuncture (5x/week) during 3 weeks Group 2 (n=41): Acupuncture (5x/week) during 3 weeks	Frequency of urinary symptoms significantly decreased in between group comparison favoring Group 1. Number of patients continent after treatment showed no difference in the between-group comparison.	Adverse effects: NR Follow-up: post-intervention (3 weeks)
Liu (2013) (399)	RCT	Stroke Single centre China	Group 1 (n=35): Electroacupuncture (20 minutes, 1x/day) during 10 days Group 2 (n=36): Sham electroacupuncture (20 minutes, 1x/day) during 10 days	Frequency UI significant difference between group comparison after treatment and 3 months follow-up favoring Group 1.	Adverse effects: NR Follow-up: post-intervention (10 days) and 3 months

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Meng (2015) (400)	RCT	Spinal Cord Injury China	All patients were treated with usual care including indwelling catheterization and PFMT Group 1 (n=20): Electroacupuncture (40 minutes, 6x/week) + botulinum toxin-A (200 IU/4ml via perineum external urethral sphincter) during 4 weeks Group 2 (n=15): Botulinum toxin-A (200 IU/4ml via perineum external urethral sphincter)	Episodes and volume of urinary incontinence showed significant reduction ($p<0.05$). Between group comparison showed decrease in Group 1 ($p<0.05$).	Adverse effects: NR Follow-up: post-intervention (4 weeks)
Song (2013) (401)	RCT	Stroke China	Group 1 (n=136): Electroacupuncture (5x/week) during 4 weeks Group 2 (n=68): Indwelling catheter intervals of 2-4 hours + bladder irrigation + bladder training during 4 weeks	Number of participants continent significant difference between group comparison favoring Group 1.	Adverse effects: Group 1: 45/136 (33%) bruises on arms and torso with full recovery; 17/136 (13%) had abdominal pain post-acupuncture with resolution after warm compress. Follow-up: post-intervention (4 weeks)
Wang (2015) (402)	RCT	Stroke China	Group 1 (n=38): Acupuncture (cycles of 1x/day during 10 days with two day breaks per cycle, 30 minutes during 4 weeks + usual care Group 2 (n=38): Indwelling catheter during 4 weeks + usual care	Effective rate of Urinary Incontinence – cured and occasional UI: between group comparison showed no difference. Degree of UI for general activities and Score of Urinary Incontinence were better in Group 1 than Group 2 in the between-group comparison.	Adverse effects: NR Follow-up: post-intervention (4 weeks)
Wen (2014) (403)	RCT	Stroke China	Group 1 (n=48): Acupuncture (5x/week during 30 minutes) + ginger-salt-separated moxibustion (2x/day during 5x/week) + Medication (0.1g Aspiring and 75mg Plavix) (1x/day) during 4 weeks Group 2 (n=24): Acupuncture (5x/week during 30 minutes) + Medication (0.1g Aspiring and 75mg Plavix) (1x/day) during 4 weeks	Score of Urinary Incontinence was significant decreased in both Groups post-treatment and in Group 1 in between-group comparison.	Adverse effects: skin burn (Group 1: n=2) Follow-up: Post-treatment (4 weeks)
Wu (1999) (404)	RCT	Stroke China	Group 1 (n=40): Eye acupuncture and electriferous scalp acupuncture (daily, 6 days/week) + Medication therapy (Hua Duo Zai shi tablet, Xi bi lin, Nao Fu Kang, vitamins C and E) during 4 weeks. Group 2 (n=40): Medication therapy (Hua Duo Zai shi tablet, Xi bi lin, Nao Fu Kang, vitamins C and E.	Number of participants continent showed significant difference between group comparison favoring Group 1.	Adverse effects: NR Follow-up: NR

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Zhang (1996) (405)	RCT	Stroke Single centre China	Group 1 (n=32): Elongated needle (50 minutes, 6x/week) during 4 weeks Group 2 (n=25): Filiform needle (50 minutes, 6x/week) during 4 weeks	Micturition completely controlled significant difference between group comparison favoring Group 1. Partially controlled urination no significant difference between group comparison. No urination control significant difference between group comparison with increased numbers in Group 2.	Adverse effects: NR Follow-up: Post-treatment (4 weeks)
Zhang (2002) (406)	RCT	Stroke China	Group 1 (n=36): Acupuncture (daily for 7 times) Group 2 (n=28): Mannite and other medicines to do general treatment with the partial foment on the bladder.	Number of participants continent (cured)- significant difference in group comparison favoring Group 1.	Adverse effects: NR Follow-up: NR

Abbreviations: RCT: randomized controlled trial; UI: urinary incontinence; OABSS: Overactive Bladder Symptom Score; PFMT: pelvic floor muscle training; NR: not reported.

4. TOILET ASSISTANCE

4.1. Prevention

There were no studies identified

4.2. Treatment

There were seven RCTs identified (407-414) across participants post-stroke, PD and incomplete SCI, and the characteristics of these studies are presented in Table 57. Different interventions were studied including BT (408, 410, 412), timed voiding (409, 411), and prompted voiding (413, 414). One study evaluated the addition of moxibustion to BT compared to BT alone (407).

Quality of data

Randomisation was considered appropriate in only three studies (407, 412-414) and could not be determined in the remaining studies. Allocation concealment was unclear in all studies. The evaluator was blinded in one study (412). Information regarding an ITT analysis was obtainable in one study (413, 414) and loss to follow up was rated low ROB in four studies (407, 408, 410, 411).

Results

Table 57 summarizes the results of these studies. A significant improvement in UI symptoms in participants post-stroke, PD and incomplete SCI was reported in some studies that added other treatments to the toilet assistance programme compared to routine nursing, biofeedback, and conservative advice including fluid management (407, 410, 412) and greatest improvement was observed at 12 weeks in participants with PD (412). Three studies (408, 411, 413, 414) with active interventions added to the toilet assistance programme compared to usual care, such as checking for urinary tract infection, overflow incontinence, containment and some toileting schedule, and a toilet assistance programme alone in post-stroke participants did not demonstrate improvement. One study (409) in post-stroke participants comparing the toilet assistance programme alone with other active treatments did not show any statistically significant difference.

No serious adverse effects were reported in any of the studies. However, one study (413, 414) reported the following adverse events: fall, urinary tract infections and bladder catheterizations.

Summary

A total of seven RCTs across participants post-stroke, PD and incomplete SCI assessed the effects of toilet assistance on UI, OAB symptoms and/or LUTS. The interventions that were evaluated, and the study designs adopted, differed considerably between studies. The quality of many studies could not be determined. Data from three studies provided evidence for safety, efficacy and improvement in UI. (**Level of evidence 3)**

Recommendation

Based on the evidence available, toilet assistance regimens could be recommended for treatment for managing OAB and related UI in post-stroke, PD and incomplete SCI patients**.** Further trials are needed. **(Grade of recommendation: C New)**

Table 57. RCT studies evaluating toilet assistance

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Chen (2016) (407)	RCT	Incomplete spinal cord injury	Group 1 (n=42): Bladder training + comprehensive rehabilitation treatment – 20 minutes and exercises training during 8 weeks Group 2 (n=42): Bladder training + umbilical moxibustion during 8 weeks	Daily number of urinary incontinence Significant reduction in both groups after treatment. Between group comparison showed significant difference favoring Group 2. LUTS score Significant reduction in both groups after treatment. Between group comparison showed significant difference favoring Group 2. LUTS Quality of Life Significant reduction in both groups after treatment. Between group comparison showed significant difference favoring Group 2.	Adverse effects: NR Follow-up: post-intervention (8 weeks)
Feng (2012) (408)	RCT	Stroke Single centre China	Group 1 (n=30): Bladder training + standing training + emotional care during 60 days Group 2 (n=30): Routine treatment + nursing during 60 days	UI cure no significant difference between group comparison. Occasional UI no significant difference between group comparison	Adverse effects: NR Follow-up: post-intervention (60 days)
Gelber (1997) (409)	RCT	Stroke USA	Normal urodynamic studies Group 1 (n=10): Void on request Group 2 (n=8): Timed voiding Bladder hyperreflexia Group 1 (n=10): Timed voiding Group 2 (n=9): Oxybutynin	Number of UI episodes per day: no statistical significance between groups.	Adverse effects: NR Follow-up: Each month of treatment for 1 year
Gong (2013) (410)	Quasi-RCT	Stroke China	Group 1 (n=30): Biofeedback + Routine nursing Group 2 (n=35): Water drinking plan + bladder training during 60 days	UI cure: no significant difference between groups. Number of incontinent patients showed significant differene between group comparison favoring Group 2.	Adverse effects: NR Follow-up: NR
Lewis (1990) (411)	RCT	Stroke USA	Group 1 (n=11): Timed prompted voiding + Biofeedback during 2 weeks Group 2 (n=12): Timed prompted voiding during 2 weeks	Number of continent participants and episodes after treatment no significant difference between group comparison.	Adverse effects: NR Follow-up: post-intervention (2 weeks)

Author, year	Type of study	Population	Intervention	Outcome	Notes:
McDonald (2020) (412)	RCT	Parkinson's Disease Single centre UK	Group 1 (n=18): Conservative advice (Advice and instructions to reduce alcohol and caffeine, constipation management and available containment products) Group 2 (n=20): Bladder training (instructions on urge suppression and distraction techniques, coaching PFMT, personalized voiding schedule and video training) + conservative advice during 12 weeks	Incontinence episodes: significant difference between group comparison at 12 weeks favoring Group 2. No significant difference between group comparison at 20 weeks. ICIQ-OAB: -Symptom score significant difference between group comparison at 12 weeks favoring Group 2. No significant difference between group comparison at 20 weeks. -Bother score significant difference between group comparison at 20 weeks favoring Group 2. No significant difference between group comparison at 12 weeks. -Quality of life no significant difference between group comparison at 12 and 20 weeks. -Quality of life interference for daily life significant difference between group comparison at 12 and 20 weeks favoring Group 2.	Adverse effects: NR Follow-up: post-intervention (12 weeks) and follow-up (20 weeks)
Thomas (2014) (413, 414)	Cluster RCT	Stroke Multi centre UK	Group 1 (N=124): Usual continence care (checking urinary tract infection, overflow incontinence, containment and some toileting schedule) Group 2 (N=164): Systematic voiding programme with 3-day bladder diary and comprehensive continence assessment (participants cognitively able: bladder training; participants cognitively impaired: prompted voiding) + usual continence care Group 3 (N=125): Systematic voiding programme with supported implementation (facilitation to assist the process of embedding into practice)	Number of continent participants International Consultation on Incontinence Questionnaire Urinary Incontinence – Short Form (ICIQ-SF) Incontinence Severity Index (ISI) Types of Incontinence: Urge incontinence present; Stress incontinence present Incontinence Quality of Life Instrument (IQoL) (post-treatment; median IQR) No difference between group comparison at all follow-up.	Adverse effects: Number of participants Fall Group 1: 16 Group 2: 11 Group 3: 4 Urinary tract infection Group 1: 13 Group 2: 18 Group 3: 23 Bladder catheterization Group 1: 1 Group 2: 4 Group 3: 1 Follow-up: Post-stroke (6, 12 and 52 weeks)

Abbreviations: RCT: randomized controlled trial; NR: not reported; PFMT: pelvic floor muscle training; UI: urinary incontinence; LUTS: Lower Urinary Tract Symptoms; ICIQ-OAB: International Consultation on Incontinence Questionnaire on Overactive Bladder.

5. MULTIMODAL REHABILITATION INTERVENTION

5.1. Prevention

There were no studies identified

5.2. Treatment

Data from two well-designed studies (415, 416) in participants with MS and spina bifida assessing the effectiveness of multimodal rehabilitation intervention including incontinence treatment with BT, timed voiding, medication, and PFMT associated with cognitive behavioural strategies and psychological adjustments. These interventions were compared with standard outpatient rehabilitation including monitoring by general practitioners and neurologists.

Quality of data

Randomisation and allocation concealment were considered appropriate in all studies (415, 416). Given the nature of intervention in the two studies (415, 416), blinding of participants was rated as high ROB. However, both studies (415, 416) blinded the outcome assessor, employed ITT analysis and were rated as low ROB for loss of follow-up.

Results

Table 58 summarizes the results of these studies. A statistically significant improvement in UI symptoms and QoL in participants with MS and spina bifida was reported in all studies, reaching a clinically important difference. No adverse effects were reported in any of the studies.

Summary

A total of two RCTs of participants with MS and spina bifida assessed the effects of a multimodal rehabilitation intervention on UI symptoms and health related QoL. The interventions were considered homogeneous, and the study designs adopted were similar. One study (415), reported of intervention effectiveness in 12 month follow-up

The studies were considered high-quality with limitations related to blinding of participants. **Level of evidence: 2.**

Recommendation

Based on the evidence available, multimodal rehabilitation interventions in MS and spina bifida patients can be recommended as first line treatment. **(Grade of recommendation: B New)**

Table 58. RCT studies evaluating multimodal rehabilitation intervention

Author, year	Type of study	Population	Intervention	Outcome	Notes:
Khan (2010) (415)	RCT	Multiple sclerosis Single centre Australia	Group 1 (N=40): Individualized inpatient (3h/day – therapy, during 6 weeks) or outpatient (30min 2-3x/week) therapy during 6 weeks + Bladder rehabilitation programme (assessment of bladder type, pattern and function, bladder re-education, behavior management, PFMT, strategies for timed and double voiding, intermittent catheterization techniques, use of prophylactic medication, and strict bowel programme) + Behavioral therapy Group 2 (N=34): Usual care (regular reviews by GP and neurologists)	Significant difference between group comparison in the UDI6, IIQ7 and AUA total score and QoL favoring Group 1.	Adverse effects: none Follow-up: post-intervention (12 months)
Khan (2015) (416)	RCT	Spina bifida Single centre Australia	Group 1 (n=27): Usual care (2-3x/week, 30 minutes) during 6 weeks + bladder management (assessment of bladder type, pattern and function, bladder re-education, behavior management, PFMT, timed/double voiding, catheter care and medication review) + Bowel programme + skin and pressure care education sessions + cognitive behavioral therapy for an additional 4-6 weeks beyond the usual care Group 2 (n=27): Usual care - physical reconditioning programme, wheelchair/seating evaluation, task reacquisition skills and whole-body adaptive techniques (2-3x/week, 30 minutes) during 6 weeks	Significant difference between group comparison in the UDI6, IIQ7 and AUA and QoL favoring Group 1.	Adverse effects: none Follow-up: post-intervention (3 months)

Abbreviations: RCT: randomized controlled trial; PFMT: pelvic floor muscle training; GP: general practitioner; UDI6: Urogenital Distress Inventory; IIQ7: Incontinence Impact Questionnaire; AUA: American Urological Association Symptom Index; QoL: quality of life.

APPENDIX 1

7th ICI – conservative treatment in adults – terms used to search the Cochrane Incontinence Specialised Register

The updated literature search covered from September 9th, 2015 to December 31st, 2020 inclusive (ie from the date of the last search for the 6th ICI to the 7th ICI search cut-off date of December 31st, 2020) according to the following search methods. The searches were conducted between March 1st to 9th, 2021 inclusive. We did not impose any language or other limitations on any of the searches described below.

Please find below details of the search terms used to search the Cochrane Incontinence Specialised Register for each section of this chapter. The Register is maintained in EndNote X8.2 (1) and all searches are of the 'Keywords' field (which contains the Cochrane Incontinence Specialised Register controlled vocabulary terms).

Lifestyle interventions for urinary incontinence (UI)
design.rct* OR design.cct*
AND
topic.urine*
AND
intvent.lifestyle*

PFMT for prevention or treatment of UI and/or faecal incontinence (FI) in childbearing women
design.rct* OR design.cct*
AND
intvent.prevent.pfe* OR intvent.prevent.pfmt* OR intvent.prevent.physicaltherapies OR topic.urine.incon.prevent. OR topic.urine.incon.prevent.postpartum. OR topic.faecal.incon.prevent. OR topic.faecal.incon.prevent.PostObstet. OR topic.urine.incon.postobstetric* OR topic.faecal.incon.postobstetric* OR topic.urine.incon.preg* OR topic.urine.incon.stress.postnatal. OR intvent.phys.biofeed* OR intvent.phys.pfe* OR topic.urine.incon.mixed.postnatal. OR topic.urine.incon.mixed.preg. OR topic.urine.incon.stress.preg. OR topic.faecal.incon.preg*

Different types of PFMT program or PFMT versus other treatment or PFMT combined with other treatment - in women
design.rct* OR design.cct*
AND
Topic.urine*
AND
intvent.phys.pfe* OR intvent.prevent.pfmt* OR intvent.prevent.pfe*

Vaginal Cones
design.rct* OR design.cct*
AND
Intvent.phys.cones*

Male UI - all modalities (except magnetic or electrical stimulation)
design.rct* OR design.cct*
AND
Topic.urine.incon.postprost*

PTNS - men and women – for UI
design.rct* OR design.cct*
AND
Topic.urine*
AND
intvent.phys.electstim.percut* OR intvent.phys.electstim.ptns* OR intvent.phys.electstim.pudendal.percut* OR intvent.phys.electstim.sacral.percut* OR intvent.phys.electstim.tibialnervstim.transcut* OR intvent.phys.transcutmechnervstim. OR intvent.prevent.electstim*

Electrical stimulation - men and women - for UI
design.rct* OR design.cct*
AND
Topic.urine*
AND
intvent.phys.electstim* OR intvent.phys.tens. OR intvent.phys.acupuncture.electro. OR intvent.phys.bladderstimulationtherapy. OR intvent.phys.complex. OR intvent.phys.energoneuroadaptiveregulator. OR intvent.phys.nerveStim.laser. OR intvent.phys.tuina. OR intvent.phys.vesicalpacemaker. OR intvent.phys.vibrationtherapy OR intvent.phys.myofascialphysicaltherapy. OR intvent.prevent.electstim* OR intvent.phys.transcutmechnervstim*

Magnetic stimulation - men and women - for UI
design.rct* OR design.cct*
AND
topic.urine*
AND
intvent.phys.electstim.magnetic* OR intvent.prevent.electstim.magnetic* OR intvent.phys.acupuncture.magnetic. OR intvent.phys.electstim.microwavetherapy. OR intvent.phys.energoneuroadaptiveregulator. OR intvent.phys.transcutmechnervstim. OR intvent.phys.vesicalpacemaker.

Acupuncture - men and women - for UI
design.rct* OR design.cct*
AND
topic.urine*
AND
intvent.phys.acu* OR intvent.prevent.acupuncture. OR intvent.complementary.auriculotherapy*
Complementary medicine - men and women - for UI
design.rct* OR design.cct*
AND
topic.urine*
AND
intvent.complementary* OR intvent.prevent.complementary*

Conservative management of UI for people with neurogenic or neurological conditions - men and women
(a very broad search for all conservative interventions for UI was conducted)
design.rct* OR design.cct*
AND
topic.urine*
AND
intvent.phys* OR intvent.education* OR intvent.lifestyle* OR intvent.delivery* OR intvent.rehab* OR intvent.nurse* OR intvent.chem.diet* OR intvent.chem.homeopath* OR intvent.psych* OR intvent.complementary*

Scheduled voiding (includes toileting assistance programmes and bladder training) - men and women
design.rct* OR design.cct*
AND
topic.urine*
AND
Intvent.psych* OR intvent.phys.toilet* or intvent.phys.urge* OR intvent.prevent.bladderDrill.
PFMT vs no treatment/inactive control (treatment or prevention)
design.rct* OR design.cct*

AND
topic.urine*
AND
intvent.phys.pfe* OR intvent.phys.biofeed* OR intvent.phys.physicaltraining. OR intvent.phys.physiotherapy. OR intvent.prevent.pf*

Abdominal muscle/hypopressive exercises/Paula method
design.rct* OR design.cct*
AND
topic.urine*
AND
intvent.phys.complex. OR intvent.phys.hypopressiveexercise. OR intvent.phys.muscleexercises* OR intvent.prevent.hypopressiveexercise.

Pessaries for pelvic organ prolapse (POP)
design.rct* OR design.cct*
AND
topic.prolapse*
AND
intvent.mech*

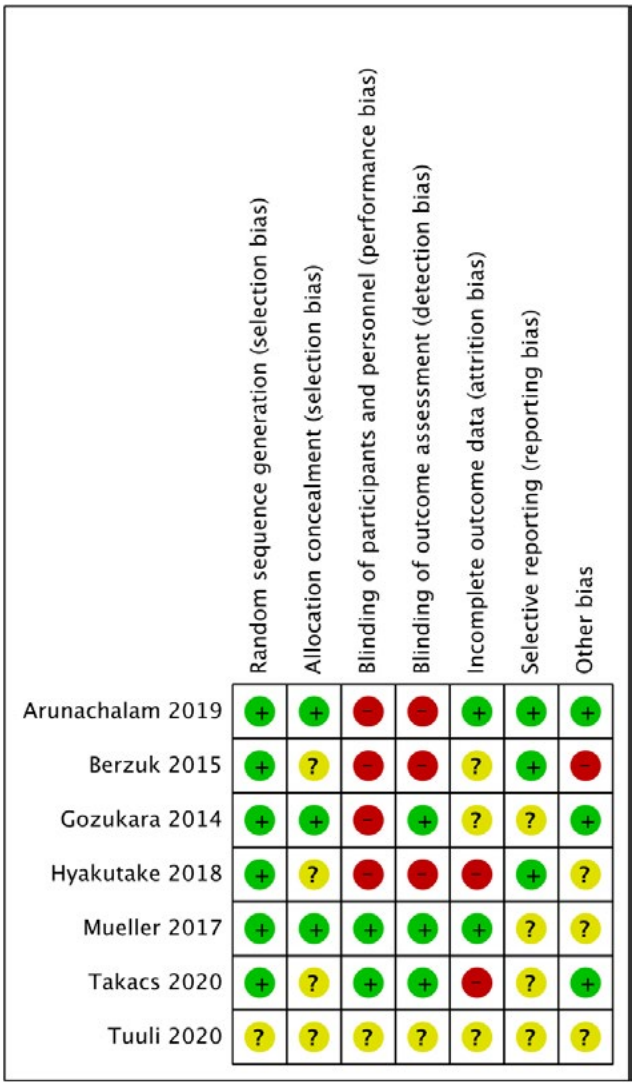
Lifestyles/conservative interventions for POP
design.rct* OR design.cct*
AND
topic.prolapse*
AND
intvent.phys* OR intvent.education* OR intvent.lifestyle* OR intvent.delivery* OR intvent.rehab* OR intvent.nurse* OR intvent.chem.diet* OR intvent.chem.homeopath* OR intvent.psych* OR intvent.complementary*

Key
* = truncation.

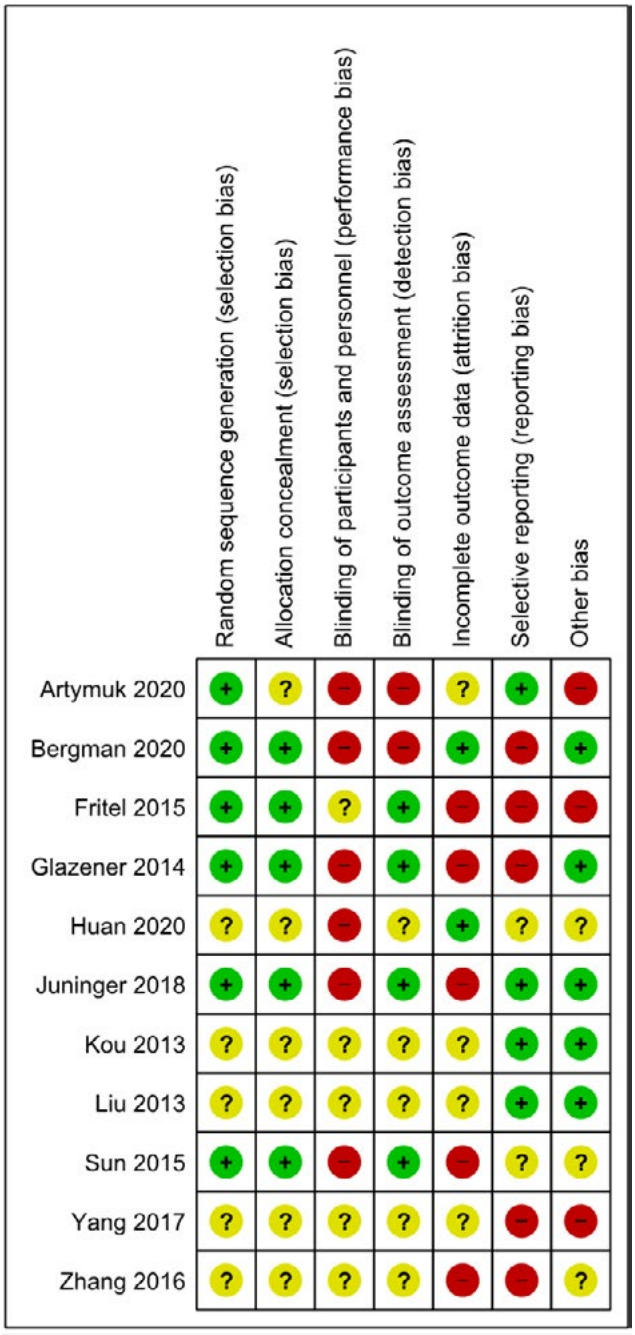
Reference

1. EndNote [Computer program]. Version X8.2. Philadelphia (PA): Clarivate Analytics, 2018.

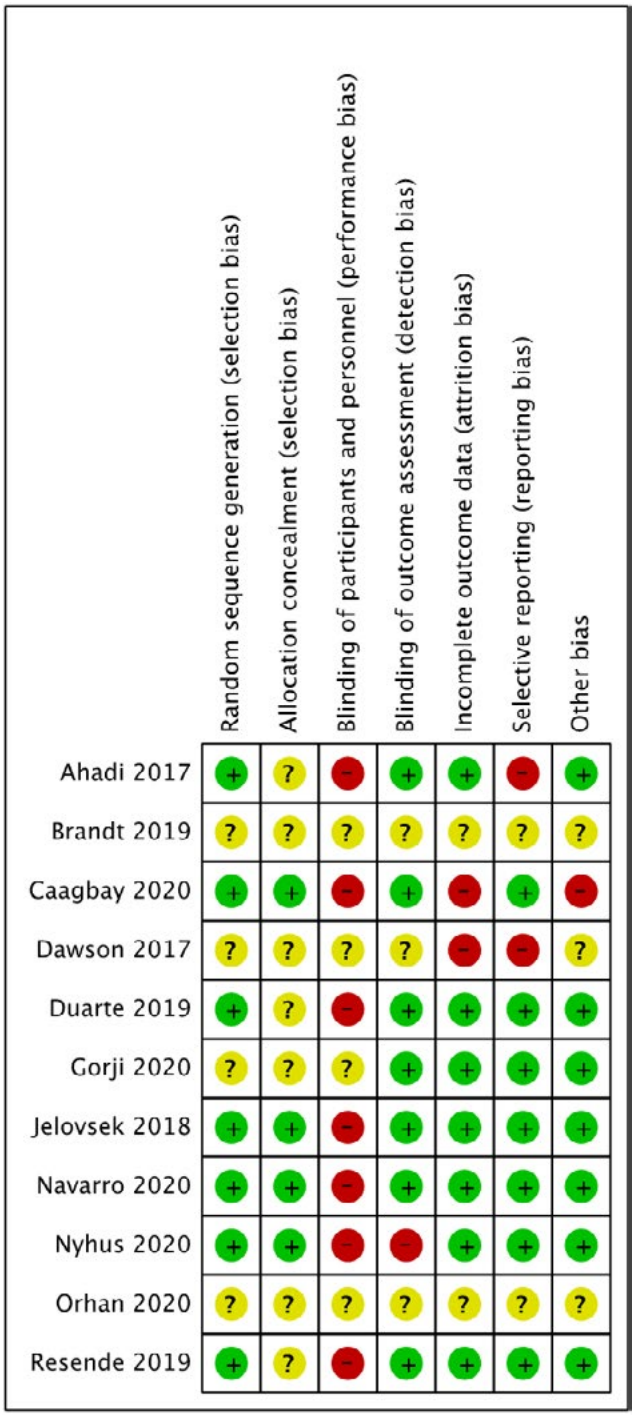
APPENDIX 2. RISK OF BIAS



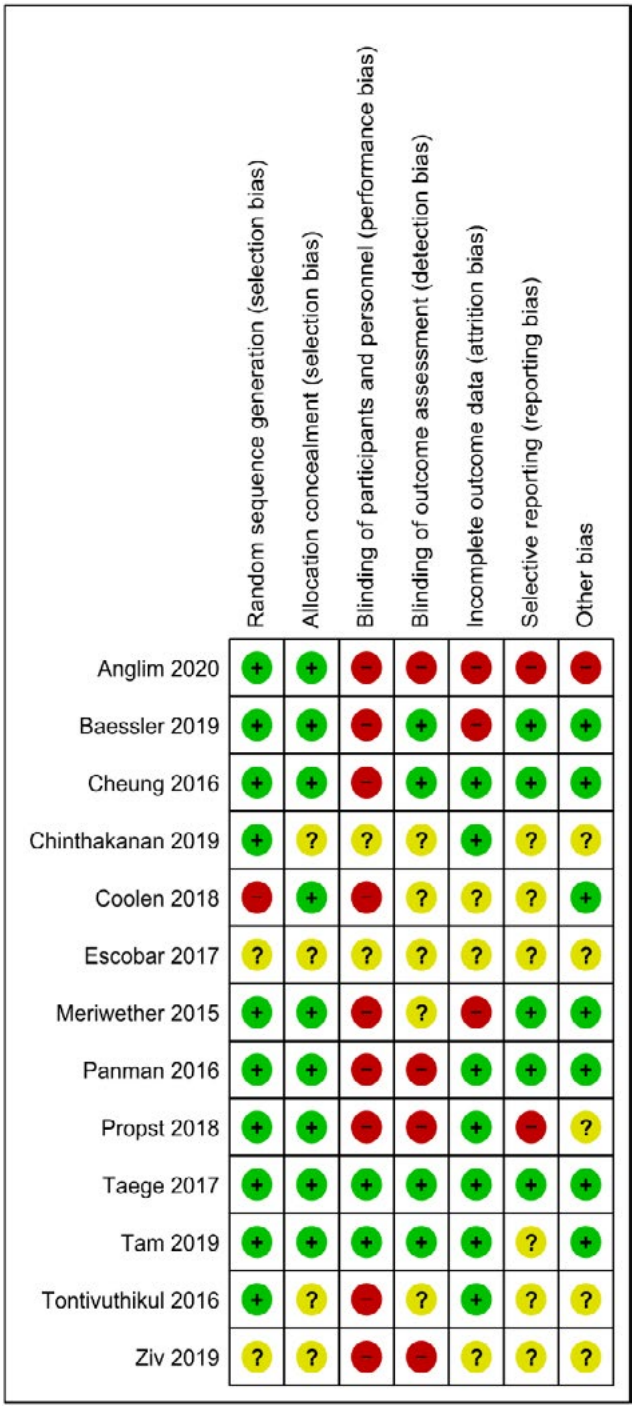
A. Risk of bias for educational and lifestyle interventions in prolapse.



B. Risk of bias for physical intervention trials focussed on preventing prolapse.



C. Risk of bias for physical intervention treatment trials.



D. Risk of bias for pessary trials.

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COMMITTEE 9

PHARMACOLOGICAL TREATMENT OF URINARY INCONTINENCE

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Co-Chairs:
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Cruz Miranda Rodrigues, Francisco (Portugal)

Members:
Cardozo, Linda (United Kingdom)
Chermansky, Christopher (United States)
Igawa, Yasuhiko (Japan)
Lee, Kyu-Sung (Korea, Republic of)
Michel, Martin (Germany)
Sahai, Arun (United Kingdom)
Wein, Alan (United States)

Correspondence:
K-E Andersson, MD, PhD
Mobile: 0046 705522722
e-mail: Karl-Erik.Andersson@med.lu.se

COMMITTEE 9

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I. INTRODUCTION

The function of the lower urinary tract (LUT) is to store and periodically release urine. It is dependent on the activity of smooth and striated muscles in the bladder, urethra, and pelvic floor. These structures form a functional unit, which is controlled by a complex interplay between the central and peripheral nervous systems and local regulatory factors [Andersson, 1993; de Groat and Yoshimura, 2001; 2015; Andersson and Wein, 2004; see, Andersson and Michel., 2011]. Recently, Abelson et al. [2018] reviewed current understanding of the development, function, and biology of the LUT in females and males on a cellular level with focus on sex differences. Malfunction at various levels may result in bladder control disorders, which roughly can be classified as disturbances of filling/storage or disturbances of voiding/emptying. Failure to store urine may lead to various forms of incontinence (mainly urgency and stress incontinence), and failure to empty can lead to urinary retention, which may result in detrusor underactivity (DU) and underactive bladder (UAB). A disturbed filling/storage function can, at least theoretically, be improved by agents decreasing detrusor activity, increasing bladder capacity, and/or increasing outlet resistance [Wein, 2012].

In the treatment of LUT disorders, many drugs have been tried, but the results are often disappointing, partly due to poor treatment efficacy and/or side effects. The development of pharmacologic treatment of the different forms of urinary incontinence has been slow, but several promising targets and drug principles have been identified [see, Andersson 2016; Andersson et al., 2017; Peyronnet et al., 2018; Abreu-Mendes et al., 2020; De Nunzio et al., 2020].

In this report, we update the recommendations from the 2016 International Consensus meeting [Andersson et al., 2017]. The most relevant information obtained since the last meeting is briefly reviewed and summarised. Agents specifically used for treatment of urinary tract infections and interstitial cystitis, have not been included. We have used a modification of the Oxford system **(Table 1)** for our clinical drug recommendations **(Table 2).** The terminology used is that recommended by the International Continence Society (ICS) [Drake 2018).

Table 1. ICI assessments 2008: Oxford guidelines (modified)

Levels of evidence
Level 1: Systematic reviews, meta-analyses, good quality randomized controlled clinical trials (RCTs) Level 2: RCTs, good quality prospective cohort studies Level 3: Case-control studies, case series Level 4: Expert opinion
Grades of recommendation
Grade A: Based on level 1 evidence (highly recommended) Grade B: Consistent level 2 or 3 evidence (recommended) Grade C: Level 4 studies or " majority evidence" (optional) Grade D: Evidence inconsistent/inconclusive (no recommendation possible) or the evidence indicates that the drug should not be recommended

Table 2: Drugs used in the treatment of LUTS/OAB/ DO. Assessments according to the Oxford system (modified)

	Level of Evidence	Grade of Recommendation
Antimuscarinic drugs		
Darifenacin	1	A
Fesoterodine	1	A
Imidafenacin	1	A
Solifenacin	1	A
Tolterodine	1	A
Trospium	1	A
Drugs with mixed actions		
Oxybutynin	1	A
Propiverine	1	A
Beta-AR antagonists		
Vibegron	1	A
Mirabegron	1	A
Drugs acting on membrane channels		
Calcium antagonists	2	D
K-Channel openers	2	D
Antidepressants		
Imipramine	3	C
Duloxetine	2	C
Alpha-AR antagonists		
Alfuzosin	3	C
Doxazosin	3	C
Prazosin	3	C
Terazosin	3	C
Tamsulosin	3	C
Silodosin	3	C
Naftopidil	3	C
PDE-5 Inhibitors+		
(Sildenafil, Taladafil, Vardenafil)	1	A
COX-inhibitors		
Indomethacin	2	C
Flurbiprofen	2	C
Toxins		
Botulinum toxin (neurogenic)***	1	A
Botulinum toxin (idiopathic)***	1	A
Capsaicin (neurogenic)**	2	C
Resiniferatoxin (neurogenic)**	2	C
Other drugs		
Baclofen*	3	C
Hormones		
Estrogen	2	C
Desmopressin#	1	A

+(male LUTS/OAB); * intrathecal; ** intravesical; *** bladder wall; #nocturia (nocturnal polyuria), caution hyponatremia, especially in the elderly!

1. PUBLICATION SEARCHES

The review undertook a comprehensive search of all major literature databases and the abstract books from several major conferences: American Urological Association, ICS, European Association of Urology, International Urogynaecological Association, International Consultation of Incontinence and Societe Internationale d'Urologie. There were no restrictions on the inclusion of publications by language; publications in languages other than English were translated into English. The literature searches were completed by early summer of 2021.

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II. BLADDER PHYSIOLOGY/ PATHOPHYSIOLOGY

1. CENTRAL NERVOUS CONTROL

In the adult individual, the normal micturition reflex is mediated by a spinobulbospinal pathway, which passes through relay centers in the brain (Figures1-4). In infants, the central pathways seem to be organized as on-off switching circuits, but after the age of four to six years, voiding is initiated voluntarily by the cerebral cortex [de Groat et al., 1999; Beckel and Holstege, 2011; Lovick, 2016]. Studies in humans and animals have identified areas in the brainstem and diencephalon (Figure 5) that are specifically implicated in micturition control, including Barrington's nucleus also known as the pontine micturition center (PMC) in the dorsomedial pontine tegmentum [Fowler et al., 2008]. These structures directly excite bladder motoneurons and indirectly inhibit urethral sphincter motoneurons of the Onuf's nucleus via inhibitory interneurons in the medial sacral cord. Other structures involve in micturition control are the cerebellum [Bastied and Herbaut, 2020] and the periaqueductal grey (PAG) [Zare et al., 2019]. Cerebellum modulates the micturition reflex, participates to the bladder sensory-motor information processing, and is involved in the reflex micturition modulation through direct or indirect pathways to major brainstem or forebrain centres. The PAG receives bladder filling information, and the pre-optic area of the hypothalamus is probably involved in the initiation of micturition. According to PET-scan and functional imaging studies in humans, these supraspinal regions are active during micturition [Blok et al., 1998; Nour et al., 2000; Athwal et al., 2001; Griffiths 2007; 2011; Griffiths et al., 2008; Hruz et al., 2008; Mehnert et al., 2008; Tadic et al., 2008; Deruyver et al., 2016; Groenendijk et al 2021].

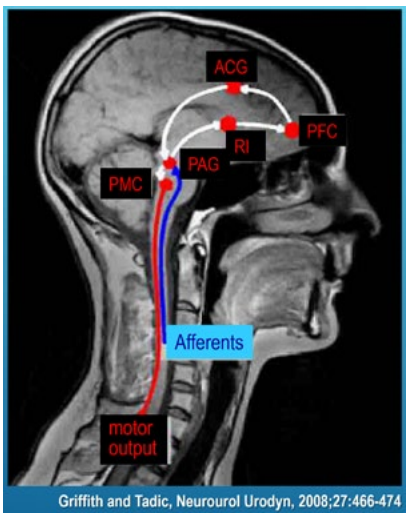

Figure 1: Simplified model of the supraspinal control system of micturition

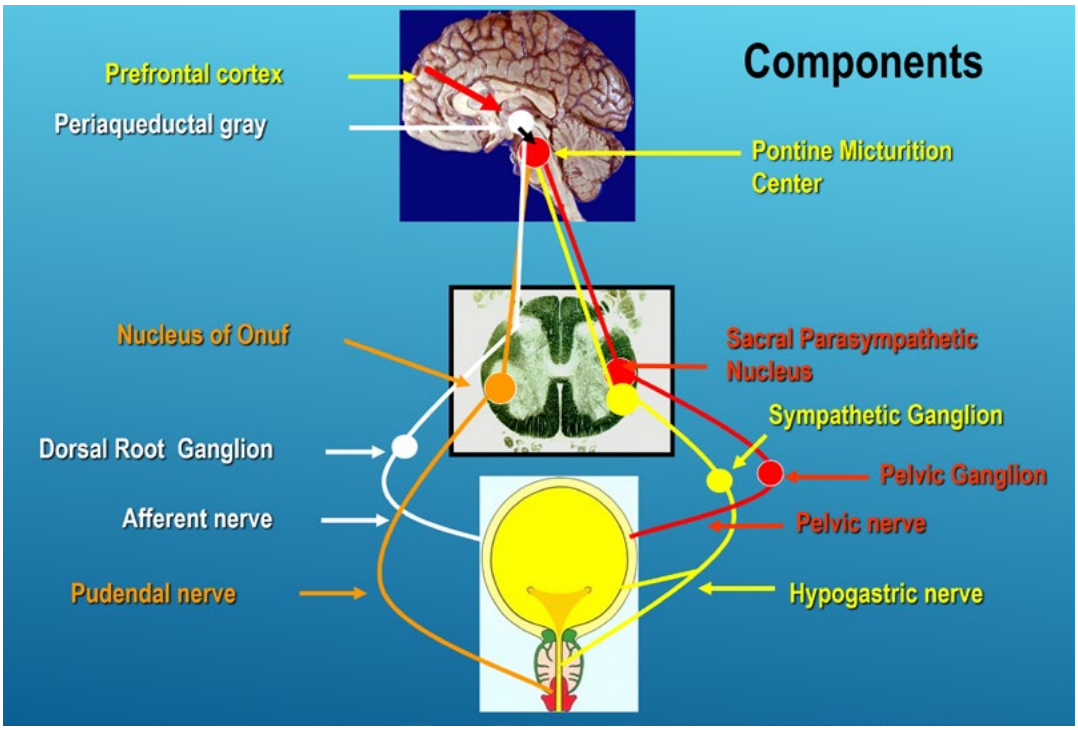

Figure 2: Components of the micturition reflex

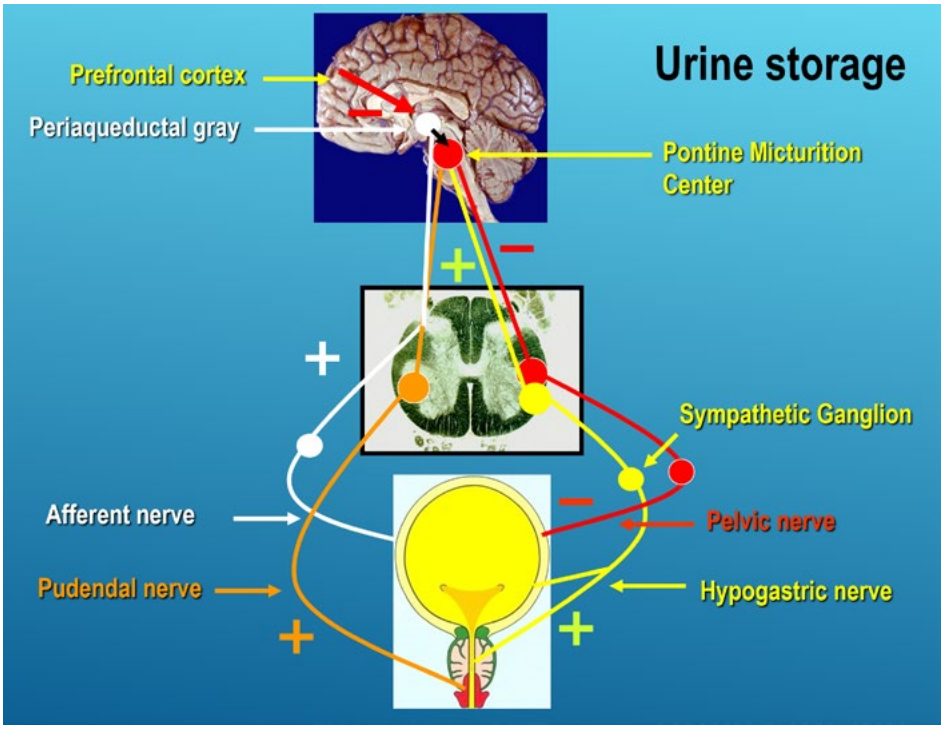

Figure 3: Reflex activity during urine storage

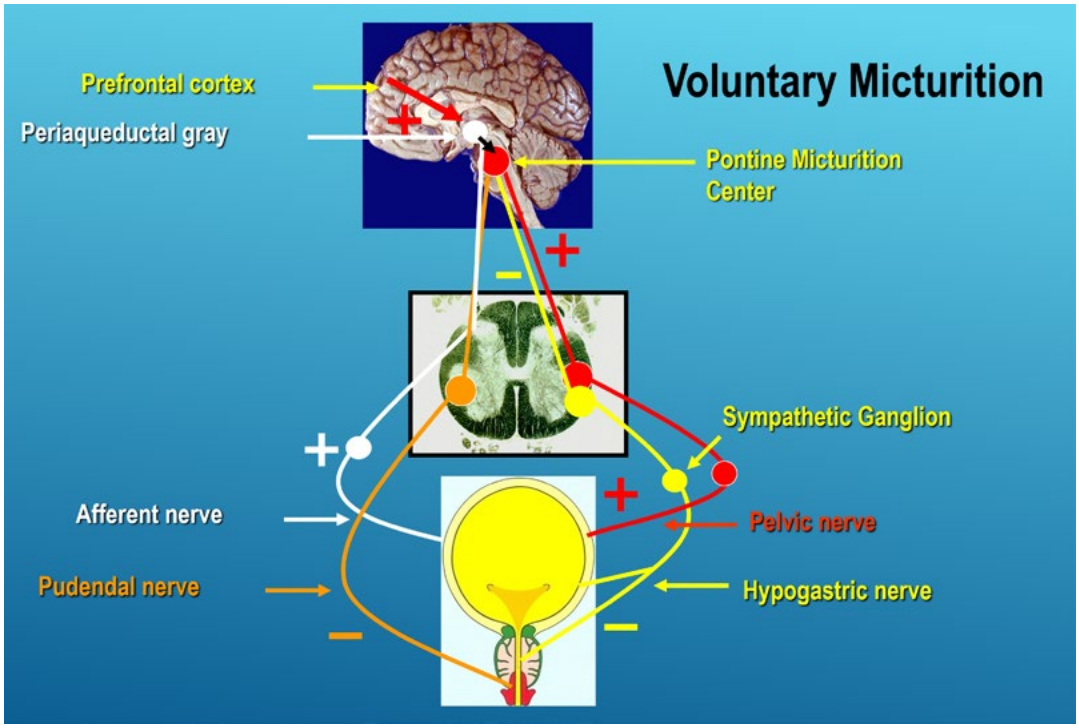

Figure 4: Reflex activity during voluntary micturition

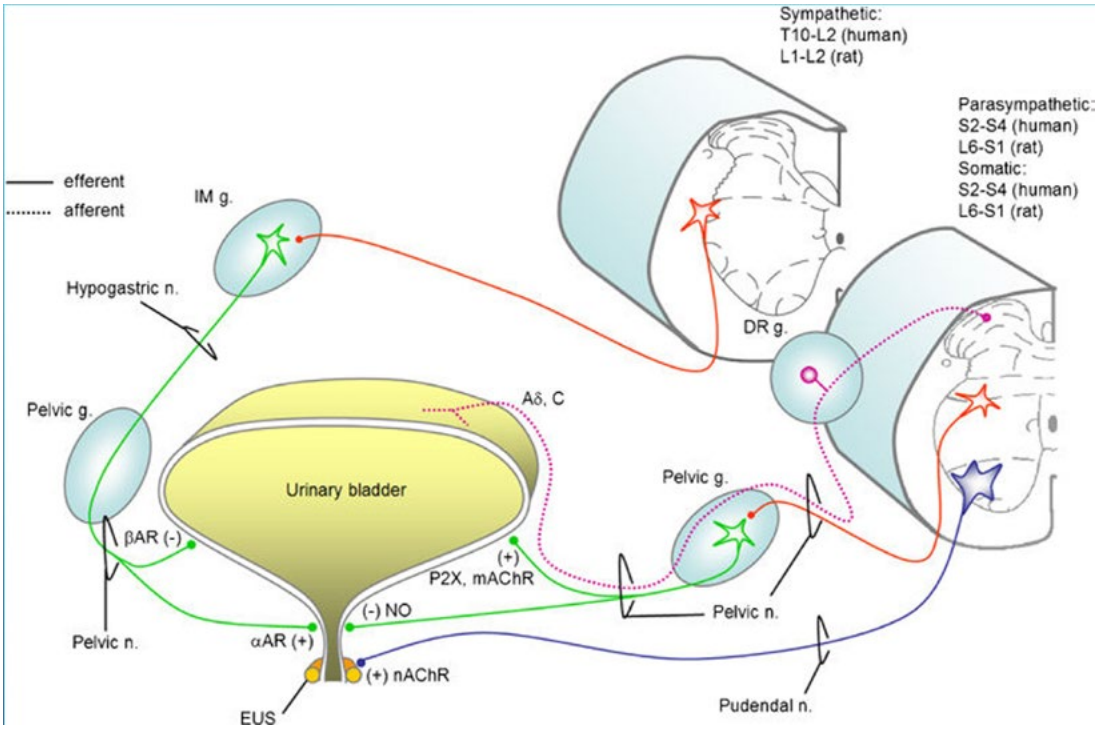

Figure 5: Peripheral innervation of the LUT

2. PERIPHERAL NERVOUS CONTROL

Bladder emptying and urine storage involve a complex pattern of efferent and afferent signalling in parasympathetic, sympathetic, somatic, and sensory nerves (**5**) [de Groat et al., 1993; Beckel and Holstege, 2011; Kim 2019; Ikeda 2021]. These nerves are parts of reflex pathways, which either keep the bladder in a non-contracted state, enabling urine storage at low intravesical pressure, or which initiate micturition by relaxing the outflow region and contracting the bladder smooth muscle. Contraction of the detrusor smooth muscle and relaxation of the outflow region result from activation of *parasympathetic* neurones located in the sacral parasympathetic nucleus (SPN) in the spinal cord at the level of S2-S4 (**5**) [de Groat et al., 1993; Beckel and Holstege, 2011; Kim 2019; Ikeda 2021]. The postganglionic neurones in the pelvic nerve mediate the excitatory input to the human detrusor smooth muscle by releasing acetylcholine (ACh) acting on muscarinic receptors. However, an atropine-resistant component has been demonstrated, particularly in functionally and morphologically altered human bladder tissue (see below). The pelvic nerve also conveys parasympathetic fibres to the outflow region and the urethra. These fibres exert an inhibitory effect and thereby relax the outflow region. This is mediated partly by release of nitric oxide [Andersson and Persson, 1993], although other transmitters might be involved [Hashimoto et al., 1993; Werkström et al., 1995].

Most of the *sympathetic* innervation of the bladder and urethra originates from the intermediolateral nuclei in the thoraco-lumbar region (T10-L2) of the spinal cord (**5**) [Beckel and Holstege, 2011]. The axons travel either through the inferior mesenteric ganglia and the hypogastric nerve or pass through the paravertebral chain and enter the pelvic nerve. Thus, sympathetic signals are conveyed in both the hypogastric and pelvic nerves [Andersson, 1993; De Groat et al., 1993; Ikeda, 2021].

The predominant effects of the sympathetic innervation of the lower urinary tract are inhibition of the parasympathetic pathways at spinal and ganglion levels (demonstrated in animals), and mediation of contraction of the bladder base and the urethra (shown in animals and man, see [Andersson, 1993; Ikeda, 2021]. However, the adrenergic innervation of the bladder body is believed to inactivate the contractile mechanisms in the detrusor directly. Noradrenaline (norepinephrine) is released in response to electrical stimulation of detrusor tissues *in vitro*, and the normal response of detrusor tissues to released noradrenaline is relaxation [Andersson, 1993].

The *somatic* innervation of the urethral rhabdosphincter and of some perineal muscles (for example compressor urethrae and urethrovaginal sphincter), is provided by the pudendal nerve (**5**) [Beckel and Holstege, 2011; Ikeda 2021]. These fibers originate from sphincter motor neurons located in the ventral horn of the sacral spinal cord (levels S2-S4) in the region called Onuf´s (Onufrowicz's) nucleus.

Most of the *sensory* innervation of the bladder and urethra reaches the spinal cord via the pelvic nerve and dorsal root ganglia (Kanai and Andersson, 2010; De Wachter, 2011; Ikeda 2021). In addition, some afferents travel in the hypogastric nerve. The sensory nerves of the striated muscle in the rhabdosphincter travel in the pudendal nerve to the sacral region of the spinal cord [Andersson 1993]. The most important afferents for the micturition process are myelinated Ad-fibres and unmyelinated C-fibres travelling in the pelvic nerve to the sacral spinal cord, conveying information from receptors in the bladder wall to the spinal cord. The Ad-fibres respond to passive distension and active contraction, thus conveying information about bladder filling [Janig and Morrison, 1986]. C-fibres have a high mechanical threshold and respond primarily to chemical irritation of the bladder mucosa [Habler et al., 1990] or cold [Fall et al., 1990]. Following chemical irritation, the C-fibre afferents exhibit spontaneous firing when the bladder is empty and increased firing during bladder distension [Habler et al., 1990]. These fibres are normally inactive and are therefore termed "silent fibres" [de Groat and Yoshimura, 2001; 2015].

3. BLADDER CONTRACTION

Mammalian detrusor contractions are generated by a transient rise of the intracellular Ca2+ concentration ([Ca2+]), initiated by intracellular release of Ca2+ from stores and/or Ca2+ influx via L-type and T-type Ca2+ channels (**6**). Co-ordinated contraction of the bladder is evoked by parasympathetic post-ganglionic fibres releasing ACh and ATP, and driven by descending fibres, emerging at sacral levels S2-S4, Normal bladder contraction in humans is mediated mainly through stimulation of muscarinic receptors in the detrusor muscle and can be blocked by atropine [Andersson and Arner, 2004]. Atropine resistance, i.e., contraction of isolated bladder muscle in response to electrical nerve stimulation after pretreatment with atropine, has been demonstrated in most animal species, but seems to be of little importance in normal human bladder muscle [Sjögren et al., 1982; Andersson, 1993; Bayliss et al., 1999; Rouget et al., 2014].

Such atropine-resistant (non-adrenergic, non-cholinergic: NANC) contractions may be caused mainly by adenosine triphosphate (ATP) [Andersson, 1993; Bayliss et al., 1999, Andersson and Wein, 2004; Kennedy et al., 2007]. ATP acts on two families of purinergic receptors: an ion channel family (P2X) and a G-protein-coupled receptor family (P2Y). Seven P2X subtypes and eight P2Y subtypes have been identified. In several species (rabbit, cat, rat, and human), various studies suggested that multiple purinergic excitatory receptors are present in the bladder [de Groat and Yoshimura, 2001; Ford and Cockayne, 2011; Burnstock. 2013; Ford and Undem., 2013; North and Jarvis, 2013; Andersson, 2015]]. Immunohistochemical experiments with specific antibodies for different P2X receptors showed that $P2X_1$ receptors are the dominant subtype in membranes of rat detrusor muscle and vascular smooth muscle in the bladder. Excitatory receptors for ATP are present in parasympathetic ganglia, afferent nerve terminals, and urothelial cells [de Groat and Yoshimura, 2001]. $P2X_3$ receptors, which have been identified in small-diameter afferent neurons in dorsal root ganglia, have also been detected immunohistochemically in the wall of the bladder and ureter in a suburothelial plexus of afferent nerves. In $P2X_3$ knockout mice, afferent activity induced by bladder distension was significantly reduced [Cockayne et al., 2000; Ford et al., 2006; Ruggieri et al., 2006; Ford and Cockeyne, 2011; Burnstock, 2013]. These data indicate that purinergic receptors are involved in mech anosensory signaling in the mammalian bladder.

A significant degree of atropine resistance may exist in morphologically and/or functionally changed bladders and has been reported to occur in hypertrophic bladders [Sjögren et al., 1982], interstitial cystitis [Palea et al., 1993], neurogenic bladders [Wammack et al., 1995], and in the aging bladder [Yoshida et al., 2001]. The importance of the NANC component to detrusor contraction in vivo, normally, and in different micturition disorders, remains to be established [Andersson, 2006; Fry and McCloskey, 2021**].**

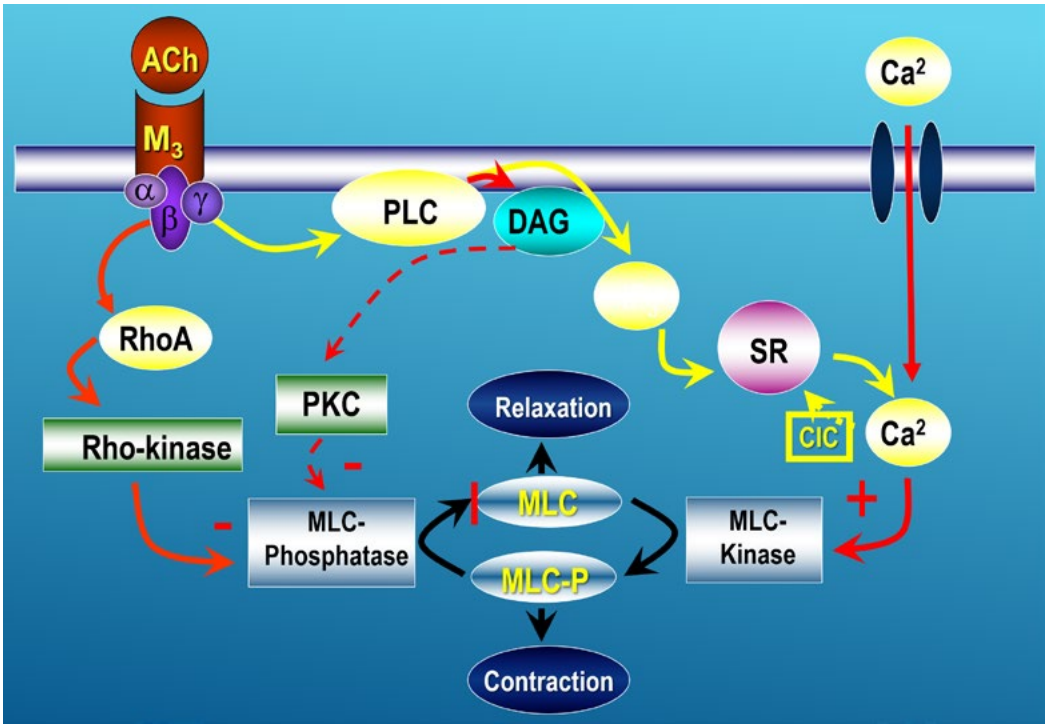

Figure 6: Pathways involved in acetylcholine induced bladder contraction

In the isolated bladder strips from both animals and man local bladder wall small spontaneous contractions can be observed. In isolated whole bladders these contractions are mirrored by small transient increases of intravesical pressure. These pressure movements are not co-ordinated; they are autonomous, with a non-neurogenic origin and thus intrinsic to detrusor smooth muscle itself, but they can be modulated or initiated by stretch of the bladder wall and by local factors. In pathologically changed animal bladders in vivo large pressure variations can occur. Several theories, not mutually exclusive, have been advanced for the origin of such spontaneous contractions: myogenic, neurogenic or urotheliogenic and have been extensively discussed [Fry and McCloskey, 2019]. Characterisation of these spontaneous contractions is important to understand how normal bladder compliance is maintained during filling and the pathophysiology of detrusor overactivity [Fry and McCloskey, 2019].

The urothelium can release neurotransmitters and modulators such as acetylcholine, ATP, nitric oxide, prostaglandins, neuropeptides and nerve growth factor [Guan et al., 2017; Sellers et al., 2018]. In addition, several studies have reported the existence of an urothelium-derived unknown inhibitory factor in the urinary bladder. These factors exert both excitatory and inhibitory effects in modulating urinary tract motility and may also affect function and growth of smooth muscle cells and afferent nerves. The urothelium of the human proxima urethra can generate sensory input through a cross-talk between paraneuronal cells releasing serotonin embedded in the urethral urothelium and sub-urothelial sensory fibers experssing 5HT receptors (**7**) [Coelho et al, 2018].

It has been pointed out [Sellers et al., 2018] that the morphology and function of the urothelium undergo changes with aging and in many pathophysiological conditions. It cannot be excluded that the urothelium may contribute to the therapeutic effects of established drugs to treat lower urinary tract dysfunction and may also serve as a target for novel therapeutics.

4. PATHOGENESIS OF BLADDER CONTROL DISORDERS

As pointed out previously, bladder control disorders can be divided into two general categories: disorders of filling/storage and disorders of voiding [Wein, 2012]. Storage problems can occur as a result of weakness or anatomical defects in the urethral outlet, causing stress urinary incontinence. Failure to store also occurs if the bladder is overactive, as in the overactive bladder (OAB) syndrome (8). The prevalence varies with the criteria used for diagnosis, but according to Irwin et al. (2006), using the ICS definition of 2002 [Abrams et al., 2002], the overall prevalence of OAB, based on computer assisted telephone interviews (the EPIC study) was 11.8%; rates were similar in men and women and increased with age [Irwin et al., 2006]. A similar study based on a cross Canada telephone survey found the prevalence of OAB to be 13 % in men and 14.7% in women [Herschorn et al., 2008]. In a Finnish study, taking into account bother, the prevalence of *clinically meaningful OAB,* was was much lower than reported in these studies [Vaughan et al., 2011].

OAB (symptomatic diagnosis) is often assumed to be caused by detrusor overactivity (DO; urodynamic diagnosis), even if this does not always seem to be the case [Hyman et al., 2001; Digesu et al., 2003; Hashim and Abrams, 2004; Peyronnet et al., 2019]. DO/OAB can occur as a result of sensitization of afferent nerve terminals in the bladder or outlet region, supersensitivity to acetylcholine of the bladder smooth muscle secondary to denervation, or consequent upon damage to the central nervous system (CNS) inhibitory pathways, as can be seen in various neurological disorders, such

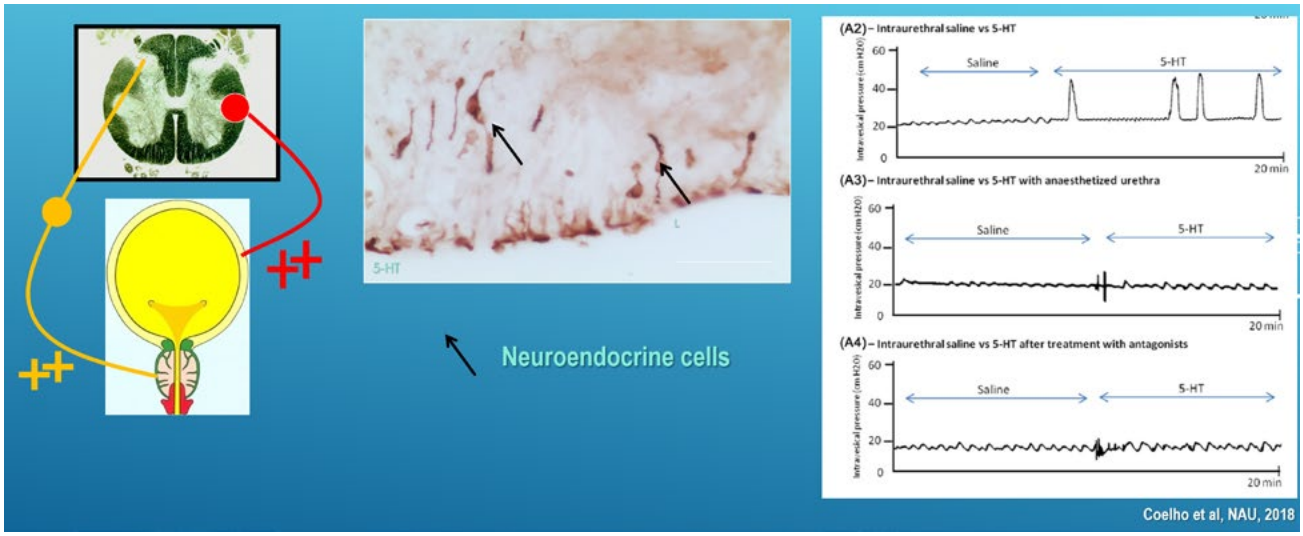

Figure 7: The urethral-bladder reflex initiated by neuroendocrine cells releasing 5HT. From Coelho et al. 2018 Nov;37(8):2389-2397

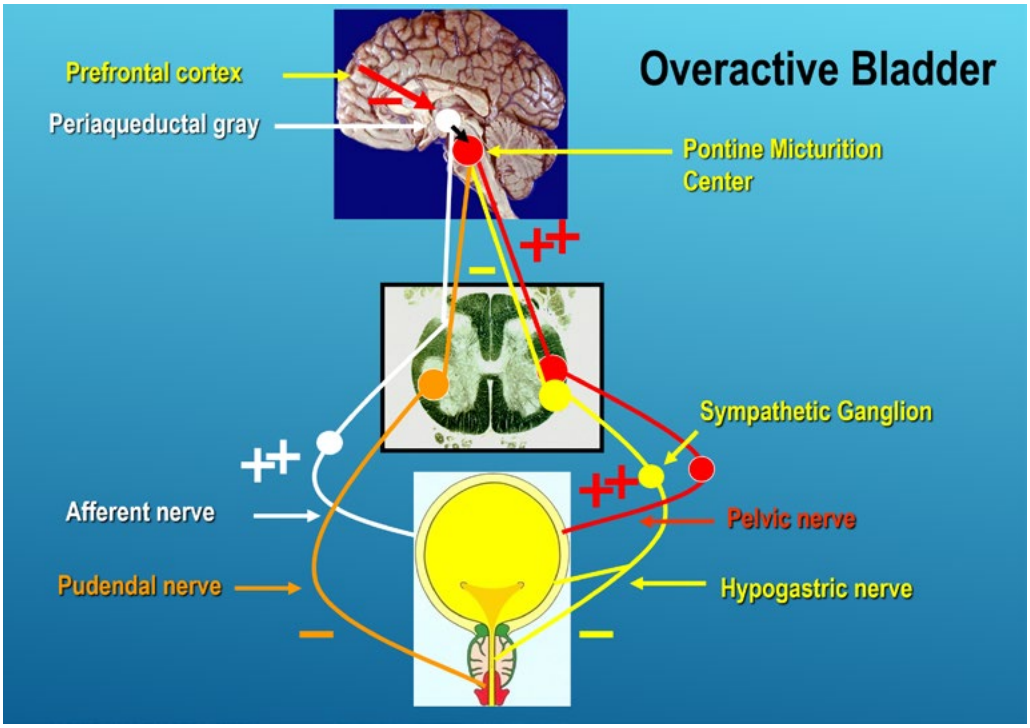

Figure 8: Reflex activity in the overactive bladder

as multiple sclerosis, cerebrovascular disease, Parkinson's disease, brain tumors, and spinal cord injury [Andersson and Pehrson, 2003; Apostolidis et al. 2018; Hamid et al 2018; Sakakibara, 2019; Peyronnet et al., 2019]. The pathophysiologies of OAB refractory to treatment include occult neurogenic bladder, undetected bladder outlet obstruction, urethral-related OAB, urothelial dysfunction with aging, chronic bladder ischemia, chronic bladder inflammation, central sensitization, and autonomic dysfunction [Chen and Kuo, 2018]. The urinary microbiota may contribute to the sensitization of afferents nerves by releasing excitatory compounds including ATP [Abbasian et al, 2019]

Urinary retention and overflow incontinence can be observed in patients with urethral outlet obstruction (e.g., prostate enlargement), decreased detrusor contractility, or both), neural injury, and/or diseases that damage nerves (e.g., diabetes mellitus), or in those who are taking drugs that depress the neural control of the bladder or bladder smooth muscle directly [Wein, 2012].

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III. BLADDER PHARMACOLOGY

1. MUSCARINIC RECEPTORS

The neurotransmitter ACh acts on two classes of receptors, the nicotinic and the muscarinic receptors. While the former play a role in the signal transduction between neurones or between neurones and skeletal muscle (e.g., in the distal urethra), the signal transduction between parasympathetic nerves and smooth muscle of the detrusor involves muscarinic receptors (Abrams and Andersson, 2007). Importantly, the endogenous muscarinic receptor agonist ACh is not necessarily derived only from parasympathetic nerves in the urinary bladder but can also be formed and released non-neuronally by the urothelium (Kummer and Krasteva-Christ, 2014; Yoshida et al., 2008). Five subtypes of muscarinic receptors have been cloned in humans and other mammalian species, which are designated M_{1-5} (Caulfield and Birdsall, 1998). Based upon structural criteria and shared preferred signal transduction pathways, the subtypes can be grouped into M_1, M_3 and M_5 on the one hand and the subtypes M_2 and M_4 on the other. The former prototypically couple via pertussis toxin-insensitive G_q proteins to stimulation of a phospholipase C followed by elevation of intracellular calcium and activation of a protein kinase C, whereas the latter prototypically couple via pertussis toxin-sensitive G_i proteins to inhibition of adenylyl cyclase and modulation of several ion channels (Caulfield and Birdsall, 1998).

Sensitive molecular techniques such as reverse transcriptase polymerase chain reaction can detect mRNA for all five subtypes in the mammalian bladder (Abrams et al., 2006; Hegde, 2006), studies at the protein level, e.g. based upon radioligand binding, have typically detected only M_2 and M_3 receptors, with the former dominating quantitatively (Abrams et al., 2006; Andersson, 2011b; Goepel et al., 1998; Hegde, 2006; Mansfield et al., 2005). The results of radioligand binding studies in tissue homogenates are probably dominated by the expression of subtypes in detrusor smooth muscle. However, muscarinic receptors have also been detected in the urothelium, where M_2 and M_3 subtypes also dominate (Bschleipfer et al., 2007; Leonhäuser et al., 2019; Ochodnicky et al., 2012; Zarghooni et al., 2007). Muscarinic M_3 receptor protein has also been reported in bladder interstitial cells (Grol et al., 2011). On the other hand, muscarinic receptors can also exist pre-junctionally where they modulate neurotransmitter release. Pre-junctionally inhibitory receptors in the bladder have been classified as M_2 in the rabbit and rat, and M_4 in the guinea-pig, rat and human, and a mixture of M_2 and M_4 in the mouse (Andersson, 2011a; D'Agostino et al., 1997; Trendelenburg et al., 2005), whereas pre-junctional facilitatory receptors appear to be of the M_1 subtype in the rat and rabbit urinary bladder, but have also been detected in human bladders (Braverman et al., 1998a). The muscarinic facilitatory mechanism seems to be upregulated (M_3 receptors) in overactive bladders from chronic spinal cord transected rats.

While the detrusor expresses far more M_2 than M_3 receptors, it appears that detrusor contraction under physiological conditions is largely if not exclusively mediated by the M_3 receptor based on organ bath experiments with subtype-selective agonists and antagonists (Chess-Williams et al., 2001; Fetscher et al., 2002; Hegde et al., 1997; Kories et al., 2003; Schneider et al., 2004a; Schneider et al., 2004b; Witte et al., 2011) or on knock-out mice (Ehlert et al., 2007; Matsui et al., 2002; Matsui et al., 2000; Stengel et al., 2002). Under physiological conditions M_2 receptor-selective stimulation causes little contraction (Schneider et al., 2005b) but rather appears to act mainly by inhibiting β-adrenoceptor-mediated detrusor relaxation (Ehlert et al., 2007; Hegde et al., 1997; Matsui et al., 2003). It has been proposed that M_2 receptors can also directly elicit bladder contraction under pathological conditions (Braverman et al., 2006; Braverman et al., 1998a; Braverman et al., 1998b; Braverman and Ruggieri, 2003; Braverman et al., 2002) but such observations have not been confirmed by other investigators using distinct methodological approaches (Schneider et al., 2005a; Schneider et al., 2005b). Studies in the bladder (Cernecka et al., 2014; Michel and Sand, 2009) and in several other tissues (Dale et al., 2014) have observed that β-adrenoceptor agonists including β_3-selective agonists are less potent and/or efficacious in causing relaxation when tested against muscarinic agonists as compared to a variety of other contractile stimuli. Thus, muscarinic receptors make it harder to cause relaxation than other contractile stimuli, an effect apparently involving both M_2 and M_3 receptors (Witte et al., 2011).

Based upon the prototypical signalling pathway of M_3 receptors (Caulfield and Birdsall, 1998) and the presence of phospholipase C stimulation by muscarinic agonists in the bladder (Kories et al., 2003), it had originally been believed that muscarinic receptor-mediated contraction is largely mediated by an activation of phospholipase C (Ouslander, 2004). While some earlier data had supported this concept, it now appears clear that, at least in rat, mice and humans, muscarinic receptor-mediated bladder contraction occurs

largely independent of phospholipase C (Frazier et al., 2007; Schneider et al., 2004a; Schneider et al., 2004b; Wegener et al., 2004). Rather, alternative signalling pathways such as opening of L-type calcium channels and activation of a rho-kinase appear to contribute to muscarinic receptor-mediated bladder contraction in a major way (Frazier et al., 2008).

The functional role of muscarinic receptors in the urothelium has largely been studied indirectly, i.e., by investigating the effects of urothelium removal or of administration of pharmacological inhibitors. These data indicate that muscarinic stimulation of the urothelium causes release of an as yet unidentified factor which inhibits detrusor contraction (Birder, 2010; Dalghi et al., 2020; Sellers et al., 2018). Some data indicate that muscarinic receptors in the urothelium may partly act by releasing nitric oxide (NO) (Andersson et al., 2009). Muscarinic receptor blockade in urothelial cells may also reduce ATP release induced by stretch (Young et al., 2012). Thus, it appears that muscarinic receptors in the urothelium also contribute to the regulation of overall bladder function but their specific roles in health and disease have not been fully established.

Assuming an involvement of muscarinic receptors in physiological *voiding* contractions of the bladder, numerous studies have explored whether an overactivity of the muscarinic system may play a causative role in bladder dysfunction. This could involve, e.g., an enhanced expression of such receptors and/or an increased functional responsiveness. In vitro, an increased sensitivity to muscarinic receptor stimulation was found in both idiopathic and neurogenic overactive human detrusors (Stevens et al., 2006). However, the overall balance of available studies suggests that the muscarinic receptor system is not hyperactive under conditions of DO and, if anything, can be even hypoactive (Michel and Barendrecht, 2008). This does not exclude a contribution to DO of ACh and muscarinic receptor stimulation during *bladder filling* (see below). It appears that the contribution of muscarinic mechanisms to the overall regulation of bladder contractility decreases in favour of non-cholinergic mechanisms under pathological conditions (Rapp et al., 2005; Yoshida et al., 2001; Yoshida et al., 2008). These observations may help to explain the moderate efficacy of muscarinic receptor antagonists relative to placebo in controlled clinical studies (Buser et al., 2012; Chapple et al., 2008; Novara et al., 2008; Reynolds et al., 2015; Shamliyan et al., 2008).

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2. β-ADRENOCEPTORS (β-ARS)

The body of the bladder receives a relatively sparse innervation by noradrenergic nerves. The density of noradrenergic nerves increases markedly toward the bladder neck, where the smooth muscle receives a dense noradrenergic nerve supply, particularly in the male [Gosling et al., 1999]. Noradrenergic nerves also occur in the lamina propria of the bladder, only some of which are related to the vascular supply. Their functional significance remains to be established [Gosling et al., 1999].

In the human detrusor, b-ARs dominate over a-ARs with an order of abundance of $b > a_2 >> a_1$ with the amount of a_1-ARs too small for a reliable quantification; the situation is different in the trigone, and may differ between species for both [Michel & Vrydag, 2006). Accordingly, the primary detrusor response to noradrenaline is relaxation. Even if the a-ARs have no significant role in normal human detrusor contraction, there is evidence from animal models that this may change after, for example, bladder outlet obstruction, parasympathetic decentralization, and in overactive bladders.

The relaxant effect of noradrenaline on the detrusor can be exerted both pre- and postjunctionally [Åmark, et al., 1986]. Stimulation of a_2-ARs on cholinergic neurons may lead to a decreased release of acetylcholine. b-ARs including b_3-AR also exist prejunctionally, including those on cholinergic neurons, but their functional role has remained controversial [Okeke, Gravas, & Michel, 2017]. Since b-ARs dominate over a-ARs post-junctionally in the bladder [Andersson & Wein, 2004; Nomiya & Yamaguchi, 2003], noradrenaline relaxes the detrusor through stimulation of b-ARs. b-AR agonists are considered to stimulate adenylyl cyclase to increase cAMP. In turn, cAMP activates protein kinase A to mediate the biological effects. However, it remains unclear whether this signaling pathways mediates detrusor relaxation [Frazier, Peters, Braverman, Ruggieri, & Michel, 2008]. Both normal and neurogenic human detrusors express b_1-, b_2-, and b_3-AR mRNAs, but relaxation of human detrusor is mediated predominantly if not exclusively by b_3-AR [Igawa, Aizawa, & Michel, 2019; Michel & Vrydag, 2006]. However, other b-AR subtypes may be involved in other species, for instance b_2-AR contribute to relaxation in rat detrusor and even dominate in mouse detrusor [Yamazaki, et al., 1998; Propping, et al., 2016]. These findings suggest b-AR, and particularly b3-AR, stimulation as a way of promoting bladder relaxation during filling. However, this does not necessarily mean that this mechanism is active during normal filling. The importance of the sympathetic input for human bladder function is controversial. Sympathectomy has no distinct effect on bladder filling, and neither has blockade of b-ARs [Andersson & Wein, 2004]. The sympathetic nervous system may not be essential for urine storage in humans. However, if released noradrenaline contributes to bladder relaxation during filling, it may be through stimulation of both b_2- and b_3-ARs.

2.1. Expression of β-ARs in the bladder

2.1.1. mRNA level

All three β-AR subtypes are expressed at the messenger RNA (mRNA) level in the urinary bladder [Michel & Vrydag, 2006]. While initial studies on relative abundance of subtype mRNA have indicated that $β_3$-AR account for more than 95% of all β-AR mRNA in the human detrusor [Nomiya & Yamaguchi, 2003], a later study based on whole bladder rather than detrusor reported a comparable expression of all three subtypes [Uhlen et al., 2015]. A similar abundance of all three subtypes has also been reported in rat bladder (Barendrecht et al., 2009a). In situ hybridization studies have localized expression of $β_3$-AR mRNA in the human detrusor [Takeda et al., 1999]. However, the predictive value of $β_3$-AR mRNA for presence of functional receptor protein remains uncertain.

2.1.2. Protein level

The detection of AR subtypes can in principle be based on radioligand binding (including autoradiography) studies or on antibody-based approaches. Radioligands with high affinity and specificity for $β_3$-AR became available only recently (van Wieringen, et al., 2013). Other radioligands preferentially label b_1- and b_2-AR, which depending on assay conditions have technically been challenging to interpret [Schneider & Michel, 2010] or failed to detect b_3-AR [Michel & Vrydag, 2006; Schneider & Michel, 2010]. The latter studies suggested that b_2-ARs are much more abundant than b_1-ARs.

Antibody-based approaches including immunohistochemistry have the potential for high selectivity in detecting AR subtypes and mapping them to distinct morphological structures. Thus, most reported β-AR subtype antibodies lack specificity or have not been tested for it under stringent conditions. Some antibodies have been proven to have some degree of selectivity for β_3-AR [Cernecka, et al., 2012; Chamberlain et al., 1999; Guillaume et al., 1994] but the degree of selectivity is only moderate and may depend on application being used (i.e., histochemistry vs. immunoblotting) and limited to certain species. Moreover, even minor differences in applied methods may lead to differences in detecting β-AR subtypes [Jositsch et al., 2009].

This is illustrated by recent immunohistochemistry studies in the human bladder: Despite using the same antibodies, some investigators detected β_3-AR in smooth muscle fibres and, to a lesser extent, in urothelium and suburothelium [Silva et al., 2017], whereas others found them colocalized with the vesicular acetylcholine (ACh) transporter and primarily in nerve fibres in the mucosa and muscular layers of the bladder but not in urothelium or smooth muscle [Coelho,et al., 2017]). Based on other antibodies, others reported β_3-AR expression to a greater extent in urothelium than smooth muscle of the human bladder and also in sub-urothelial myofibroblast-like cells, intramural ganglions, Schwann cells and intramural nerves [Limberg et al., 2010]. Thus, the localization of β_3-AR in the human bladder remains at least partly controversial. This is unfortunate because a robust understanding of the cell types expressing β_3-AR in the bladder could guide an understanding which cell types contribute to the clinical effects of β_3-AR agonists.

2.2. Roles of β-ARs in the bladder physiology and pathophysiology

The physiological voiding in humans, and perhaps dogs [Frara et al., 2021] is predominantly mediated by muscarinic M_3 receptor, which differs from rodents where other transmitters contribute to a major degree; however, additional mediators may also such as ATP may also play relevant roles in humans under pathophysiological conditions [Ouslander, 2004]. Limited evidence indicates that pathophysiological states do not cause major changes in β-AR subtype mRNA expression in the detrusor [Barendrecht et al., 2009b; Nomiya & Yamaguchi, 2003]. Accordingly, relaxant effects of β_3-AR in samples of patients with BOO and BOO with detrusor overactivity (DO) were similar [Svalo et al., 2013], which is in line with findings from various animal models [Michel & Barendrecht, 2008].

2.2.1. Detrusor smooth muscle

β-AR-mediated relaxation of the human detrusor is mediated predominantly, if not exclusively, by β_3-AR; however, this appears to be species dependent with similar contributions of β_2- and β_3-AR involved in rats and β_2-AR even dominating in mouse [Michel & Vrydag, 2006; Propping et al., 2016]. Such species differences can complicate extrapolation from animal data to humans. In addition to causing smooth muscle relaxation, β-AR agonists can also counteract contraction elicited by stimulation of other receptors such as muscarinic receptors [Ehlert et al., 2007; Klausner, et al., 2009]. In this regard, studies in rat bladder show β-AR agonists are more potent and more effective against any contractile stimulus other than muscarinic agonists [Cernecka, et al., 2014; Michel & Sand, 2009]. Similar observations have been made in several other smooth muscle preparations [Dale et al., 2014]. Accordingly, β_3-AR agonists may preferentially inhibit detrusor contractions by pathological stimuli such as bradykinin, but largely be sparing those mediated by muscarinic receptors involved in physiological voiding [Igawa, Aizawa & Michel, 2019].

2.2.2. Urothelium

The urothelium plays an active role in the regulation of bladder function: it senses input from its environment by virtue of express-

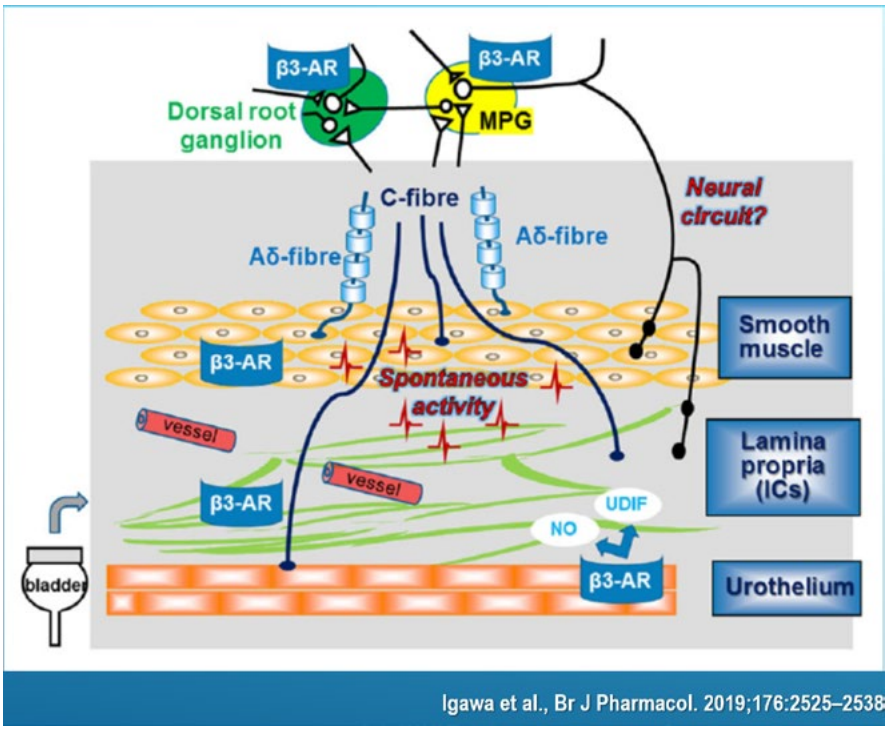

Figure 9: Expression of β3-ARs and possible mechanism that might be involved in the afferent pathway and modulation of spontaneous activity in the bladder. Reproduced with permission from (Igawa et al Br J Pharmacol, 2019; 176: 2525-2538).

ing receptors for various stimuli and releasing neurotransmitters in response to those stimuli [Birder & Andersson, 2013; Sellers, Chess-Williams, & Michel, 2018]. All three β-AR subtypes are expressed in the urothelium at the mRNA level [Ochodnicky et al., 2012; Otsuka, et al., 2008; Tyagi, et al., 2009]. Based on immunohistochemical studies, β_3-AR may be more abundant in the urothelium than in the detrusor (**9**); nonetheless, it may be functionally less important as compared to urothelial β_2-AR, which appears more relevant for the regulation of urothelial function [Sellers et al., 2018]. The stimulation of urothelial β_3-AR leads to release of nitric oxide (NO) to modulate afferent nerves and release of urothelial-derived inhibitory factor to modulate detrusor function (Fig 9) [Igawa, Aizawa & Michel, 2019].

2.2.3. Suburothelial interstitial cells

The bladder suburothelium consists of various cell types including microvessels, sensory nerve endings and interstitial cells (ICs, **9**). A similar level of β_3-AR expression at the protein level in ICs and detrusor has been suggested [Otsuka et al., 2013], but these data are difficult to interpret based on poor validation of the antibody being used. Suburothelial ICs may be a possible origin of spontaneous contractile activity of the mucosa, for instance in guinea pigs and pigs [Igawa, Aizawa & Michel, 2019]. It has been proposed that hyperactivity of bladder afferent nerves may at least partly result from spontaneous contraction of the mucosa, and that β_3-AR agonists can inhibit spontaneous contractile activities by acting on ICs [Aizawa et al., 2017]. This would be consistent with the observation that the β_3-AR agonist mirabegron lowered non-voiding contractions (NVCs) in rats with BOO [Gillespie et al., 2012]. However, these data would not align with observations that β_3-ARs in the human bladder were primarily located in smooth muscle with a more limited expression in the urothelium and suburothelium [Silva et al., 2017]. While these conflicting data need to be resolved, most findings are in line with a theory in which a urothelium-associated sensory web links bladder sensory function (**Fig 9**) [Apodaca, 2004].

2.2.4. Afferent nerves

Two types of afferent nerve fibres are found in the bladder, which differ in morphology, localization and function [Christie et al., 2021]: The myelinated Aδ-fibres appear to dominate in the detrusor and may mainly be involved in physiological sensing of bladder filling. In contrast, the unmyelinated C-fibres are found in the detrusor and the lamina propria (including ICs) and are largely involved in the sensing of pathophysiological signals [de Groat, 2004; Gabella & Davis, 1998; Ouslander, 2004; Vera & Nadelhaft, 2000]. Morphological studies suggest a presence of β_3-ARs in bladder afferent nerves [Coelho et al., 2017) as well as in the major pelvic ganglion (MPG) in rats [Eastham, et al., 2015]. Functional studies in normal rats demonstrated that mirabegron can inhibit the mechanosensitive Aδ-fibres, which may be related to suppression of the bladder micro-contractions [Aizawa, Homma & Igawa, 2012]. Furthermore, afferent activities of both Aδ- and C-fibres were intermittently enhanced by propagation of bladder myogenic micro-contractions in BOO rats [Aizawa et al., 2017]. These findings suggest a possibility of involvement of β3-AR on neural circuits in the regulation of afferent outflow and sensation [Igawa, Aizawa, & Michel, 2019] (**9**).

2.2.5. Bladder vasculature

It is increasingly recognized that hypoperfusion of the bladder may play a causative role in functional disorders of the lower urinary tract [Michel, Chess-Williams, & Hegde, 2015; Thurmond, Yang, & Azadzoi, 2016], which makes blood vessels supplying the bladder as a potential target for the treatment of LUTS. Although the regulation of vascular tone has traditionally been attributed to β_2-AR, β_3-AR can contribute to such regulation in various vascular beds [Bhadada, et al., 2011]. Accordingly, initial reports indicate that β_3-AR agonists can improve bladder function in animal models of LUTS based on experimental atherosclerosis and ischemia [Bayrak et al., 2015; Sawada et al., 2013]. Whether this at least partly reflects direct effects on bladder perfusion or a generally beneficial effect of β_3-AR agonists on bladder function, remains to be explored.

2.2.6. Possible roles in pathophysiology of OAB

Most studies using isolated detrusor strips have reported a potency of mirabegron for causing relaxation in the low micromolar range [Igawa & Michel, 2013]. On the other hand, plasma concentrations observed upon therapeutic doses of mirabegron do not exceed 100 nM [Krauwinkel et al., 2012].This discrepancy may propose that the cellular target of β3-AR agonists in the treatment of OAB may not be the detrusor small muscle cells [Eastham, et al., 2015] but rather a different cell types, including urothelial cells, interstitial cells, efferent, afferent neurons, the major pelvic ganglion and/or blood vessels supplying the urinary bladder [Okeke, Gravas & Michel, 2017].

Mirabegron had high potency for inhibiting the nerve-evoked contraction and ACh-release in human bladder preparation, with EC_{50} value of 123 nM and 129 nM, respectively [D' Agostino, Maria Condino & Calvi, 2015],which are more potent than those producing direct relaxation of human detrusor smooth muscle. Moreover, a recent immuno-histochemisty study on human bladder tissue indicated that *β*3-ARs are expressed only on cholinergic nerve fibres, but are not present on urothelial or smooth muscle cells [Coelho, et al.,, 2017]. These findings may lead to the hypothesis that β3-AR agonists act, at least in part, by inhibiting ACh- release from cholinergic, most probably parasympathetic, nerve terminals through a prejunctional mechanism [Coelho, et al., 2017].

However, another study showed a controversial finding that *β*3-ARs are diffusely distributed among detrusor smooth muscle cells, but are not present on cholinergic nerve fibres, while adenosine A1 receptor predominantly expressed on cholinergic nerve fibres [Silva et al., 2017]. Furthermore, both isoprenaline and mirabegron decreased ACh-release induced by electrical field stimulation in human detrusor preparation, which was prevented by *β*3-AR antagonists and DPCPX, an adenosine A1 antagonist [Silva et al., 2017]. These findings suggest that the decrease in ACh-release induced by isoprenaline or mirabegron did not necessarily occur via *β*3-ARs located in the nerve ending but rather indirectly by intermediate formation of adenosine and subsequent activation of A1 inhibitory receptors (**Fig 10**). However, it remains to be clarified whether such inhibition of ACh-release occurs exclusively indirectly via adenosine formation and A1 adenosine receptor activation or whether it may also involve a neuronally expressed *β*3-ARs. Nevertheless, β3-AR agonists would preferentially inhibit pathologically increased detrusor tone during bladder filling over physiological detrusor contraction during voiding and enable to inhibit an increased cholinergic tone in OAB [Igawa, Aizawa, & Michel, 2019].

It has been demonstrated in women with OAB that an increase in localized contractile activities (micro-contractions) developed during occurrence of urinary urgency without apparent increasing intravesical pressure [Drake, et al., 2005]. Cystometric studies in a decerebrated rat model demonstrated that intravesical administration of mirabegron increased inter-voiding intervals and compliance and decreased the amplitude of non-voiding contractions [Sadananda, et al., 2013].

Studies with monitoring bladder mechanosensitive single-unit afferent activities (SAAs) in rats revealed that the afferent activities of both A*δ*- and C-fibres decreased after mirabegron-adminis-

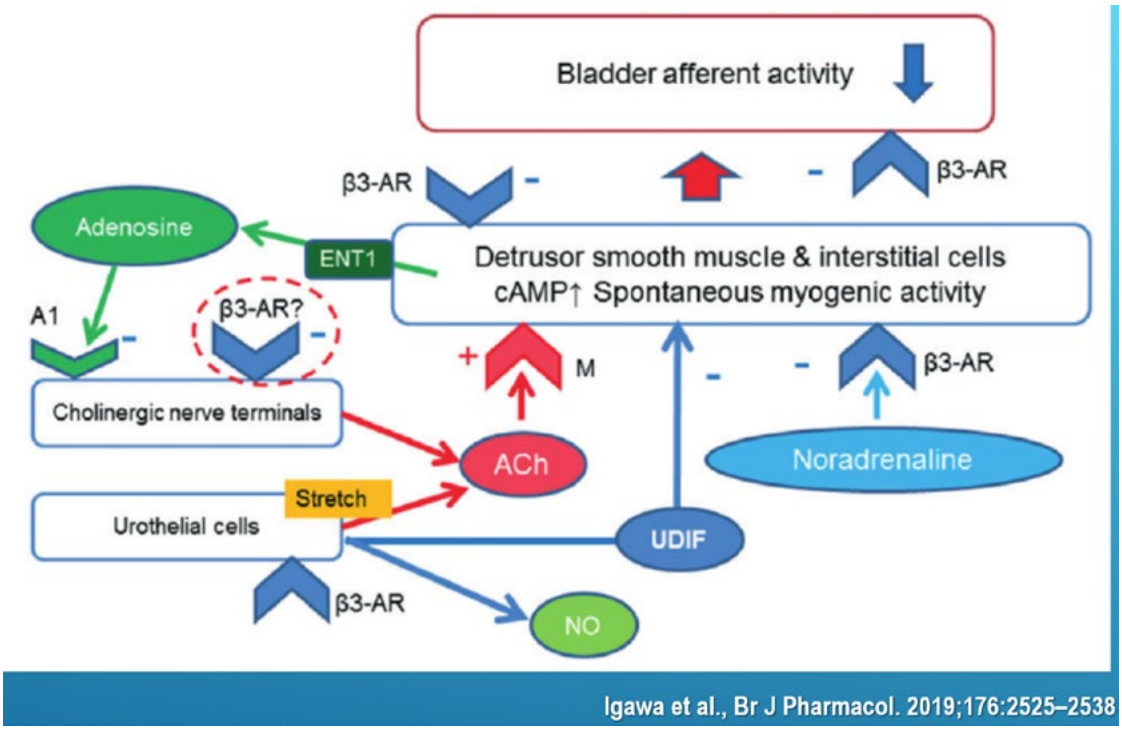

Figure 10: Hypothetic mechanism of mirabgron's inhibitory action on ACh-release through the A1 receptors. Reproduced with permission from (Igawa et al Br J Pharmacol, 2019; 176: 2525-2538).

tration in a dose-dependent manner, which was more remarkable for Aδ-fibres than C-fibres; moreover, such inhibition of afferent activities appeared to synchronize with the decrease in bladder pressure fluctuation (micro-contractions), whereas bladder compliance did not change significantly from the base-line value [Aizawa, Homma & Igawa, 2012]. These authors further confirmed in an isovolumetric condition that mirabegron at 0.3 mg/kg suppressed micro-contractions concomitantly with Aδ-fibre activity but not C-fibre activity with [Aizawa, Homma & Igawa, 2015]. Another β3-AR agonist, CL316,243 (10 μg/kg intravenously) similarly decreased Aδ-fibre, but not C-fibre, activities during bladder filling with saline. Intravesical instillation of prostaglandin E_2 (PGE_2) significantly increased C- but not Aδ-fibre activities. Pretreatment with CL316,243 inhibited the increase in C-fibre activities induced by PGE_2 [Aizawa, et al., 2010]. A recent study with similar monitoring bladder mechanosensitive SAAs in rats with BOO showed a higher number of micro-contractions and lower SAAs of Aδ-fibres, but SAAs of both Aδ- and C-fibres were intermittently enhanced by micro-contractions. These pathophysiological findings may contribute to the development of OAB associated with BOO [Aizawa et al., 2017].

Taken all together, the possible mechanisms of action exerting inhibition of urgency by β3-AR agonists may include: 1) relaxing detrusor muscle-decreasing bladder tone, 2) inhibiting micro-contractions/Aδ-fibre activity, 3) inhibiting urotheliogenic afferent activation-C-fibre activity (**Fig 11**) [Igawa, Aizawa, & Michel, 2019].

3. β-ARS IN THE URETHRA

While we are not aware of studies demonstrating b-AR mRNA expression in the urethra, recent immunohistochemical studies have suggested the presence of β3-ARs in the human female urethra, which was found in the epithelial layer of all parts but highest in the mid urethra [Kummeling et al., 2020]. This finding provides a mechanistic basis for reports that b3-AR agonists, including mirabegron, a clinically used one, can cause relaxation of the urethral smooth muscle of several animal species and humans [Alexandre et al., 2016; Yamanishi, et al., 2003]. How such in vitro findings relate clinical observations in patients with LUTS remains to be determined.

4. β-ARS IN THE PROSTATE

All three β-AR subtypes appear to be expressed in the prostate at the mRNA and protein levels, but precise quantitative information on their relative contribution is lacking [Michel & Vrydag, 2006]. While earlier studies concluded that relaxation of human prostate was primarily mediated by β_1- and β_2-AR, more recent findings with mirabegron suggest a role for β_3-AR [Calmasini et al., 2015]. Such findings could provide a mechanistic basis for ongoing evaluation of β_3-AR agonists in the treatment of LUTS suggestive of benign prostatic hyperplasia.

5. IN VIVO STUDIES

Most *in vivo* studies of β_3-AR agonists on bladder function have been performed in rats and mice. They have demonstrated increases of bladder capacity with little effect on micturition pressure or the residual volume [Fujimura et al., 1999; Hicks et al., 2007; Kaidoh et al., 2002; H. Takeda et al., 2002; Woods, et al., 2001,Takasu et al., 2007].

However, the cellular target underlying such effects remains unclear because of the following dilemma: With very few exceptions, the reported potency of mirabegron to relax isolated bladder strips

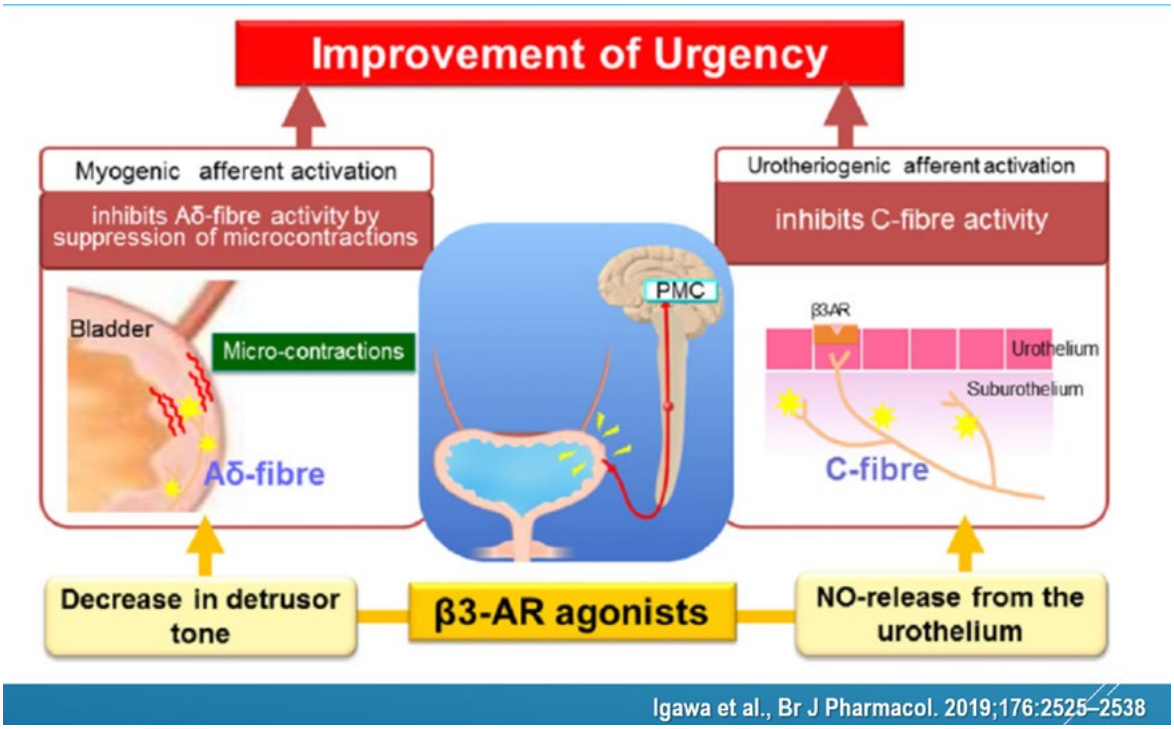

Figure 11: Hypothetic mechanisms involved in urgency-improvement by β3-AR agonists. Reproduced with permission from (Igawa et al Br J Pharmacol, 2019; 176: 2525-2538).

is in the low micromolar range [Igawa & Michel, 2013], whereas plasma concentrations observed upon therapeutic doses of mirabegron typically are less than 100 nM [Krauwinkel et al., 2012]. This led to proposals that the primary cellular target of mirabegron (and perhaps β_3-AR agonists in general) may not be detrusor smooth muscle [Eastham et al., 2015]. Potential alternative targets include the urothelium, ICs, efferent and afferent nerves, the major pelvic ganglion and/or blood vessels supplying the urinary bladder. All of these proposals are intriguing and have some degree of plausibility. However, it remains unclear whether mirabegron has a potency for those targets that is more in line with its therapeutic plasma levels. Of note, the list of potential targets is not necessarily mutually exclusive and rather could be a combination of several of them. This will require additional investigation, a situation which also applies to identifying the true cellular target of muscarinic receptor antagonists in the treatment of OAB [Andersson, 2004].

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IV. DRUGS TO TREAT OVERACTIVE BLADDER SYMPTOMS/DETRUSOR OVERACTIVITY

It has been estimated that more than 50 million people in the developed world are affected by urinary incontinence, and an abundance of drugs has been used for treatment (Table 2). Helfand and co-workers showed that in a cohort of 7,244,501 patients over 45 years with an OAB diagnosis, 24.4% of these were treated mainly with antimuscarinic agents; 75.6% went untreated. Only 25.6% of those treated were men [Helfand et al., 2010]. As underlined by several other subcommittees, drugs may be efficacious in some patients, but they do have side effects, and frequently are not continued indefinitely. Hence it would be worth considering them as an adjunct to conservative therapy.

1. ANTIMUSCARINIC (ANTICHOLINERGIC) DRUGS (MUSCARINIC RECEPTOR ANTAGONISTS)

Since the last edition of this section a limited number of studies have been added to the literature. Clinically important information has been updated in the clinical use section below. For the individual antimuscarinic agents, selected studies have been identified and presented and where updated information is available and relevant, has been added. A more exhaustive and detailed selection of individual studies is presented in the previous iteration of this book (Incontinence, 6th edition). Finally, where drugs have essentially become obsolete, they have been removed e.g., atropine, propantheline bromide and flavoxate but can be reviewed in the previous edition, if required. Comparison of individual antimuscarinics with other modalities of managing overactive bladder have not been included and in general the number of studies in this area are small. Cost effectiveness of antimuscarinics has also not been included due to the different healthcare systems around the world, however, a recent article has reviewed the available literature [Giannitsas and Athanasopoulos, 2015] and a further study looking at a UK health system has been published [Hakimi, Kelleher et al., 2018]. Furthermore, combination pharmacotherapy of antimuscarinics with other agents will be discussed in another section in this chapter.

1.1. Pharmacology

1.1.1. Mechanism of action.

Muscarinic receptor antagonists (antimuscarinics) bind to muscarinic receptors to prevent their activation by agonists including the endogenous agonist acetylcholine (ACh) [Caulfield and Birdsall, 1998]. This occurs throughout the entire body. Acetylcholine is released from three types of neurons: those within the CNS, the motor neurons innervating skeletal muscle, and parasympathetic nerves; moreover, ACh can be formed by and released from non-neuronal sources such as the urothelium [Yoshida, Masunaga et al. 2008]. While ACh released from motor neurons acts on nicotinic receptors, that from parasympathetic nerves and non-neuronal sources largely acts on muscarinic receptors; ACh released within the central nervous system acts on both types of receptors.

ACh released from parasympathetic nerves plays a major role in the execution of voiding by contracting muscarinic receptors on detrusor smooth muscle cells. While release of ACh from parasympathetic nerves is assumed to occur largely during the micturition phase of the voiding cycle, non-neuronally released ACh can also be released during the storage phase, which makes it a candidate to cause non-voiding contractions [Andersson, 2011, Sellers, Chess-Williams et al., 2018].

It had long been believed that antimuscarinics reduce OAB symptoms blocking muscarinic receptors on detrusor smooth muscle cells [Sellers and Chess-Williams, 2012]. However, muscarinic receptors on various other cell types including the urothelium and afferent and efferent nerves may also contribute to the control of

urine storage and micturition [Andersson, 2004]. For instance, muscarinic antagonists can modulate the activity of both C- and Ad-type afferent nerves [Andersson, 2011; Michel 2015] (Figure 9). A role for muscarinic receptors expressed in the urothelium in the regulation of physiological voiding, and even more so that of OAB/DO has been suggested [Andersson, 2011; Sellers and Chess-Williams, 2012; Birder and Andersson 2013; Michel 2015], such role has not been firmly established.

The competitive antagonism exerted by clinically used antimuscarinics implies that their effects can be overcome by the massive release of ACh occurring during micturition; this may explain why antimuscarinics in clinically used doses have little effect on voiding contractions [Finney, Andersson et al., 2006] the others mainly report bladder capacity, frequency and sensation of urgency. Nonetheless, (acute) urinary retention can occur, however, it is rare in humans in doses typically applied for the treatment of OAB/DO (**Fig 12**).

1.1.2. Pharmacodynamic properties

Antimuscarinics can be classified based on their relative affinity for subtypes of muscarinic receptors. While most antimuscarinics bind with similar affinity to all five muscarinic receptor subtypes, darifenacin exhibits a moderate and oxybutynin and solifenacin a minor selectivity for the M_3 subtype, i.e., the subtype predominantly mediating contraction of detrusor smooth muscle [Glavind and Chancellor, 2011; Yamada et al., 2018]. The clinical relevance of subtype-selectivity may be limited because the most frequent AE (dry mouth and constipation) are also mediated by M_3 receptors. An exception may be increased heart rate, which is largely mediated by M_2 receptors [Glavind and Chancellor, 2011]. However, elevation of heart rate typically is very minor with therapeutic doses of all antimuscarinics used in the treatment of OAB/DO [Rosa, Baccino et al., 2018]. Thus, none of the clinically used antimuscarinics exhibits relevant selectivity for the bladder as compared to other organs upon oral administration.

The antimuscarinics can be divided chemically into tertiary and quaternary amines [Guay, 2003; Abrams and Andersson, 2007]. While trospium is a quaternary amine, all other clinically used antimuscarinics are tertiary amines. Tertiary amines are more lipophilic and for this reason exhibit penetration into the brain [Callegari, Malhotra et al., 2011; Yamada, Ito et al. 2018]; however, this is compensated in some cases, e.g., darifenacin, by active transport out of the brain, for instance by transport via the product of the MDR1 gene. In contrast, quaternary amines exhibit lower oral bioavailability [Guay, 2003], but exhibit little passage through the blood-brain-barrier [Staskin et al., 2010]. This may have implications for the ability of antimuscarinics to impair cognition, which has been documented for all members of this drug class to some extent – except for trospium [Müderrisoglu et al., 2019].

1.1.3. Pharmacokinetic properties

The antimuscarinics used in the treatment of OAB/DO differ considerably in their absorption and ability to penetrate into the brain [Callegari et al., 2011, Yamada et al. 2018], but also in their routes of metabolism and excretion [Guay, 2003; Witte et al. 2009]. Such differences impact the extent and variability of absorption, with quaternary amines typically exhibiting smaller and more variable oral bioavailability. They also determine the potential for drug-drug-interactions and their restrictions of use in patients with impaired hepatic or renal function **(Table 3).** They also impact the half-lives of the various drugs after becoming systemically available, ranging from 2-3 h for oxybutynin to 45-68 h for solifenacin. Moreover, the metabolism of some antimuscarinics leads to metabolites that are pharmacologically active, with the metabolites sometimes exhibiting a different pharmacological profile than the parent compound [Michel and Hegde, 2006]); examples of the latter include fesoterodine, oxybutynin and propiverine.

The main pathways of metabolism of antimuscarinics involve cytochrome P450 enzymes, specifically CYP2D6 and CYP3A4 [Guay, 2003; Witte et al. 2009]. Considerable differences exist in the fraction excreted renally in unchanged or otherwise pharmacologically active form ranging from <1% for oxybutynin to 16% for fesoterodine. Such renal excretion raises the possibility of exposing the bladder to the antimuscarinic not only via the blood stream but also from the luminal side, particularly because some antimuscarinics can be reabsorbed from the bladder to become systemically available again [Krause et al., 2013]. However, no evidence is available that differences in renal excretion of active compound have clinical consequences. These differential routes of metabolism and excretion lead to specific recommendations for each drug related to dosing choices or even contraindications in patients with hepatic or renal impairment and/or those with concomitant medication affecting the metabolism (**Table 3**).

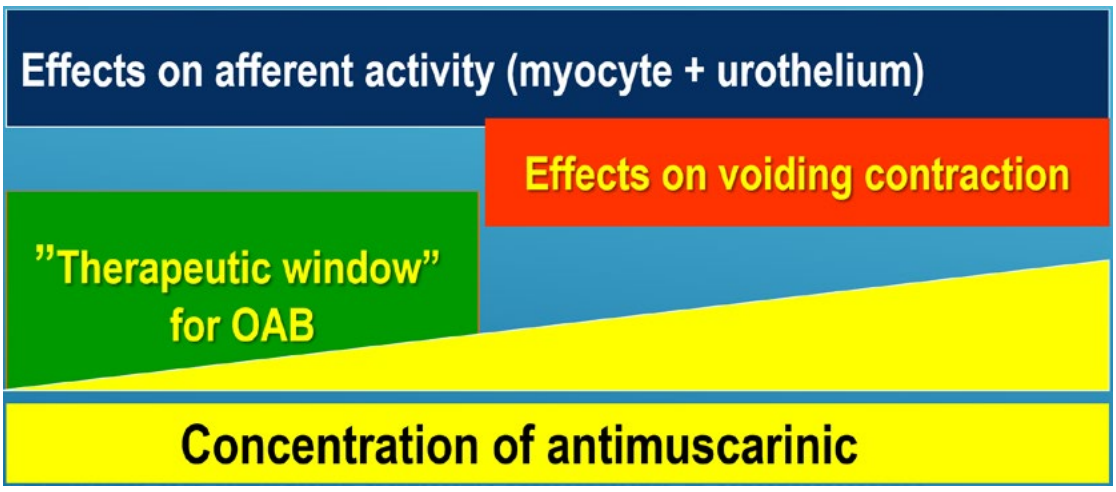

Figure 12: Concentration-dependent effects of antimuscarinics

Table 3: Impact of renal or hepatic impairment and of comedications on dosing recommendations in Europe and the US as based upon regulatory authority-approved summary of product characteristics/package insert. If recommendations differed between countries, the more conservative recommendation is listed. IR, immediate release; ER, extended release; max, maximally. All dosages refer to total daily doses. Unless otherwise noted, the recommendations relate to all available formulations of a given drug. Reproduced with permission from (Witte, Mulder, et al. 2009)

Drug (recommended daily dose)	Renal impairment	Hepatic impairment	Comedications
Darifenacin (7.5/15 mg)	caution	Child Pugh A: none, but risk of increased exposure Child Pugh B: max 7.5 mg, if benefit outweighs risk Child Pugh C: not recommended	CYP2D6 inhibitors: starting dose 7.5 mg, titrate to 15 mg if well tolerated Moderate CYP3A4 inhibitors: starting dose 7.5 mg Potent CYP3A4 inhibitors: do not use
Fesoterodine (4/8 mg)	Mild/moderate: start with 4 mg, increase dose cautiously to 8 mg Severe: 4 mg"	Child Pugh A: start with 4 mg, increase to 8 mg with caution Child Pugh B: max 4 mg Child Pugh C: not recommended	CYP2D6 inhibitors: start with 4 mg Potent CYP3A4 inhibitors: max 4 mg
Oxybutynin (5-30 mg)	Caution	Caution	Potent and moderate CYP 3A4 inhibitors: caution
Propiverine (5/15 IR/30 mg ER)	Max dose 30 mg	Child Pugh A and B: no advice on dose adjustments Child Pugh C: not studied"	Potent CYP 3A4 inhibitors: no studies available but in vitro data point to possible interactions
Solifenacin (5/10 mg)	Mild/moderate: no adjustment Severe: max 5 mg	Child Pugh A: caution Child Pugh B: max. 5 mg Child Pugh C: not recommended	Potent CYP 3A4 inhibitors: max 5 mg
Tolterodine (1/2/4 mg)	Mild/moderate: no data Severe: max 2x1 mg IR or 2 mg ER	max 2x1 mg IR or 2 mg ER	CYP2D6 inhibitor: none potent CYP3A4 inhibitors: max 2x1 mg IR or 2 mg ER
Trospium (40 mg)	Mild/moderate: caution Severe: max 20 mg	Child Pugh A, B and C: caution	-

Darifenacin is metabolized via CYP2D6 and CYP3A4, but the resulting metabolites are considered not to contribute to the clinical effects [Skerjanec, 2006]; about 3% of are excreted renally as active drug [Michel and Hegde, 2006; Witte et al., 2009]. Accordingly, caution should be applied in patients with renal impairment. Hepatic impairment with Child-Pugh A scores, results in an increased exposure but does not result in a need for dose adjustment. If hepatic impairment reaches Child-Pugh B, doses should be limited to 7.5 mg/day and the drug should only be used if anticipated benefit outweighs the risk. It should not be used in patients with Child-Pugh C. In the presence of CYP2D6 inhibitors, the starting dose should be no higher than 7.5 mg/day and it should only be up-titrated to 15 mg/day if the lower dose was well-tolerated. Concomitant use of potent CYP3A4 inhibitors can increase exposure to darifenacin 10-fold and is not recommended.

Fesoterodine is metabolized by non-specific esterases to the pharmacologically active 5-hydroxmethyl tolterodine; the latter is partly excreted renally (16% of administered dose), but partly also metabolized further by CYP2D6 and CYP3A4 [Michel and Hegde, 2006; Witte et al., 2009]. Accordingly, fesoterodine should be started at a dose of 4 mg/day in patients with renal impairment and increased to 8 mg/day with caution in those with mild-moderate renal impairment; the dose should be limited to 4 mg/day in those with severe renal impairment. In patients with hepatic impairment with Child-Pugh A, it should be started at 4 mg/day and increased to 8 mg/day only with caution. In Child-Pugh B, the dose should be limited to 4 mg/day, and fesoterodine is not recommended in patients with Child-Pugh C. In the presence of CYP2D6 inhibitors, treatment should start at 4 mg/day, in the presence of potent CYP3A4 inhibitors 4 mg/day should be the maximum dose.

Oxybutynin undergoes marked first-pass metabolism in the liver upon oral administration; while one of the resulting metabolites is inactive, the other metabolite formed by CYP3A4 is the pharmacologically active N-desmethyl-oxybutynin, which is mainly responsible for the observed clinical profile after oral administration [Michel and Hegde, 2006]. It is postulated that N-desmethyl-oxybutynin is more prone to cause antimuscarinic AE and that this may explain why some oral modified release and transdermal formulations of oxybutynin

may be better tolerated [Michel, 2002; Michel and Hegde, 2006]. In contrast, renal excretion in active form of oxybutynin and N-desmethyl-oxybutynin combined accounts for <1% of administered dose. Accordingly, oxybutynin should be used with caution in patients with renal or hepatic impairment and in those with co-medication with moderate or potent inhibitors of CYP3A4 [Witte et al., 2009].

Propiverine undergoes extensive first-pass metabolism yielding three main, active metabolites among which M5 appears most relevant; these metabolites exhibit a qualitatively and quantitatively distinct pharmacological profile – not only regarding muscarinic receptors but also additional targets such as L-type Ca^{2+} channels and α_1-adrenoceptors [Michel and Hegde, 2006]. These metabolites are partly generated by CYP3A4, and partly by flavin monoxygenases. Less than 1% of an administered dose is excreted renally as unchanged compound. In patients with impaired renal function, the daily dose should not exceed 30 mg; no advice exists on dose adjustment in patients with hepatic impairment, and no clinical studies are available related to an interaction with CYP3A4 inhibitors; however, in vitro data point to possible interactions [Witte et al., 2009].

Solifenacin undergoes extensive hepatic metabolism, partly by CYP3A4, but the metabolites are either considered pharmacologically inactive or to exhibit only low abundance [Michel and Hegde, 2006]. Accordingly, no dose adjustment is required with mild-moderate renal impairment, whereas the dose should be limited to 5 mg/day with severe renal impairment [Witte et al., 2009]. In patients with hepatic impairment, caution should be applied with Child-Pugh A, the dose be limited to 5 mg/day with Child-Pugh B, and use is not recommended with Child-Pugh C. In the presence of potent CYP3A4 inhibitors, the dose should be limited to 5 mg/day.

Tolterodine undergoes hepatic metabolism by CYP3A4 to yield N-desalkyl-tolterodine and by CYP2D6 to yield the pharmacologically active 5-hydroxymethyl-tolterodine (5-HMT) [Michel and Hegde, 2006]. Less than 1% of an administered dose is excreted renally as tolterodine, but 5-14% as 5-hydroxmethyl-tolterodine; the renal excretion in active form is much lower in subjects who are poor metabolizers for CYP2D6. The metabolism of 5-hydroxmethyl-tolterodine is described above for fesoterodine. While dosing recommendations are available for mild-moderate renal impairment, the dose should be limited to 2 mg/day in severe renal impairment or in hepatic impairment or in the presence of potent CYP3A4 inhibitors; no dose adjustment is required in the presence of CYP2D6 inhibitors [Witte et al., 2009].

Trospium undergoes only minor metabolism and is largely excreted in unchanged form in faeces upon oral administration, reflecting the limited oral bioavailability of this drug [Michel and Hegde, 2006]. The pathways of metabolism of absorbed trospium are not fully defined by cytochrome P450 enzymes apparently play only a minor role. About 3.5% of administered dose is excreted renally in unchanged form. Accordingly, caution should be applied in patients with mild-moderate renal impairment, and doses be limited to 20 mg/day in severe renal impairment. Caution should also be applied in patients with hepatic impairment. Dose adjustment in the presence of comedications are not required.

1.2. Clinical Use

Several muscarinic receptor antagonists are available for the treatment of OAB/DO. The amount of information for the individual drugs varies, and so does the degree of details from the different studies presented. The randomized controlled trials (RCTs) for some of the antimuscarinics, underlying their approval by the regulatory authorities, have been performed in some cases more than 20 years ago. Some drugs have never been approved in this indication or are no longer in wide clinical use because of unfavorable benefit/risk ratios. These include compounds such as atropine, emepronium, propantheline, and flavoxate; information on these drugs is not included below, but can be found elsewhere [Andersson et al. 1999, Andersson et al., 2017].

Antimuscarinics as a class are effective in the treatment of OAB/DO by reducing symptoms and improving OAB-related quality of life (QoL); clinically noticeable improvements often manifest with 1-2 weeks after initiation of treatment [Chapple et al., 2008; Novara et al., 2008; Wang et al. 2014]. No major difference of efficacy has been observed between compounds, between men and women or between younger and older patients. While urgency is the defining symptom of OAB [Abrams et al., 2002; D'Ancona et al., 2019], approval by regulatory authorities has been based on their effects against incontinence and frequency. Interestingly, antimuscarinics as a class appear more effective against these two OAB symptoms than against urgency, although also some degree of improvement of urgency has also been demonstrated [Chapple et al., 2008; Novara et al., 2008; Wang et al., 2014]. In contrast, antimuscarinics exhibit only little improvement of nocturia relative to placebo in RCTs [Schneider et al., 2009; Cornu et al., 2012], although some exceptions have been reported [Michel and de la Rosette, 2005; Weiss et al., 2013]. A consistent improvement of nocturia is seen in observational studies for instance with darifenacin [Schneider et al., 2010], propiverine [Oelke et al., 2011], solifenacin [Witte et al., 2009] or tolterodine [Michel et al., 2005], possibly reflecting at least partly a placebo effect. More detailed information on specific studies for the individual antimuscarinics has been summarized in the past [Andersson et al., 1999; 2017].

The efficacy of antimuscarinic drugs relative to placebo had been questioned [Herbison et al., 2003]. The authors stated that anticholinergics produce significant improvements in overactive bladder symptoms compared with placebo but the benefits maybe of limited clinical significance. Since that study, large meta-analyses of studies performed with the 'at the time' most widely used drugs [Chapple et al., 2005; Novara et al., 2008], clearly show that antimuscarinics are of significant clinical benefit. Novara et al., reviewed 50 RCTs and 3 pooled analyses, which they considered of good methodological quality [Novara et al., 2008]. The review concluded that ER formulations should be preferred to the IR ones and that with IR formulations, dose escalation might yield some improvements in the efficacy but with significant increase in the AE. Reviewing information from more than 12,000 references, Chapple et al., based their conclusions that "antimuscarinics are efficacious, safe, and well tolerated treatments" on 73 RCTs selected for their meta-analysis [Chapple et al., 2005]. There were significant differences between the antimuscarinics in rates of withdrawal and rates and range of adverse events and efficacy outcomes.

The most frequent AEs observed with antimuscarinics in the treatment of OAB/DO include dry mouth and constipation (**Fig 13**). Most RCT and specific studies with head-to-head comparisons of multiple antimuscarinics were neither designed nor powered for AEs as an endpoint. Analysis of specific AEs such as dry mouth, constipation or blurred vision has been reported but is also difficult to interpret because sample sizes often were insufficient for clear differentiation. Another hard tolerability-related endpoint is withdrawal due to AE, but again incidences mostly were too low with the given sample sizes to allow clear differentiation. With these limitations in mind, meta-analyses of tolerability have been reported [Chapple et al., 2008; Maman et al., 2014]. Two general trends appear from these analyses. Firstly, immediate-release oral oxybutynin appears

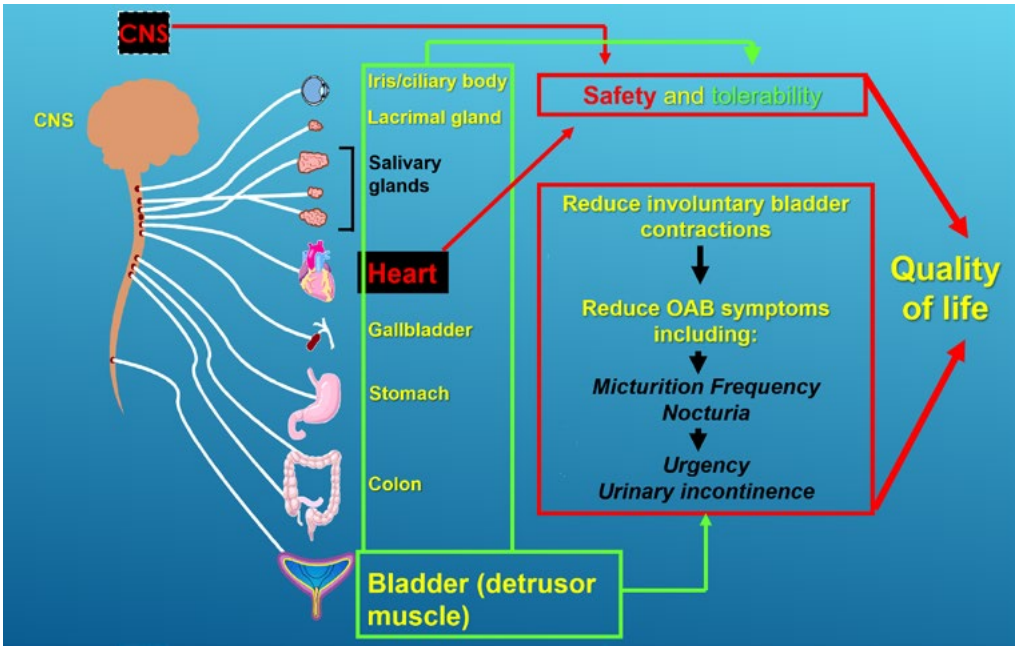

Figure 13: Adverse effects of antimuscarinics

to have the highest incidence of AE. Second, slow-release, extended-release and transdermal formulations appear to have fewer AE than immediate-release formulations.

While effects on heart rate could be expected upon use of antimuscarinics based on mechanistic considerations [Brodde and Michel, 1999], increases in heart rate or cardiovascular AE in general have rarely been observed; when they occurred, increases in heart rate typically were only minor, i.e., not exceeding 2-3 beats/min [Rosa et al., 2018] The clinically used antimuscarinics do not increase QT intervals to a meaningful extent [Rosa et al., 2018].

Impairment of cognition is a typical AE of antimuscarinics, whether administered for the treatment of OAB/DO or other indications. The risk for cognitive impairment upon administration of antimuscarinics increases with total exposure over time, defined as number of drugs with antimuscarinic properties and total number of doses for each of them [Ancelin et al., 2006; Herbison et al., 2003]. A recent population based longitudinal prospective cohort study examined the cumulative effect of anticholinergics (tricyclic antidepressants, 1st generation anti-histamines and bladder antimuscarinics) and the risk of dementia [Gray et al., 2015]. The authors found a dose dependent relationship for the development of dementia and Alzheimer's disease and noted the anticholinergic indication was not relevant to the development of dementia. Cumulative anticholinergic dose was measured utilizing the total standardized daily doses (TSDD) in this study and for dementia, adjusted hazard ratios for cumulative anticholinergic use compared with non-use were 1.23 (95% CI, 0.94-1.62) for TSDDs of 366 to 1095; and 1.54 (95% CI, 1.21-1.96) for TSDDs greater than 1095. Moreover, Dmochowski et al., recently conducted a systematic review and meta-analysis assessing at least 3 months of anticholinergic use and the impact on cognitive function and risk of dementia [Dmochowski et al., 2021]. The risk of incident dementia increased with increasing exposure and 2 studies from the meta-analysis reported an increase risk of dementia with ≥ 3 months use of bladder antimuscarinics (adjusted odds ratio 1.21 to 1.65). Barthold et al. (2020) recently published a large retrospective mediclaims based study involving > 71,000 individuals assessing whether bladder selectivity of the antimuscarinic used effected impact on dementia and Alzheimer's disease. The authors compared solifenacin and darifenacin vs fesoterodine, flavoxate, oxybutynin, tolterodine, trospium (non-selective) and found an increased risk of Alzheimer's and other dementia related disorders in general but with no difference between the groups. In general the RCTs of antimuscarinics used in the treatment of OAB/DO typically were not designed to capture adverse effects on cognition, but such effects have been reported for all members of this drug class [Yamada et al., 2018; Müderrisoglu et al., 2019], except for trospium which does not penetrate the blood-brain-barrier [Staskin et al., 2010]. The incidence of cognitive impairment upon use of different antimuscarinics is difficult to quantify, but preclinical models [Yamada et al., 2018], indirect clinical comparisons [Müderrisoglu et al., 2019] and direct head-to-head studies in volunteers [Kay and Granville, 2005] all suggest that the risk is highest with oxybutynin in its immediate-release formulation. Limited data indicate that cognitive impairment caused by antimuscarinics may largely be reversible upon discontinuation of treatment [Müderrisoglu et al., 2019].

To compare the effects of different antimuscarinic drugs for OAB symptoms, Madhuvrata et al. [2012] analyzed 86 trials, 70 with parallel and 16 with cross-over designs (31,249 adults). They concluded that when the prescribing choice is between oral immediate release oxybutynin or tolterodine, tolterodine might be preferred for reduced risk of dry mouth. ER preparations of oxybutynin or tolterodine might be preferred to immediate release preparations because there is less risk of dry mouth. Comparing solifenacin and immediate release tolterodine, solifenacin might be preferred for better efficacy and less risk of dry mouth. Fesoterodine might be preferred over ER tolterodine for superior efficacy but has higher risk of withdrawal due to adverse events and higher risk of dry mouth. Kessler et al., analyzed 69 trials enrolling 26'229 patients with OAB where the aim was to compare adverse events of antimuscarinics using a network meta-analytic approach that overcomes shortcomings of conventional analyses [Kessler et al., 2011]. They found similar overall adverse event profiles for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, and

trospium chloride, but not for oxybutynin orally administered when currently used starting dosages were compared. They concluded that most currently used antimuscarinics seem to be equivalent first choice drugs to start the treatment of OAB, except for oral oxybutynin dosages of ≥ 10 mg/day, which may have more unfavorable adverse event profiles.

The durability of the effects of antimuscarinics is not known and the relapse rate of symptoms after discontinuation of treatment has not been systematically studied. In 173 women with OAB symptoms for >6 months, Lee et al., studied in a prospective, randomized, open-label, trial what happened 3 months after the patients had been successfully treated for 1, 3, or 6-months [Lee et al., 2011]. The relapse rate was 62%, and the request for treatment was 65%, indirectly suggesting an efficacy of treatment. None of the antimuscarinic drugs in common clinical use (darifenacin, fesoterodine, imidafenacin, oxybutynin, propiverine, solifenacin, tolterodine or trospium) is ideal as a first-line treatment for all OAB/DO patients. Optimal treatment should be individualized, based on the patients' co-morbidities and concomitant medications, and the pharmacological profiles of the different drugs, should be taken into consideration [Chapple et al., 2008].

Several studies have documented that the persistence with prescribed antimuscarinic therapy for overactive bladder is low [Basra et al., 2008; Sears et al., 2010; Wagg et al., 2012]. The most common causes seem to be lack of efficacy and adverse effects. However, there is some evidence suggesting that the tolerability of the different antimuscarinics may differ. Wagg et al. [analysed prescription data for patients receiving antimuscarinics for treatment of the OAB syndrome over a 12-month period [Wagg et al., 2012]. At 12 months, they found that the proportions of patients still on their original treatment were: solifenacin 35%, tolterodine ER 28%, propiverine 27%, oxybutynin ER 26%, trospium 26%, tolterodine IR 24%, oxybutynin IR 22%, darifenacin 17%, and flavoxate 14%. The longest mean persistence was reported for solifenacin (187 days versus 77 − 157 days for the other treatments). Goodson et al., in a large retrospective cohort study assessed 26,775 patients and found that 39% persisted with antimuscarinics at 1 year [Goodson et al., 2018]. Using extended release tolterodine as a reference, better persistence rates were observed for solifenacin (RR = 1.08, 95% CI = 1.03-1.13) and fesoterodine (RR = 1.25, 95% CI = 1.09-1.43), and a lower rate for IR tolterodine (RR = 0.90, 95% CI = 0.85-0.94). Patient factors associated with higher persistence rates included older age, male sex, and comorbidities such as multiple sclerosis, Parkinson's disease, and diabetes. Similar trends in other healthcare systems have been reported [Mauseth et al., 2013; Kalder et al., 2014]. Gomes et al., compared the persistence of oxybutynin or tolterodine therapy among older patients newly prescribed one of these drugs [Gomes et al., 2012]. This was a retrospective cohort study of Ontarians aged 66 years and older and the exact formulations of the drugs were not stipulated. The authors identified 31,996 patients newly treated with oxybutynin and 24,855 newly treated with tolterodine. After 2 years of follow-up, persistence on oxybutynin (9.4%) was significantly lower than that on tolterodine (13.6%, $p < 0.0001$). The median time to discontinuation of oxybutynin and tolterodine was 68 and 128 days, respectively. Vouri et al. [2019] suggested in an elderly population that persistence was better for patients who were initiated on oxybutynin extended-released (ER), tolterodine, trospium, darifenacin, solifenacin, or fesoterodine when compared to oxybutynin IR ($p < 0.001$). Another systematic review concluded that persistence rates regardless of antimuscarinic was generally poor, with median rates 12-39.4% at 12 months and 6-12% at 24 months [Veenboer and Bosch, 2014]. Risk factors for discontinuation included younger age group, use of IR formulations and oxybutynin. A UK retrospective study has suggested that persistence is better for beta 3 agents such as Mirabegron when compared to other antimuscarinics used to treat overactive bladder [Chapple, Nazir et al., 2017]). The median time-to-discontinuation was significantly longer for mirabegron (169 d, interquartile range [IQR] 41-not reached) compared to tolterodine ER (56 d, IQR 28-254; adjusted hazard ratio [HR] 1.55, 95% confidence interval 1.41-1.71; $p<0.0001$) and other antimuscarinics (range 30-78 d; adjusted HR range 1.24-2.26, $p<0.0001$ for all comparisons). Lua et al., in a large commercial claims database study suggested adherence to antimuscarincs was better in men and worse in the obese [Lua, Pathak et al., 2017].

Antimuscarinics are recommended in treating OAB when lifestyle interventions and dietary modification have failed. However, many guidelines would recommend when one antimuscarinic fails due to lack of efficacy or poor tolerability that a second and even third should be tried. A recent retrospective medicine and pharmacy claims analysis in the US linked to a one-time patient survey of members with OAB-wet was recently reported with the specific aim of assessing antimuscarinic treatment patterns and outcomes [Chancellor, Yehoshua et al., 2016]. A total of 620 patients were finally included after exclusions. Patients cycled through 1-6 different antimuscarinics. In general adherence to the medication was poor and 35% of the population used ≥ 2 antimuscarinics. Moreover, UI episodes and burden was fairly consistent despite antimuscarinic cycling and whether patients continued or discontinued their medication. Discontinuation rates were high being 71% of the whole population at study end. Approximately 89% of patients continued to be bothered by their bladder symptoms and requested additional help, whether they remained on antimuscarinics or not. The study suggests that antimuscarinic cycling does not have a positive impact on patients in terms of UI. As a result, alternative therapies should be sought for patients who have failed 1-2 antimuscarinics. It seems logical that if there is inadequate efficacy with 1 antimuscarinic that the maximum dose should be trialed in those with a flexible dosing option. In those where tolerability is an issue switching to an alternative muscarinic is also reasonable. However, thereafter treatment should be escalated to include non-antimusacrinic options.

The use of antimuscarinics to treat the storage component of lower urinary tract symptoms in combination with other classes of drugs is increasing. Furthermore, the evidence base to support this is also expanding. Details of the use of antimuscarinics in combination with β_3-AR agonist agents to treat refractory OAB, in combination with alpha blockers and 5 alpha reductase inhibitors to combat lower urinary tract symptoms attributable to benign prostatic enlargement are covered in later sections of this chapter.

1.3. Antimuscarinics with "specific" action

Below data on the different antimuscarinics are presented. These drugs are assumed to selectively block muscarinic receptors (motivating the term "specific"). The information has been chosen to give a reasonable efficacy and adverse effect profile of each individual drug. Grades of recommendation are demonstrated in Table 2.

1.3.1. Darifenacin hydrobromide

Darifenacin is a tertiary amine with moderate lipophilicity, well absorbed from the gastrointestinal tract after oral administration, and extensively metabolised in the liver by the cytochrome P450 isoforms CYP3A4 and CYP2D6, the latter saturating within the therapeutic range [Skerjanec, 2006]. UK-148,993, UK-73,689, and UK-88862 are the three main circulating darifenacin metabolites of which only UK-148,993 is said to have significant anti-muscarinic activity. However, available information suggests that various me-

tabolites of darifenacin contribute little to its clinical effects [Michel and Hegde, 2006]. The metabolism of darifenacin by CYP3A4 suggests that co-administration of a potent inhibitor of this enzyme (e.g. ketoconazole) may lead to an increase in the circulating concentration of darifenacin [Kerbusch, Wählby et al., 2003]. Darifenacin is a relatively selective muscarinic M_3 receptor antagonist. In vitro, it is selective for human cloned muscarinic M_3 receptors relative to M_1, M_2, M_4 or M_5 receptors. Darifenacin has been developed as a controlled-release formulation, which allows once-daily dosing. Recommended dosages are 7.5 and 15 mg per day.

The clinical effectiveness of the drug has been documented in several RCTs [Haab, Stewart et al., 2004; Steers, Corcos et al., 2005; Zinner, Susset et al., 2006] including in those > 65 years of age [Chapple, DuBeau et al., 2007]. The time to effect with darifenacin was analyzed in a pooled analysis of efficacy and safety data from 1,059 patients participating in three double-blind 12-week studies [Khullar, Foote et al., 2011]. Darifenacin significantly improved all OAB symptoms as early as 6 to 8 days after beginning administration.

A review of the pooled darifenacin data from the three phase III, multicentre, double blind clinical trials in patients with OAB has been reported [Chapple, Steers et al., 2005]. After a 4-week washout/run-in period, 1,059 adults (85% female) with symptoms of OAB (urgency incontinence, urgency and frequency) for at least six months were randomized to once-daily oral treatment with darifenacin: 7.5 mg (n = 337) or 15 mg (n = 334) or matching placebo (n = 388) for 12 weeks. Relative to baseline, 12 weeks of treatment with darifenacin resulted in a dose-related significant reduction in median number of incontinence episodes per week (7.5 mg, –8.8 [–68.4%; placebo -54%, P<004]; 15 mg, –10.6 [–76.8%; placebo 58%, p<0.001]. Significant decreases in the frequency and severity of urgency, micturition frequency, and number of incontinence episodes resulting in a change of clothing or pads were also apparent, along with an increase in bladder capacity. Darifenacin was well tolerated. The most common treatment-related adverse events were dry mouth and constipation, although together these resulted in few discontinuations (darifenacin 7.5 mg 0.6% of patients; darifenacin 15 mg 2.1%; placebo 0.3%). The incidence of CNS and cardiovascular adverse events were comparable to placebo.

The results were confirmed in other RCTs, including a pooled analysis of three phase III studies in older patients (≥65 years), showing that darifenacin (7.5 and 15 mg) had an excellent efficacy, tolerability and safety profile[(Foote, Glavind et al., 2005]. A 2-year open label extension study of these studies, confirmed a favorable efficacy, tolerability and safety profile [Haab, Corcos et al., 2006], including in those > 65 years of age [Hill, Elhilali et al., 2007].

Further studies have demonstrated that darifenacin treatment is associated with clinically relevant improvements on health related quality of life (HRQoL) in patients with OAB [Abrams, Kelleher et al., 2008], and such improvements were sustained as shown in a two-year extension study [Dwyer, Kelleher et al. 2008].

1.3.2. Fesoterodine fumarate

Fesoterodine functions as an orally active prodrug that is converted to the active metabolite 5-hydroxymethyltolterodine (5-HMT) by non-specific esterases [Malhotra, Guan et al., 2008]. This compound, which is chemically identical to the 5-hydroxy metabolite of tolterodine, is a non-subtype selective muscarinic receptor antagonist [Ney, Pandita et al., 2008]. All of the effects of fesoterodine in man are thought to be mediated via 5-HMT, since the parent compound remains undetectable upon oral dosing. 5-HMT is metabolized in the liver, but a significant part of 5-HMT is excreted renally without additional metabolism. Since the renal clearance of 5-HMT is about 250 mL/min, with >15% of the administered fesoterodine dose excreted as unchanged 5-HM, this raises the possibility that 5-HMT also could work from the luminal side of the bladder [Michel, 2008]. The bioavailability of fesoterodine, averaging 52%, was independent of food intake and the drug may be taken with or without a meal. Peak plasma concentration of 5-HMT is reached at 5 h following oral administration and has a half-life of 7–9 h [Malhotra, Guan et al., 2008]. The suggested starting dose, 4 mg/day, can be used in patients with moderately impaired renal or hepatic function due to the combination of renal excretion and hepatic metabolism of 5-HMT [Malhotra, Guan et al., 2008; de Mey, Mateva et al., 2011]. Two doses exist at 4mg and 8mg, allowing flexible dosing.

A multicenter, double-blind, placebo-controlled trial with tolterodine extended release (ER) 4mg, and fesoterodine 4 and 8mg enrolled 1132 patients [Chapple, Van Kerrebroeck et al., 2007]. The trial showed that both the 4 and 8 mg doses of fesoterodine were effective in improving symptoms of OAB, with the 8 mg dose having a greater effect at the expense of a higher rate of dry mouth. There appeared to be little difference between fesoterodine 4 mg and tolterodine ER 4mg. The dose-response relationship was confirmed in another study that pooled data from two phase III RCTs [Khullar, Rovner et al., 2008]. Fesoterodine 8 mg performed better than the 4 mg dose in improving urgency and UUI as recorded by 3-day bladder diary, offering the possibility of dose titration. Subsequently the Eight Trial, a large randomised double-blind placebo-controlled trial compared fesoterodine 8 and 4mgs (n=1745) [Chapple, Schneider et al., 2014]. At 12 weeks UUI, urgency, micturition frequency, diary dry rates, PPBC, UPS and OAB-q scores were significantly better with fesoterodine 8mg compared to 4mg or placebo. Dry mouth and constipation rates were 26.1% and 4%, 12.9% and 1.5%, 3.4% and 1.8% in the fesoterodine 8mg, 4mg and placebo groups, respectively, suggesting that although higher dose of fesoterodine may improve outcomes this comes at the cost of more AEs [Chapple, Schneider et al., 2014].

In another randomized trial assessing flexible-dosing of fesoterodine, statistically significant improvements at week 12 in the mean number of micturition per 24 h and in both UUI and urgency episodes were seen compared to placebo (all P<0.05) [Dmochowski, Peters et al., 2010]. Those taking fesoterodine had improved PPBC and UPS scores at weeks 2,6, and 12 weeks. Interestingly, 63% and 73% in those taking fesoterodine and placebo, respectively opted for dose escalation at week 2. A systematic review of all flexible dosing trials with fesoterodine (10 met the inclusion criteria) suggested 51-63% opted for dose escalation. Escalators in general had more significant OAB symptoms, worse bother and worse QoL at baseline when compared to non-escalators [Wyndaele, Schneider et al., 2014].

A pooled analysis of 2 phase III trials confirmed superiority of fesoterodine 8mg to tolterodine ER 4mg with regards to patient reported outcomes [Ginsberg, Schneider et al., 2013]. This study also assessed outcomes by gender. In women fesoterodine 8mg was superior to tolterodine at 12 weeks in UUI, urgency, micturition episodes, diary dry rates, PPBC, UPS and OAB-q scores. In men superiority with fesoterodine 8mg was only demonstrated for severe urgency and the symptom bother domain of the OAB-q. In women dry mouth rates were 29%, 15%, 6%, constipation rates were 5%, 4%, 2%, urinary retention rates were <1%, <1%, 0% for fesoterodine 8mg, tolterodine ER 4mg and placebo, respectively. In men dry mouth rates were 21%, 13%, 5%, constipation rates were 5%, 3%,

1% and urinary retention rates were 2%, <1%, 2% for fesoterodine 8mg, tolterodine ER 4mg and placebo, respectively [Ginsberg, Schneider et al., 2013].

Nitti et al., determined whether the presence of DO in patients with OAB and urgency urinary incontinence was a predictor of the response to treatment with fesoterodine in a phase 2 randomized, multicentre, placebo-controlled trial [Nitti, Rovner et al., 2010]. They concluded that regardless of the presence of DO, the response to fesoterodine treatment was dose-proportional and associated with significant improvements in OAB symptoms.

Kelleher et al., evaluated the effect of fesoterodine on HRQoL in patients with OAB syndrome [Kelleher, Tubaro et al., 2008]. Pooled data from two randomized placebo-controlled phase III studies were analysed. Eligible patients were randomized to placebo or fesoterodine 4 or 8 mg for 12 weeks; one trial also included tolterodine extended release (tolterodine-ER) 4 mg. By the end of treatment, all active-treatment groups had significantly improved HRQoL compared with those on placebo. In a post hoc analysis of data pooled from these studies, significant improvements in all King's Health Questionnaire (KHQ) domains, ICIQ-SF scores, and bladder related problems were observed at months 12 and 24 compared to baseline [Kelleher, Dmochowski et al., 2012]. The authors concluded that treatment satisfaction was high throughout the open-label treatment regardless of gender and age.

Longer term effects were analysed in a pooled analysis of 2 open label extension studies which demonstrated sustained improvement in OAB with fesoterodine [Sand, Heesakkers et al., 2012]. Mean duration of exposure was 21 months with 51% of patients receiving fesoterodine for ≥ 24 months. 77% elected to remain on fesoteroding 8mg during the open label extension. Discontinuations were seen in 51% before the 24-months visit with insufficient clinical response, adverse events or withdrawal of consent being the main reasons for stopping treatment. Significant improvements were seen in UUI, urgency and micturition epsiodes over the study period compared to open label baseline. The most common adverse events were dry mouth and constipation.

A post-hoc analysis of 2 fixed dose trials, stratified by age, suggested fesoterodine 4 and 8 mg doses were efficacious compared to placebo in those < 75 years of age, but only fesoterodine 8mg in those ≥ 75 years of age [Kraus, Ruiz-Cerda et al., 2010]. As a result, the SOPHIA trial recruited patients ≥ 65 years of age with at least 30% of the population being older than 75 years of age, in this flexible fesoterodine dosing placebo-controlled study [Wagg, Khullar et al., 2013]. At week 4, 52% and 66% opted for dose escalation in the fesoterodine 4mg and placebo groups, respectively. At week 8 de-escalation was allowed and occurred in 4% and 3% in the fesoterodine and placebo groups, respectively. Urgency, severe urgency, micturition and nocturnal micturition episodes, as well as pad use significantly improved in the fesoterodine group compared to placebo at 12 weeks. However, in the 46% who were OAB wet no significant difference in UUI episodes were demonstrated between the groups. Patient reported outcomes using the TBS, PPBC, UPS, OAB-S were significantly greater in the fesoterodine group compared to placebo. Age stratification ie less than or greater than 75 years of age did not alter the results. Mini mental state examination did not change from baseline to end of study and was not different between groups. Dry mouth and constipation rates were 33.9% vs 5.3% and 8.9% vs 2.5% in the fesoterodine and placebo groups, respectively. Central nervous system adverse events occurred very rarely and 6 patients went into retention (5 in the active arm). The authors concluded that fesoterodine was tolerated well and was efficacious in an elderly population [Wagg, Khullar et al., 2013]. Subsequently Wagg et al., have published on a 12-week open label extension of this trial [Wagg, Khullar et al., 2014]. Of the original 655 patients in the SOPHIA trial, 581 completed the open label extension with approximately half the population being male. Significant improvements were observed in bladder diary measures as well as patient reported outcome measures in those that originally had placebo who switched to fesoterodine and efficacy was maintained in those that were originally treated with fesoterodine by study end. Treatment withdrawal due to emergent adverse events were 9.1% in those switched to fesoterodine from placebo and 1.3% in those that continued with fesoterodine [Wagg, Khullar et al., 2014]. Dubeau et al., looked at the use of fesoterodine with dose escalation / de-escalation design vs placebo in a vulnerable elderly population with complex co-morbidities [Dubeau, Kraus et al., 2014]. Patients had to have moderate bladder problems based on PPBC, UUI 2-15 episodes, daytime frequency ≥ 8, vulnerable elderly score (VES-13) of ≥ 3 and a MMSE ≥ 20. The proportion of patients who completed the study were similar in both groups. Approximately 50% of the population were greater than 75 years of age and both groups had complex patients with functional impairment and polypharmacy. Significant reductions in daytime micturition, daytime and nocturnal urgency, UUI episodes per 24 hours and a reduction for the need of absorbent products was seen with fesoterodine compared to placebo. A greater proportion reported improvements in their bladder condition based on PPBC and OAB-q scores and satisfaction were better in the fesoterodine group compared to placebo. In the fesoterodine group 9.3% vs 5% in the placebo group discontinued treatment due to adverse events. Dry mouth and constipation rates were 23.5% and 11%, respectively, in the fesoterodine group. Urinary retention occurred in 3.2% in those treated with fesoterodine but only 3/9 patients were catheterized. No significant changes in MMSE were observed. No significant changes in blood pressure or heart rate were observed in either group until end of study and there were no deaths [Dubeau, Kraus et al., 2014].

When assessing the pooled fixed dosing studies of fesoterodine (n=6689) approximately 1/3 of patients reported a 50% reduction in urgency and roughly 3/4 reported a 50% resolution of incontinence [Wagg, Herschorn et al., 2021]. Furthermore in comparing 14 different agents in managing OAB using multicriteria decision analysis (experts weighted relative importance of favourable and unfavourable effects) and when benefits are judged as more relevant than safety, fesoterodine 4 or 8 mg utilised in a flexible dosing pattern was the favoured drug of choice [Chapple, Mironska et al., 2020]).

The FOXY study assessed the use of oxybutynin 10-20mg and fesoterodine 4-8mg in a randomized double blind crossover trial in children with OAB aged 5-14 years [Ramsay, Naud et al., 2020]. In 60 patient's efficacy was similar for both drugs with documented improvements in bladder capacity. The authors suggested that both drugs were efficacious in the population with acceptable side effect profiles.

1.3.3. Imidafenacin

Imidafenacin (KRP-197/ONO-8025, 4-(2-methyl-1H-imidazol-1-yl)-2,2-diphenylbutanamide) is an antagonist for the muscarinic ACh receptor with higher affinities for M_3 and M_1 receptors than for the M_2 receptor. Metabolites of imidafenacin (M-2, M-4 and M-9) had low affinities for muscarinic ACh receptor subtypes [Kobayashi, Yageta et al., 2007]. The drug blocks pre- as well as post-junctional muscarinic receptors and was shown to block both detrusor contractions and acetylcholine release [Murakami, Yoshida et al., 2003]. The receptor binding affinity of imidafenacin in vitro was found to be significantly lower in the bladder than submaxillary

gland or colon [Yamada, Seki et al., 2011]. In rats orally administered imidafenacin distributes predominantly to the bladder and exerts more selective and longer-lasting effect here than on other tissues. Whether this can be translated to the human situation has to be established before claims of clinical bladder selectivity can be made. Imidafenacin is well absorbed from the gastrointestinal tract and its absolute bioavailability in human is 57.8% [Ohmori, Miura et al., 2007; Ohno, Nakade et al., 2008]. It is rapidly absorbed with maximum plasma concentration occuring 1-3h after oral administration [Ohno, Nakade et al., 2008]. Metabolites in the plasma are produced mainly by first-pass effects. The major enzymes responsible for the metabolism of the drug are CYP3A4 and UGT1A4. The oxidative metabolism is reduced by concomitant administration of CYP3A4 inhibitors. In contrast, imidafenacin and its metabolites have no inhibitory effect on the CYP-mediated metabolism of concomitant drugs [Kanayama, Kanari et al., 2007].

A randomized, double-blind, placebo-controlled phase II dose-finding study in Japanese OAB patients was performed to evaluate the efficacy, safety/tolerability, and dose-response relationship of imidafenacin [Homma, Yamaguchi et al., 2008]. Overall, 401 patients were enrolled and randomized for treatment with 0.1 mg of imidafenacin/day (99 patients), 0.2 mg of imidafenacin/day (100), 0.5 mg of imidafenacin/day (101), or a placebo (101). After 12 weeks of treatment, the number of incontinence episodes was reduced in a dose-dependent manner, and a significant difference between the imidafenacin treatment and the placebo was observed ($P < 0.0001$). Compared with the placebo, imidafenacin caused significant reductions in urgency incontinence, voiding frequency, and urinary urgency, and a significant increase in the urine volume voided per micturition. Imidafenacin was also well tolerated. The incidence of dry mouth in the imidafenacin groups increased dose-dependently. Even though the percentage of patients receiving 0.5 mg/day who discontinued treatment due to dry mouth was high (8.9%), the percentages in the 0.1 mg/day and 0.2 mg/day groups (1.0% and 0.0%, respectively) were comparable with that in the placebo group (0.0%).

A randomized, double-blind trial of 781 Japanese patients with OAB symptoms randomized patients to imidafenacin 0.1mg twice daily (n=324), propiverine 20mg once daily (n=310), or a placebo (n=147) [Homma and Yamaguchi, 2009]. After 12 weeks of treatment, a significantly larger reduction in the mean number of incontinence episodes was observed in the imidafenacin group than in the placebo group ($P<0.0001$). The non-inferiority of imidafenacin compared with propiverine was confirmed for the reduction in incontinence episodes ($P = 0.0014$, non-inferiority margin:14.5%). Imidafenacin was well tolerated. The incidence of adverse events with imidafenacin was significantly lower than with propiverine ($P = 0.0101$). Dry mouth, the most common adverse event, was significantly more common in the propiverine group than in the imidafenacin group. There were no significant increases in either the imidafenacin or placebo group in the mean QTc interval, whereas there was a significant increase in the mean QTc interval in the propiverine group ($P < 0.0001$). However, there were no clinical arrhythmia and clinical arrhythmic events in any of the treatment groups. Similar results have also been published in a population of OAB patients in Korea [Park, Park et al., 2014].

The long-term safety, tolerability, and efficacy imidafenacin 0.1 mg twice daily was studied in Japanese OAB patients [Homma and Yamaguchi, 2008], of whom 478 received treatment and 376 completed a 52-week program. Imidafenacin was well tolerated, the most common adverse event being a dry mouth (40.2% of the patients). Long-term treatment did not produce an increase in the frequency of adverse events compared with short-term treatment. A significant efficacy of the drug was observed from week 4 through week 52. After 52 weeks, imidafenacin produced mean changes from baseline in the number of incontinence episodes (-83.51%), urgency incontinence episodes (-84.21%), voiding frequency (-2.35 micturitions/day), urgency episodes (-70.53%), and volume voided per micturition (28.99 mL). There were also significant improvements from baseline in all domains of the KHQ in those who received the treatment and 376 patients completed the 52-week program. Imidafenacin had no significant effects on the corrected QT interval, vital signs, results from laboratory tests, or post-void residual volume. Yokoyama et al., in their comparative long-term study reported equivalent efficacy and better tolerability for imidafenacin compared to solifenacin and lower dicontinuation rates (5.8% vs 13.5%) at study end [Yokoyama, Koide et al., 2013].

Recently in Korea a multi-center non-inferiority phase IV trial of imidafenacin 0.1mg twice daily versus fesoterdine 4mg was conducted [Lee, Park et al., 2013]. No significant differences were observed between the 2 treatments for OAB symptoms or KHQ scores. Dry mouth rates were 39.4 and 37.3% in the imidafenacin and fesoterodine groups, respectively and no statistically differences were shown for adverse events, blood pressure, pulse or residual volume betwen the groups. Furthermore, in a recent study, imidafenacin 0.2mg was shown to be non-inferior to tolterodine 4mg as assessed by bladder diary parameters and the OAB awareness tool [Pushkar, Kasyan et al., 2019]. However, UUI episodes were statistically less with imidafenacin when compared to tolterodine (-1.7 +/- 1.7 vs -1.5 +/- 1.4; P=0.01).

1.3.4. Solifenacin succinate

Solifenacin succinate (YM905) is a tertiary amine and well absorbed from the gastrointestinal tract (absolute bioavailability 90%). The mean terminal half-life is 45-65 hours [Smulders, Krauwinkel et al., 2004]. It undergoes significant hepatic metabolism involving the cytochrome P450 enzyme system (CYP3A4). It is available in 5mg and 10mg doses which allows for flexible dosing. In subjects who received a single oral dose of 10 mg solifenacin on day 7 of a 20-day regimen of ketoconazole administration (200 mg) C_{max} and $AUC_{0\text{-}inf}$ were increased by only approximately 40% and 56%, respectively [Swart, Krauwinkel et al., 2006]. Solifenacin has a modest selectivity for M3 over M2 (and M1) receptors [Hegde, Mammen et al., 2004].

A large-scale dose ranging phase 2 trial, comprising men and women, evaluated solifenacin 2.5 mg, 5 mg, 10 mg, and 20 mg and tolterodine (2 mg twice daily) in a multinational placebo-controlled study of 225 patients with urodynamically confirmed DO [Chapple, Araño et al., 2004]. Patients received treatment for 4 weeks followed by 2 weeks of follow-up. Micturition frequency, the primary efficacy variable, was statistically significantly reduced in patients taking solifenacin 5 mg (-2.21), 10 mg (-2.47), and 20 mg (-2.75), but not in patients receiving placebo (-1.03) or tolterodine (-1.79). This effect was rapid with most of the effect observed at the earliest assessment visit, 2 weeks after treatment initiation. In addition, there was numerically greater reductions in episodes of urgency and incontinence when compared with placebo. Study discontinuations due to adverse events were similar across treatment groups, albeit highest in the 20-mg solifenacin group. As the 5 mg and 10 mg doses caused lower rates of dry mouth than tolterodine, and superior efficacy outcomes relative to placebo, these dosing strengths were selected for further evaluation in large-scale phase 3 studies.

In one of the early RCTs, a total of 1077 patients were randomized to 5 mg solifenacin, 10 mg solifenacin, tolterodine (2 mg twice dai-

ly), or placebo [Chapple, Rechberger et al., 2004]. It should be noted that this study was powered only to compare active treatments to placebo. Compared with placebo (-8%), mean micturitions/24 h were significantly reduced with solifenacin 10 mg (-20%), solifenacin 5 mg (-17%), and tolterodine (-15%). Solifenacin was well tolerated, with few patients discontinuing treatment. Incidences of dry mouth were 4.9% with placebo, 14.0% with solifenacin 5 mg, 21.3% with solifenacin 10 mg, and 18.6% with tolterodine 2 mg twice daily.

Another RCT randomized 911 patients to 12-week once daily treatment with solifenacin 5 mg, solifenacin 10 mg or placebo [Cardozo, Lisec et al., 2004]. Compared with changes obtained with placebo (-1.6), the number of micturitions per 24 hours was statistically significantly decreased with solifenacin 5 mg (-2.37) and 10 mg (-2.81). A statistically significant decrease was observed in the number of all incontinence episodes with both solifenacin doses (5 mg: -1.63, 61%; 10 mg: -1.57, 52%), but not with placebo (-1.25, 28%). Of patients reporting incontinence at baseline, 50% achieved continence after treatment with solifenacin (based on a 3-day micturition diary, placebo responses not given). Episodes of nocturia were statistically significantly decreased in patients treated with solifenacin 10 mg versus placebo. Episodes of urgency and mean volume voided per micturition were statistically significantly reduced with solifenacin 5 mg and 10 mg. Treatment with solifenacin was well tolerated. Dry mouth, mostly mild in severity, was reported in 7.7% of patients receiving solifenacin 5 mg and 23% receiving solifenacin 10 mg (vs 2.3% with placebo). A 40-week follow up of these studies demonstrated that the favourable profile, both in terms of efficacy and tolerability was maintained over the study period [Haab, Cardozo et al., 2005].

The STAR trial was a prospective, double blind, double-dummy, two-arm, parallel-group, 12-week flexible dosing study conducted to compare the efficacy and safety of solifenacin 5 or 10 mg and tolterodine extended release 4 mg once daily in OAB patients [Chapple, Martinez-Garcia et al., 2005]. After 4 weeks of treatment patients had the option to request a dose increase but were dummied throughout as approved product labelling only allowed an increase for those on solifenacin. The results showed that solifenacin, with a flexible dosing regimen, was “non-inferior” to tolterodine concerning the primary effect variable, micturition freqency. However, solifenacin showed significant greater efficacy to tolterodine in decreasing urgency episodes (-2.85 vs -2.42), incontinence (-1.60 vs -.83), urgency incontinence (-1.42 vs -0.83), and pad usage (-1.72 vs -1.19). More solifenacin treated patients became continent by study endpoint (59 vs 49%) and reported improvements in perception of bladder condition (-1.51 vs -1.33) assessments. However, this was accompanied by an adverse event incidence which was greater with solifenacin than with tolterodine. Dry mouth and constipation (mild + moderate + severe) were the most common (solifenacin 30% and 6.4%, tolterodine 23% and 2.5%). The majority of side effects were mild to moderate in nature, and discontinuations were comparable and low (5.9 and 7.3%) in both groups. In the SUNRISE trial solifenacin 5/10mg was significantly effective in reducing urgency and urgency bother when compared to placebo with changes noticeable as early as day 3 [Cardozo, Hessdorfer et al., 2008]. In this flexible dosing trial, 591 patients received solifenacin 5mg at 8 weeks, and 46.5% requested a dose increase to 10mg and were further randomized for 8 weeks into solifenacin 5 or 10 mgs [Cardozo, Amarenco et al., 2013]. Those that requested dose escalation had a greater severity of OAB at baseline. Solifenacin 10 mg at end of study compared to week 8 was statistically better than solifenacin 5mg for maximum urgency intensity, total urgency score and micturition frequency. PPBC and treatment satisfaction were not statistically different between the groups. Adverse events were generally low and dry mouth rates were 0.7 and 5.7% for solifenacin 5 and 10 mg, respectively [Cardozo, Amarenco et al., 2013]. In a pooled analysis of four RCTs, solifenacin demonstrated positive effects on urgency, frequency and nocturia symptoms in OAB dry patients [Abrams and Swift, 2005].

Another pooled analysis of four studies confirmed the efficacy and tolerability of solifenacin 5 and 10 mg in elderly (≥ 65 years) patients, and also showed a high level of persistence in a 40 -week extension trial [Wagg, Wyndaele et al., 2006]. Furthermore, a post-hoc analysis of two 12-week, open label, flexible-dosing studies on 2645 patients over 65 years of age with OAB, revealed that solifenacin was associated with improvements in measures assessing patients’ perception of their bladder problems, symptom bother, and aspects of QoL [Capo, Lucente et al., 2011].

Improvement in QoL as assessed by the KHQ has been demonstrated in patients treated with solifenacin [Kelleher, Cardozo et al., 2005]. Data from 2 large clinical trials and an extension study were assessed and statistical improvements compared to placebo were seen in 9 out of the 10 QoL domains. Approximately 2/3 of this improvement in QoL was seen in the first 12 weeks and the remaining third in the extension period (additional 40 weeks), suggesting an improvement over time [Kelleher, Cardozo et al., 2005].

Recently the SONIC trial assessed efficacy and tolerability of solifenacin in patients with neurogenic bladder suffering with multiple sclerosis (MS) and spinal cord injury (SCI) in a prospective randomized phase IIIb/IV parallel group study [Amarenco, Sutory et al., 2015]. Approximately a quarter of the patients were taking muscle relaxants to help with spasticity. Patients were randomized to solifenacin 5mg, solifenacin 10mg, oxybutynin 5mgs three times daily or placebo for 4 weeks after a placebo run-in. The majority of MS patients were female, and the majority of SCI patients were male. The primary endpoint of maximum cystometric capacity was significantly increased with solifenacin 10mg (134 mL) compared with placebo (5 mL). Furthermore, significant improvements were observed with regards to bladder volume at first contraction and at first leak as well as detrusor pressure at first leak. PPBC and I-QoL sub scales significantly improved in favour of solifeancin 10mg compared to placebo. Significant improvements were also seen for oxybutynin compared to placebo, but the trial was not designed to compare outcomes of the different active treatments. The overall incidence of adverse events were low and dry mouth rates were 2.3%, 4.2%, 7.8% and 17% for placebo, solifenacin 5 mg, solifenacin 10mg and oxybutynin 5 mgs three times daily, respectively.

A chart review of 138 children with therapy resistant OAB, treated with solifenacin, increased mean voided volume and improved continence [Hoebeke, De Pooter et al., 2009]. Recently an open labelled study utilizing solifenacin doses 1.25-10mg in children with refractory incontinence was reported [Nadeau, Schroder et al., 2014]. In total 112 girls and 132 boys were included (191 had IDO and 53 NDO) with mean age of 9.2 years at start of treatment. Significant improvements were seen in urodynamic parameters, PPBC, UI episodes with the dry rate being 36%. Treatment outcomes were more successful for IDO than NDO. The majority of patients reported no side effects (n=175). Results from 2 open label studies in paediatric population with NDO suggested solifenacin (2.5mg-10mg) improved maximum cystometric capacity and other urodynamic paraemetrs as well as reduing UI episodes [Franco, Hoebeke et al., 2020]. Solifenacin was generally well tolerated in this study.

1.3.5. Tolterodine tartrate

Tolterodine is is a tertiary amine, rapidly absorbed and extensive metabolized by the cytochrome P450 system (CYP 2D6). The major active 5-hydroxymethyl metabolite (5-HMT) has a similar pharmacological profile as the mother compound, and significantly contributes to the therapeutic effect of tolterodine [Brynne, Stahl et al., 1997; Nilvebrant, Hallén et al., 1997]. Both tolterodine and 5-HMT have plasma half-lifes of 2-3 h, but the effects on the bladder seem to be more long-lasting than could be expected from the pharmacokinetic data. Urinary excretion of tolterodine accounted for <1-2.4 % of the dose; 5 – 14% of 5-HMT is eliminated in the urine [Brynne, Stahl et al., 1997]. The relatively low lipophilicity of tolterodine and even lesser one of 5-HMT, implies limited propensity to penetrate into the CNS, which may explain a low incidence of cognitive side effects [Clemett and Jarvis, 2001]. However, tolterodine may disturb sleep in subjects unable to form the even less lipophilic 5-HMT due to a low activity of CYP 2D6 [Diefenbach, Jaeger et al., 2008].

Tolterodine has no selectivity for muscarinic receptor subtypes but is claimed to have functional selectivity for the bladder over the salivary glands [Stahl, Ekström et al., 1995]. In healthy volunteers, orally given tolterodine in a high dose (6.4 mg) had a powerful inhibitory effect on micturition and also reduced stimulated salivation 1 hour after administration of the drug. However, 5 hours after administration, the effects on the urinary bladder were maintained, whereas no significant effects on salivation could be demonstrated. Animal experiments have suggested that antimuscarinics may affect signaling from the bladder [Andersson, 2011]. Supportive data in humans were found by Vijaya et al., in their randomized, placebo-controlled study [Vijaya, Digesu et al., 2012]. They evaluated the effect of tolterodine on urethral and bladder afferent nerves in women with DO in comparison to placebo, by studying the changes in the current perception threshold (CPT). They found a significantly increased CPT value at 5 (described as urgency) and 250 Hz upon both urethral and bladder stimulation after 1 week of treatment. When compared with placebo, women taking tolterodine had significantly increased bladder CPT values at 5 Hz (P-value <0.05).

Tolterodine is available as immediate-release (TOLT-IR; 1 or 2 mg; twice daily dosing) and extended-release (TOLT-ER) forms (2 or 4 mg; once daily dosing). The ER form seems to have advantages over the IR form in terms of both efficacy and tolerability [Van Kerrebroeck, Kreder et al., 2001] and as such the following section will focus predominantly on the extended release formulation.

In the OPERA study, Oxybutynin extended release (OXY-ER) at 10 mg or TOLT-ER at 4 mg were given for 12 weeks to women with 21 to 60 urgency incontinence episodes per week and an average of 10 or more voids per 24 hours [Diokno, Appell et al., 2003]. Improvements in weekly urgency incontinence episodes were similar for the 790 women who received OXY-ER (n=391) or TOLT-ER (n=399). OXY-ER was significantly more effective than TOLT-ER in reducing micturition frequency, and 23.0% of women taking OXY-ER reported no episodes of urinary incontinence compared with 16.8% of women taking TOLT-ER. Dry mouth, usually mild, was more common with OXY-ER. Adverse events were generally mild and occurred at low rates, with both groups having similar discontinuation of treatment due to adverse events. The conclusions were that reductions in weekly urgency incontinence and total incontinence episodes were similar with the two drugs. Dry mouth was more common with OXY-ER, but tolerability was otherwise comparable including adverse events involving the central nervous system.

In the ACET (Antimuscarinic Clinical Effectiveness Trial) study, which consisted of two trials, patients with OAB were randomized to 8 weeks of open-label treatment with either 2 mg or 4 mg of once-daily TOLT-ER (study one) and to 5 mg or 10 mg of OXY-ER (study two) [Sussman and Garely, 2002]. A total of 1289 patients were included. Fewer patients prematurely withdrew from the trial in the TOLT-ER 4 mg group (12%) than either the OXY-ER 5 mg (19%) or OXY-ER 10 mg groups (21%). More patients in the OXY-ER 10 mg group than the TOLT-ER 4 mg group withdrew because of poor tolerability (13% vs. 6%). After 8 weeks, 70% of patients in the TOLT-ER 4 mg group perceived an improved bladder condition, compared with 60% in the TOLT-ER 2 mg group, 59% in the OXY-ER 5 mg group and 60% in the OXY-ER 10 mg group. Dry mouth was dose-dependent with both agents, although differences between doses reached statistical significance only in the oxybutynin trial (OXY-ER 5 mg vs. OXY-ER 10 mg; p=0.05). Patients treated with TOLT-ER 4 mg reported a significantly lower severity of dry mouth compared with OXY-ER 10 mg. The conclusion that the findings suggest improved clinical efficacy of TOLT-ER (4 mg) than of OXY-ER (10 mg) is weakened by the open label design of the study.

Zinner et al., evaluated the efficacy, safety, and tolerability of TOLT-ER in older (> or =65) and younger (<65) OAB patients, in a 12-week RCT including 1015 patients with urgency incontinence and urinary frequency [Zinner, Mattiasson et al., 2002]. Patients were randomized to treatment with TOLT-ER 4 mg once daily (n = 507) or placebo (n = 508) for 12 weeks. Compared with placebo, significant improvements in micturition chart variables with TOLT-ER showed no age-related differences. Dry mouth (of any severity) was the most common adverse event in both the TOLT-ER and placebo treatment arms, irrespective of age (<65: ER 22.7%, placebo 8.1%; > or =65: ER 24.3%, placebo 7.2%). A few patients (< 2%) experienced severe dry mouth. No central nervous system (cognitive functions were not specifically studied), visual, cardiac (per electrocardiogram), or laboratory safety concerns were noted in this study. Withdrawal rates due to adverse events on TOLT-ER 4 mg were comparable in the two age cohorts (<65: 5.5%; > or =65: 5.1%).

Freeman et al., presented a secondary analysis of a double-blind, placebo-controlled study evaluating the effect of once-daily TOLT-ER on urinary urgency in patients with OAB [Freeman, Hill et al., 2003]. Patients with urinary frequency (eight or more micturitions per 24 hours) and urgency incontinence (five or more episodes per week) were randomized to oral treatment with TOLT-ER 4 mg once daily (n=398) or placebo (n=374) for 12 weeks. Efficacy was assessed by use of patient perception evaluations. Of patients treated with TOLT-ER, 44% reported improved urgency symptoms (compared with 32% for placebo), and 62% reported improved bladder symptoms (placebo, 48%). The proportion of patients unable to hold urine upon experiencing urgency was decreased by 58% with TOLT-ER, compared with 32% with placebo (P<.001).

Hsiao et al., compared the urodynamic effects, therapeutic efficacy and safety of solifenacin 5 mg versus TOLT-ER 4 mg treatment in women with the OAB syndrome [Hsiao, Chang et al., 2011]. Both solifenacin and tolterodine had similar urodynamic effects, therapeutic efficacy and adverse events. Abrams et al., studied the safety and tolerability of tolterodine for the treatment of OAB symptoms in men with BOO and DO [Abrams, Kaplan et al., 2006]. They found that tolterodine did not adversely affect urinary function in these men. Urinary flow rate was unaltered, and there was no evidence of clinically meaningful changes in voiding pressure and PVR or urinary retention. It was suggested that antimuscarinics can be safely administered in men with BOO on this basis.

The use of tolterodine in paediatric populations have also been analysed in a systematic review [Medhi, Mittal et al., 2013]. Based on 17 studies with differing doses of tolterodine, the authors concluded that tolterodine was efficacious in treating non-neurogenic overactive bladder and was comparable to oxybuynin but had better tolerability. Other studies have suggested efficacy in neurogenic patients [Reddy, Borgstein et al., 2008].

1.3.6. Trospium chloride

Trospium is a quaternary ammonium compound with a biological availability less than 10% [Doroshyenko, Jetter et al., 2005]. The drug has a plasma half-life of approximately 20 h and is mainly (60% of the dose absorbed) eliminated unchanged in the urine. The concentration obtained in urine seems to be enough to affect the mucosal signaling system in a rat model [Kim, Yoshimura et al., 2005]. Whether or not it contributes to the clinical efficacy of the drug remains to be established. Trospium is not metabolized by the cytochrome P450 enzyme system [Doroshyenko, Jetter et al., 2005]. It is expected to cross the blood-brain to a limited extent since it is a substrate for the drug-efflux transporter P-glycoprotein, which restricts its entry into the brain [Geyer, Gavrilova et al., 2009]. This was demonstrated by Staskin et al., showing that trospium chloride levels in CSF samples were undetectable on Day 10 at steady-state peak plasma concentration concurrent with measurable peak plasma values [Staskin, Kay et al., 2010]. Clinically, trospium seems to have no negative cognitive effects [Chancellor, Staskin et al., 2012]. Trospium has no selectivity for muscarinic receptor subtypes. In isolated detrusor muscle, it was more potent than oxybutynin and tolterodine to antagonize carbachol-induced contractions [Uckert, Stief et al., 2000].

In a placebo-controlled, double blind study on patients with neurogenic DO, trospium was given twice daily in a dose of 20 mg over a 3-week period. It increased maximum cystometric capacity, decreased maximal detrusor pressure and increased compliance in the treatment group, whereas no effects were noted in the placebo group [Stöhrer, Bauer et al., 1991]. Side effects were few and comparable in both groups. In another RCT including patients with spinal cord injuries and neurogenic DO, trospium and oxybutynin were equally effective; however, trospium seemed to have fewer side effects [Madersbacher, Stöhrer et al., 1995].

A pooled analysis compared the effects of the drug with those of placebo in 517 patients in a urodynamic study of 3 weeks duration. Trospium 20 mg was given twice daily. Significant increases were noted in volume at first involuntary contraction and in maximum cystometric capacity. Trospium treated patients recorded ‘cure’ or ‘marked improvement’ more often than the placebo group (47.9% vs 19.7%) and the drug was well tolerated with similar frequency of adverse effects as in the placebo group.

In an idiopathic population, 523 patients with symptoms associated with OAB and urgency incontinence were treated with 20 mg trospium twice daily or placebo in a 12-week, multicenter, parallel, double-blind, placebo controlled trial [Zinner, Gittelman et al., 2004]. By week 12, trospium significantly decreased average frequency of toilet voids per 24 hours (-2.37) and urgency incontinent episodes 59% compared to placebo (-1.29; 44%). It significantly increased average volume per void (32 ml; placebo: 7.7 ml), and decreased average urgency severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 (-0.43; placebo: 0.17) and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated. The most common side effects were dry mouth (21.8%; placebo 6.5%), constipation (9.5%; placebo 3.8%) and headache (6.5%; placebo 4.6%). Similar results were seen in a large US multicenter trial with the same design, and including 658 patients with OAB [Rudy, Cline et al., 2006].

In a 12-week, randomised, double-blind, phase IIIb study including 1658 patients with urinary frequency and urgency incontinence, patients received trospium chloride 15 mg TID (n = 828) or 2.5 mg oxybutynin hydrochloride TID (n = 830) initially [Bödeker, Madersbacher et al., 2010]. After four weeks, daily doses were doubled and not readjusted in 29.2% (242/828) of patients in the trospium group, and in 23.3% (193/830) in the oxybuytnin group, until the end of treatment. At study end, there were no relevant differences between the “dose adjustment” subgroups and the respective “no dose adjustment” subgroups (trospium: $P = 0.249$; oxybutynin: $P = 0.349$). After dose escalation, worsening of dry mouth was higher in both dose adjusted subgroups compared to the respective “no dose adjustment” subgroups ($P < 0.001$). Worsening of dry mouth was lower in the trospium groups than in the oxybutynin groups.

An extended-release formulation of trospium allowing once daily dosing, has been subsequently introduced. In a pooled analysis of 2 large phase III trials (n=1027), trospium chloride extended release 60 mg once daily significantly improved micturition and UUI episodes per 24 hours compared to placebo [Staskin, Rosenberg et al., 2009]. Furthermore, trospium was superior to placebo in OAB symptom composite score, urgency episodes and mean voided volume. Dry mouth and constipation were the 2 commonest adverse events being 10.7% and 8.5% with trospium compared to 3.7% and 1.5% with placebo. The pooled analysis of the long-term extension study (n=667) with extended release once daily trospium chloride 60 mg daily also showed benefit in managing OAB [Zinner, Dmochowski et al., 2011]. Significant improvements were seen in the placebo to trospium group and efficacy maintained in the trospium-to-trospium group by end of study. Approximately 85% of the population felt their symptoms were improved with trospium chloride treatment. Significant improvements in quality of life were also demonstrated when using the KHQ. A sub-analysis of pooled data from randomised placebo-controlled trials has also demonstrated efficacy against placebo for once daily trospium chloride 60 mg extended release in patients aged ≥ 75 [Sand, Johnson Ii et al., 2011]. Trospium ER produced greater improvements in voiding diary parameters, OAB patient global assessment scores and quality of life compared to placebo.

A randomised controlled trial of differing doses of trospium and placebo has also been conducted in a paediatric population of patients with DO (n=58) [Lopez Pereira, Miguelez et al., 2003]. Of those treated with trospium 82% had a positive effect. Approximately ¾ of the responders also demonstrated urodynamic improvement. In general, trospium was well tolerated and in this study dosing between 10-25mg was not statistically different in terms of outcome.

1.4. Antimuscarinics with “mixed” action

Some drugs used for treatment of the OAB or DO have been shown to have more than one mechanism of action. They all have a pronounced antimuscarinic effect and, in addition, an often poorly defined “direct” action on [Hughes, Lang et al., 1992] bladder muscle. For several of these drugs, the antimuscarinic effects can be demonstrated at much lower drug concentrations than the direct action, which may involve blockade of voltage operated Ca^{2+} channels. Most probably, the clinical effects of these drugs can be explained mainly by an antimuscarinic action.

1.4.1. Oxybutynin chloride

Oxybutynin is a tertiary amine that is well absorbed and undergoes extensive upper gastrointestinal and first-pass hepatic metabolism via the cytochrome P-450 system (CYP3A4) into multiple metabolites. The primary metabolite, N-desethyloxybutynin (DEO) has pharmacological properties similar to the parent compound [Waldeck, Larsson et al., 1997], but occurs in much higher concentrations after oral administration [Hughes, Lang et al., 1992]. It has been implicated as the major cause of the troublesome side effect of dry mouth associated with the administration of oxybutynin. It seems reasonable to assume that the effect of oral oxybutynin to a large extent is exerted by the metabolite. The plasma half-life of the oxybutynin is approximately 2 hours, but with wide interindividual variation [Douchamps, Derenne et al., 1988; Hughes, Lang et al., 1992].

Oxybutynin has several pharmacological effects *in vitro*, some of which seem difficult to relate to its effectiveness in the treatment of DO. It has both an antimuscarinic and a direct muscle relaxant effect, and, in addition, local anesthetic actions. The latter effect may be of importance when the drug is administered intravesically, but probably plays no role when it is given orally. In vitro, oxybutynin was 500 times weaker as a smooth muscle relaxant than as an antimuscarinic agent [Kachur, Peterson et al., 1988]. Most probably, when given systemically, oxybutynin acts mainly as an antimuscarinic drug. Oxybutynin has a high affinity for muscarinic receptors in human bladder tissue and effectively blocks carbachol-induced contractions [Nilvebrant and Sparf, 1986; Waldeck, Larsson et al., 1997]. The drug was shown to have slightly higher affinity for muscarinic M_1 and M_3 receptors than for M_2 receptors, but the clinical significance of this is unclear [Nilvebrant and Sparf, 1986; Noronha-Blob and Kachur, 1991]).

The immediate release (IR) form of oxybutynin (OXY-IR) is recognized for its efficacy and most of the newer anti-muscarinic agents have been compared to it once efficacy over placebo has been determined. In general, the new formulations of oxybutynin offer patients improved dosing schedules and side-effect profile whilst maintaining efficacy. An extended-release oxybutynin (OXY-ER) once daily oral formulation and an oxybutynin transdermal delivery system (OXY-TDS) are now readily available.

Immediate-release oxybutynin (OXY-IR). Thüroff et al., summarized 15 randomized controlled studies on a total of 476 patients treated with oxybutynin [Thüroff, Chartier-Kastler et al., 1998]. The mean decrease in incontinence was recorded as 52% and the mean reduction in frequency per 24h was 33% (data on placebo not presented). The overall subjective improvement rate was reported as 74 % (range 61%-100%). The mean percent of patients reporting an adverse effect was 70 (range 17%-93%).

Extended-release oxybutynin (OXY-ER). This formulation was developed to decrease liver metabolite formation of desethyloxybutynin (DEO) with the presumption that it would result in decreased side effects. The formulation utilizes an osmotic system to release the drug at a controlled rate over 24 hours, primarily into the large intestine where absorption is not subject to first-pass metabolism in the liver. This reduction in metabolism is meant to improve the rate of dry mouth complaints. Salivary output studies have also been interesting. Two hours after administration of OXY-IR or TOLT-IR, salivary production decreased markedly and then gradually returned to normal. With OXY-ER, however, salivary output was maintained at predose levels throughout the day [Chancellor, Appell et al., 2001].

In the OBJECT study, the efficacy and tolerability of 10 mg OXY-ER was compared to a twice daily 2 mg dose of TOLT-IR. OXY-ER was statistically more effective than the TOLT-IR in reduction in weekly urgency incontinence episodes (OXY-ER from 25.6 to 6.1%; TOLT-IR 24.1 to 7.8), total incontinence episodes (OXY-ER from 28.6 to 7.1%; TOLT-IR 27.0 to 9.3), and frequency (OXY-ER from 91.8 to 67.1%; TOLT-IR 91.6 to 71.5) and both medications were equally well tolerated [Appell, Sand et al., 2001]. In the OPERA study, which was a direct comparison of the two extended-release forms, OXY-ER (10 mg) and TOLT-ER (4 mg), the results were quite different. In this study there was no significant difference in efficacy for the primary endpoint of urgency incontinence, however, TOLT-ER had a statistically lower incidence of dry mouth. OXY-ER was only statistically better at 10 mg than TOLT-ER 4 mg in the reduction of the rate of urinary frequency [Diokno, Appell et al., 2003].

In an RCT comparing different daily doses of oxybutynin (5, 10 and 15 mg), Corcos et al., found a significant dose-response relationship for both urgency incontinence episodes and dry mouth. The greatest satisfaction was with 15 mg oxybutynin/day [Corcos, Casey et al., 2006].

In a multicentre, prospective, observational, flexible-dosing study of realworld clinical practice, the dosage of oxybutynin for each OAB patient was adjusted after discussions of efficacy and tolerability between doctor and patient, over a 12-week treatment period [Yoo, Han et al., 2012]. Of the 809 patients enrolled, 590 (73.2%) continued to take study medication for 12 weeks. Most patients were prescribed 5–10 mg/day oxybutynin ER as both starting and maintenance doses, with a dose escalation rate of only 14.9%. All OAB symptoms evaluated by the POSQ were improved; 94.1% of patients reported benefits from treatment and 89.3% were satisfied.

In many parts of the world the only licensed medicine for use in paediatric OAB is oxybutynin. The FOXY study as discussed in the fesoterodine section has shown efficacy of both fesoterodine and oxybutynin ER in managing paediatric OAB [Ramsay, Naud et al., 2020].

Transdermal oxybutynin (OXY-TDS). Transdermal delivery also alters oxybutynin metabolism reducing DEO production to an even greater extent than OXY-ER. A study comparing OXY-TDS with OXY-IR demonstrated a statistically equivalent reduction in daily incontinent episodes (from 7.3 to 2.3: 66% for OXY-TDS, and 7.4 to 2.6: 72% for OXY-IR), but much less dry mouth (38% for OXY-TDS and 94% for OXY-IR) [Davila, Daugherty et al., 2001]. In another study the 3.9-mg daily dose patch significantly (vs placebo) reduced the mean number of daily incontinence episodes (from 4.7 to 1.9; placebo from 5.0 to 2.9), while reducing average daily urinary frequency confirmed by an increased average voided volume (from 165 to 198 ml; placebo from 175 to 182 ml). Furthermore, dry mouth rate was similar to placebo (7% vs 8.3%) (Dmochowski, Davila et al. 2002). A subsequent study assessed OXY-TDS to placebo and to TOLT-ER [Dmochowski, Sand et al., 2003]. Both drugs equivalently and significantly reduced daily incontinence episodes and increased the average voided volume, but TOLT-ER was associated with a significantly higher rate of antimuscarinic adverse events. The primary adverse event for OXY-TDS was application site reaction pruritis in 14% and erythema in 8.3% with nearly 9% feeling that the reactions were severe enough to withdraw from the study, despite the lack of systemic problems. Dmochowski et al., analyzing the combined results of two RCTs concluded that transdermal oxybutynin was shown to be efficacious and well tolerated [Dmochowski, Nitti et al., 2005]. The most common systemic side effect was dry mouth (7.0 % vs placebo 5.3%). Application site er-

ythema occurred in 7% and pruritus in 16.1 %. Cartwright in another study suggested that OXY-TDS was not different to placebo, however, in achieving patient selected goals of therapy [Cartwright, Srikrishna et al., 2011].

Recently the transdermal patch (3.9mg/day) has been shown to be subjectively effective in a small paediatric population but with 35% skin site irritation and 20% discontinuation rate [Gleason, Daniels et al., 2014].

Oxybutynin topical gel. Given the efficacy and tolerability of the transdermal application, limited only by skin site reactions, a gel formulation was developed. Oxybutynin topical gel (OTG) was approved by the US FDA in January 2009 [Staskin and Robinson, 2009]. OTG is applied once daily to the abdomen, thigh, shoulder, or upper arm area. The 1 gram application dose delivers approximately 4 mg of drug to the circulation with stable plasma concentrations and a "favorable" N-desethyloxybutynin metabolite: oxybutynin ratio believed to minimise antimuscarinic side effects [Staskin and Robinson, 2009].

In a multicenter RCT, 789 patients (89% women) with urgency-predominant incontinence were assigned to OTG or placebo once daily for 12 weeks [Staskin, Dmochowski et al., 2009]. The mean number of urge incontinence episodes, as recorded by 3-day voiding diary, was reduced by 3.0 episodes per day versus 2.5 in the placebo arm (P <0.0001). Urinary frequency decreased by 2.7 episodes per day and voided volume increased by 21 mL (versus 2.0 episodes [P = 0.0017] and 3.8 mL [P = 0.0018], respectively, in the placebo group). Dry mouth was reported in 6.9% of the treatment group versus 2.8% of the placebo group. Skin reaction at the application site was reported in 5.4% of the treatment group versus 1.0% in the placebo arm. Similar findings were demonstrated in another large RCT of the gel [Sand, Davila et al., 2012].

A newer 3% topical oxybutynin gel has been assessed in a phase III randomised placebo-controlled trial (randomised n=626) [Goldfischer, Sand et al., 2015]. This product is administered via a metered dose pump dispenser and was hypothesised to have less adverse events. Furthermore, it is made with propylene glycol to help with skin permeation. Two doses of 84mg/day and 56 mg/day of the 3% topical oxybutynin were assessed against placebo gel in this population of patients with urgency and / or urge predominant mixed incontinence. The 84 mg / day dose was statistically better than placebo after 12 weeks in improving weekly UI episodes (primary endpoint) and also daily urinary frequency and urine voided volumes. The lower dose of 56mg / day was not statistically better than placebo. Dry mouth and application site erythema was seen in 12.1% and 3.3% in the 84 mg / day group compared to 5% and 0.5% in the placebo arm.

Other administration forms. Administered intravesically, oxybutynin has in several studies been demonstrated to increase bladder capacity and produce clinical improvement with few side effects, both in neurogenic and in other types of DO, and both in children and adults, although adverse effects may still occur [Lose and Nørgaard, 2001,; George, Tharion et al., 2007; Guerra, Moher et al., 2008)]

1.4.2. Propiverine hydrochloride

The drug is rapidly absorbed (t_{max} 2 h), but has a high first pass metabolism, and its biological availability is about 50%. Propiverine is an inducer of hepatic cytochrome P450 enzymes in rats in doses about 100-times above the therapeutic doses in man [Walter, Ullmann et al., 2003]. Several active metabolites are formed which quantitatively and qualitatively differ from the mother compound. It is likely these metabolites contribute to the clinical effects of the drug, but their individual contributions have not been clarified [Michel and Hegde, 2006]. The half-life of propiverine itself is about 11-14 h. An extended-release preparation was shown to be effective and oral absorption of propiverine is site dependent and influenced by dosage form and circadian time– dependent elimination processes [May, Westphal et al., 2008]. Propiverine has combined antimuscarinic and calcium antagonistic actions [Haruno, 1992, Tokuno; Chowdhury et al., 1993]. The importance of the calcium antagonistic component for the drug´s clinical effects has not been established. Propiverine has no selectivity for muscarinic receptor subtypes.

Propiverine has been shown to have beneficial effects in patients with DO in several investigations. Thüroff et al., collected data from 9 randomized studies with a total of 230 patients, and found a 17% reduction in micturitions per 24 hours, a 64 ml increase in bladder capacity, and a 77% (range 33-80%) subjective improvement [Thüroff, Chartier-Kastler et al., 1998]. Side effects were found in 14 % (range 8-42%). In a comparative RCT including 131 patients with neurogenic DO, propiverine and oxybutynin were compared (Stöhrer, Mürtz et al. 2007). The drugs were found to be equally effective in increasing bladder capacity and lowering bladder pressure. Propiverine caused a significantly lower frequency of dry mouth than oxybutynin. Recently the once daily extended-release formulation of propiverine was compared to immediate release propiverine in a trial with 66 patients suffering with NDO [Stohrer, Murtz et al., 2013]. The primary endpoint was change in reflex volume which was improved and comparable between the two formulations. However, continence rates were statistically better in the ER group compared to IR. Adverse events were similar with dry mouth rates 27% and 24% for ER and IR formulations, respectively.

In a randomised, double-blind, multicentre clinical trial, patients with idiopathic DO were treated with 15 mg propiverine twice daily or 2 mg TOLT-IR twice daily over a period of 28 days [Jünemann, Halaska et al., 2005]. It was found that the mean maximum cystometric capacity increased significantly ($p < 0.01$) in both groups. The volume at first urgency and the frequency/volume chart parameters also showed relevant improvements during treatment. The most common adverse event, dry mouth, occurred in 20 patients in the propiverine group and in 19 patients in the tolterodine group. The scores for the quality of life improved comparably in both groups. Madersbacher et al., compared the tolerability and efficacy of propiverine (15 mg three times daily) oxybutynin (5 mg twice daily) and placebo in 366 patients with urgency and urgency incontinence in a randomized, double-blind placebo-controlled clinical trial [Madersbacher, Halaska et al., 1999]. Urodynamic efficacy of propiverine was judged similar to that of oxybutynin, but the incidence of dry mouth and the severity of dry mouth were judged less with propiverine than with oxybutynin.

Yamaguchi et al. conducted a multicentre, 12-week, double-blind phase III trial in Japanese men and women with OAB (n=1584), comparing solifenacin 5 or 10 mg, propiverine 20 mg, and placebo [Yamaguchi, Marui et al., 2007]. There were greater reductions in mean (SD) voids/24 hours with all drug regimens than with placebo. All active treatments improved the volume voided and QoL vs placebo; solifenacin 10 mg reduced nocturia episodes and significantly improved urgency episodes and volume voided vs propiverine 20 mg, and solifenacin 5 mg caused less dry mouth. Solifenacin 10 mg caused more dry mouth and constipation than propiverine 20 mg.

Recently the extended-release formulation of propiverine – 30mg was compared to the extended release formulation of tolterodine – 4mg in an non-inferiority trial with approximately 160 patients in each study arm [Leng, Liao et al., 2017]. Statistically more significant reductions were seen for propiverine ER compared with tolterodine ER. Discontinuation rates because of adverse events were more in the tolterodine ER group compared to propiverine ER (7.4% vs 3.1%). Based on the way the study was designed and powered the authors concluded that ER propiverine was non-inferior to ER tolterodine.

A randomized, double-blind, placebo-controlled trial with parallel-group design in children aged 5–10 yr was performed [Marschall-Kehrel, Feustel et al.. 2009]. Of 171 randomized children, 87 were treated with propiverine and 84 with placebo. There was a significant decrease in voiding frequency episodes for propiverine versus placebo. Superiority could also be demonstrated for voided volume and incontinence episodes per day. Propiverine was well-tolerated: 23% of side-effects were reported for propiverine and 20% for placebo. Another larger study compared propiverine with oxybutynin and demonstrated equivalent efficacy but a better side effect profile in favour of propiverine [Alloussi, Mürtz et al., 2010].

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2. β3-ADRENOCEPTOR (β3-AR) AGONISTS

It has been generally considered that β3-AR agonists can relieve overactive bladder (OAB) symptoms by relaxing detrusor muscle, inhibiting spontaneous contractile activity in the detrusor (*in vitro:* micro-contractions*; in vivo*: non-voiding contractions), and reducing bladder afferent activity (**Fig 11)** [Biers et al., 2006; Takasu et al., 2007; Aizawa et al., 2012; Gillespie et al., 2012; Hatanaka et al., 2013; Igawa & Michel, 2013; Michel & Igawa, 2015; Igawa, Aizawa & Michel, 2019]. While it has been believed that β-ARs induce detrusor relaxation in most species by activation of adenylyl cyclase with the subsequent formation of cAMP, adenylyl cyclase inhibitors had only small if any effects on relaxation responses; in contrast, there is evidence suggesting that in the bladder K^+ channels, particularly BK_{Ca} channels, may be more important in β-AR-mediated relaxation than cAMP [Hudman et al., 2000; Frazier et al., 2005; Uchida et al., 2005; Frazier et al., 2008].

Potency and efficacy at stimulating cAMP formation via β_1-, β_2-, and β_3-adrenoceptor for each of the compounds mentioned in this section is summarized in **Table 4** [Igawa, Aizawa & Michel, 2019].

2.1. Mirabegron

Mirabegron, a β3-AR agonist approved in Japan, the USA, Canada and Europe, for the treatment of OAB symptoms, is the first of a new class of compounds with a mechanism of action that is different from antimuscarinic agents. The recommended starting dose of

Table 4. EC_{50} values for cAMP formation by β3-AR agonists in CHO cells transfected with human β-AR subtypes

drugs	EC_{50}			references
	β1-AR	β2-AR	β3-AR	
Mirabegron (YM-178)	>10 μM	>10 μM	22.4 nM	(Takasu et al., 2007)
Ritobegron (KUC-7483)	22 μM	2.3 μM	73 nM	(Maruyama et al., 2012)
Solabegron (GW427353)	3.98 μM	1.26 μM	3.98 nM	(Uehling et al., 2006)
Vibegron (MK-4618)	>20 μM	>20 μM	1.1 nM	(Edmondson et al., 2016)

mirabegron is 25 mg in the USA, which can be increased to 50 mg based on individual efficacy and tolerability, and 50 mg in Japan and Europe; the 100 mg dose is not approved for use.

Mirabegron has higher affinity and greater intrinsic activity at β_3- as compared to β_1- and β_2-adrenoceptors **(Table 4)** [Takasu et al., 2007].

Pharmacokinetics

Mirabegron is highly lipophilic and rapidly absorbed after oral administration. The time to maximum plasma concentration (T_{max}) is about 2 hours and the terminal elimination half-life ($t_{1/2}$) is approximately 23–25 hours [Eltink et al, 2012]. Clinically, mirabegron is administered as an extended-release tablet (Oral Controlled Absorption System; OCAS). Steady state was achieved within 7 days of once daily administration, with an accumulation ratio of ~2. Mirabegron C_{max} and $AUC_{0-\tau}$ were similar in older and young subjects. Women exhibited ~40% higher mirabegron C_{max} and $AUC_{0-\tau}$ than men; weight-corrected values were ~20% higher in women [Krauwinkel et al, 2012]. The drug circulates in the plasma as unchanged active compound and as inactive metabolites. Most of an administered dose is excreted in urine, mainly as the unchanged form, and one third is recovered in feces, almost entirely as the unchanged form [Takusagawa et al, 2012a]. It is not known if the drug secreted in the urine will have any effect on bladder function. Theoretically, the drug should be able to pass the blood–brain barrier, but information on possible CNS effects of mirabegron and other β_3-AR agonists are scarce [Füllhase et al, 2011]. Mirabegron is metabolized in the liver via multiple pathways, mainly by cytochrome P450, CYP3A and to a minor extent by CYP2D6 in humans [Takusagawa et al, 2012b, c; Lee et al., 2013], theoretically creating a risk for drug–drug interactions. However, drug interaction studies suggest that mirabegron is not considered a sensitive substrate of CYP3A in vivo, as ketoconazole increased mirabegron exposure by less than 2-fold, suggesting that drugs that are CYP2D6 substrates are not expected to require dose adjustment, except for drugs with narrow therapeutic indices that are significantly metabolized by CYP2D6; caution is advised if mirabegron is co-administered with CYP2D6 substrates with narrow therapeutic indices. The effect of CYP2D6 phenotype on mirabegron exposure is small and likely of limited clinical importance [Lee et al., 2013].

Clinical efficacy and safety for overactive bladder (OAB patients

The effects of mirabegron in men and women with OAB have been summarized in several reviews [Nitti, Khullar, et al, 2013; Chapple et al., 2014; Cui et al., 2014; Rossanese et al., 2015; Chapple et al., 2020], and also in men with both voiding and OAB symptoms [Suarez et al. 2013; Otsuki et al, 2013]. Mirabegron has a documented beneficial effect in the treatment of OAB/DO and seems to have an acceptable side effect profile. Mirabegron seems to have definite advantages over the antimuscarinics with respect to adverse events. Dry mouth and constipation are essentially non-existent in comparison to placebo [Chapple et al., 2014; Cui et al., 2014; Rossanese et al., 2015].

Three large-scale, 12-week, phase III studies conducted in Europe and Australia (SCORPIO) [Khullar et al. 2013] , in the USA/Canada (ARIES) [Nitti, Auerbach, et al., 2013] and in Europe/USA/Canada (CAPRICORN) [Herschorn et al., 2013] have demonstrated the safety, tolerability and superior efficacy of mirabegron at doses of 25 mg (CAPRICORN only), 50 mg (all three studies) and 100 mg (SCORPIO and ARISE) compared with placebo for the treatment of OAB symptoms. Significant improvement of the co-primary endpoints of change from baseline to final visit in mean number of micturitions/24 hr and mean number of incontinence episodes/24 hr versus placebo was demonstrated. These improvements were seen from week 4, the earliest timepoint assessed, and were maintained over time.

Another Phase III trial conducted in Japan [Yamaguchi et al., 2014] confirmed the similar efficacy of mirabegron 50mg once daily for 12 weeks. At final assessment, mirabegron was significantly superior to placebo in terms of mean [sd] change from baseline in number of micturitions/24 h (-1.67 [2.212] vs -0.86 [2.354]; P < 0.001) and mean [sd] change from baseline in number of urgency episodes/24 h (-1.85 [2.555] vs -1.37 [3.191]; P = 0.025), incontinence episodes/24 h (-1.12 [1.475] vs -0.66 [1.861]; P = 0.003), urgency incontinence episodes/24 h (-1.01 [1.338] vs -0.60 [1.745]; P = 0.008), and volume voided/micturition (24.300 [35.4767] vs 9.715 [29.0864] mL; P < 0.001).

The benefit of mirabegron 50 and 100 mg was also evident in patients ≥65 years of age, and in both treatment-naive patients and those who previously discontinued antimuscarinic therapy [Nitti, Khullar, et al., 2013; Chapple et al., 2014]. Responder analyses showed a significant improvement with mirabegron 50 and 100 mg in terms of dry rates, ≥50% reduction in mean number of incontinence episodes/24 hr, and the proportion of patients with 8 micturitions/24 hr at final visit [Chapple et al, 2013]. To further clarify the efficacy and safety of mirabegron in elderly OAB patients a randomised placebo controlled phase IV clinical trial of 12 weeks duration, the Pillar study, was carried out in incontinent patients ≥ 65 years (Wagg et al 2020). Patients were initiated on mirabegron 25 mg, half of which increased at week 4 or 8 to 50 mg on patient or clinician discretion. Primary endpoints, the change from baseline to end of treatment in the mean number of incontinence and micturition episodes in 24h, as well as secondary endpoints, showed clear advantage of mirabegron over placebo. The advantage was also observed in the subgroup of patients ≥ 75 years (Wagg et al 2020). Adverse events were few and in line with previous studies that enrolled younger patients (Wagg et al, 2020, Herschorn et al, 2020). The exposure of the Pillar study population to Mirabegron did not contribute to a drug-related cognitive deterioration evaluated by the Montreal Cognitive Assessment (Griebling et al, 2020). Chapple et al. [2020] recently analysed pooled data from global double-blind,

12-wk studies in patients with OAB receiving mirabegron monotherapy assessed safety, tolerability, and efficacy of mirabegron, placebo, and antimuscarinics, and evaluated differences in baseline characteristics and among subgroups: age <65 versus >65 yr, age <75 versus >75 yr, and men versus women. The results reaffirm the safety and efficacy profiles of mirabegron, solifenacin, and tolterodine in different age groups and both sexes. Drug-related adverse effects were more frequent with antimuscarinics followed by mirabegron and then placebo. As expected, due to anticholinergic effects, dry mouth was more frequent with antimuscarinics versus mirabegron or placebo. Generally, hypertension frequency was similar in the mirabegron, antimuscarinic, and placebo groups. Mirabegron may be a better option than antimuscarinics for those aged >75 yr and also for elderly patients susceptible to constipation.

These data therefore demonstrate a clinically meaningful benefit with mirabegron in the objective endpoints of OAB. However, these studies also indicate that 100 mg does not confer markedly greater efficacy but may have more side effects. Assessment of measures of health-related quality of life and treatment satisfaction showed that patients perceived treatment with mirabegron as meaningful.

In OAB clinical trials of up to 12 months mirabegron appeared to be well tolerated. The most common adverse events (AEs) observed with mirabegron in clinical trials of up to 12 months were hypertension, nasopharyngitis, and urinary tract infection. The incidence of dry mouth was similar to placebo, and was between three and fivefold less than for tolterodine extended release 4 mg. Since dry mouth is the most bothersome AE associated with antimuscarinic drugs and often a reason for treatment discontinuation, the lower incidence of dry mouth would contribute to better tolerability of mirabegron.

Hypertension was the most commonly reported AEs in the pooled 12-week studies occurring in with similar incidence in patients receiving mirabegron 50 mg or placebo (7.5% vs.7.6%) [Michel & Gravas, 2016]. A recent systematic review on the cardiovascular safety of β3-AR agonists also suggested that the cardiovascular safety of mirabegron appears to be acceptable at therapeutic doses and comparable with that of antimuscarinic agents, but also pointed out that data on patients with poorly controlled hypertension, arrhythmia, or cardiac heart failure are currently missing because those patients were excluded from previous studies [Rosa et al., 2016]. As hypertension and diabetes were the two most common cardiovascular comorbidities in the OAB population with prevalence rates significantly higher than in non-OAB gender- and age-matched groups [Andersson et al., 2010], Moreover, there have been reports of hypertensive crisis and cerebrovascular and cardiac events associated with hypertension with a clear temporal relationship with the use of mirabegron [Rosa et al., 2016]. Therefore, US prescribing information concludes that periodic blood pressure determinations are recommended in patients receiving mirabegron; moreover, mirabegron is not recommended in patients with severe uncontrolled hypertension [US Food and Drug Administration, 2015] More recently, severe uncontrolled hypertension even became a contraindication for the use of mirabegron [Michel & Gravas, 2016; Rosa et al., 2016]. Additional clinical data are required for a comprehensive assessment of potential cardiac effects of mirabegron, particularly from real-life settings [Michel & Gravas, 2016].

In a study by Chapple et al. [2013] assessing the 12-mo safety and efficacy of mirabegron, tolterodine was used as active control. There were no significant differences in efficacy between drugs. Mirabegron seems to have definite advantages over the antimuscarinics with respect to adverse events. Dry mouth and constipation are essentially non-existent in comparison to placebo [Chapple et al., 2013; 2014; Cui et al., 2014; Rossanese et al., 2015].

Mirabegron 50 mg and solifenacin 5 mg were compared in OAB patients dissatisfied with previous antimuscarinic treatment. The Beyond study [Batista et al., 2015] was a randomized, double-blind, phase IIIb, noninferiority study that enrolled male and female patients aged ⩾18 years old, with symptoms of OAB for ⩾3 months, who were dissatisfied with their previous antimuscarinic drug due to lack of efficacy. For the primary endpoint, adjusted mean treatment difference (95% CI) in mean number of micturitions/24 h was -0.18 (-0.42, 0.06) and therefore noninferiority of mirabegron to solifenacin was not demonstrated. Both treatments demonstrated clinically meaningful reductions in efficacy variables and were well tolerated, with a lower incidence of dry mouth with mirabegron.

Kakizaki et al [2020] reported the efficacy of mirabegron versus placebo in men with OAB symptoms receiving tamsulosin for LUTS, based on the results of single-blind, 4-wk screening: tamsulosin plus placebo orally once daily; double-blind, 12-wk treatment: patients randomized (n=568) to mirabegron 50mg or placebo, as add-on to tamsulosin in men conducted in Japan and Korea. Mirabegron add-on therapy was superior to placebo in improving the primary endpoint, baseline to end of treatment (EoT) change in the mean number of micturitions/24h, based on a 3-d voiding diary, (adjusted mean difference [95% confidence interval] vs placebo -0.52 [-0.82 to -0.21]) and secondary endpoints, including mean volume voided/micturition (12.08 [6.33-17.84]), OAB symptom score (-0.65 [-1.04 to -0.26]), International Prostate Symptom Score total (-1.19 [-1.94 to -0.44]), storage (-0.78 [-1.13 to -0.43]), quality of life scores (-0.29 [-0.51 to -0.07]), OAB symptom bother (-4.52 [-6.91 to -2.13]), and total health-related quality of life (2.79 [1.13 to 4.44]). Differences, compared with placebo, in urgency, urgency urinary incontinence, and nocturia were not statistically significant. Mirabegron was well tolerated, with no major safety concerns.

Assessment. Mirabegron has a documented beneficial effect in the treatment of OAB and seems to have an acceptable side effect profile. However, periodic blood pressure determinations are recommended in patients receiving mirabegron; moreover, mirabegron is not recommended in patients with severe uncontrolled hypertension.

Clinical efficacy for neurogenic detrusor overactivity and low compliance bladder in adult patients

There are few studies on the efficacy of mirabegron for either neurogenic detrusor overactivity (NDO) or low compliance bladder in adult patients.

Wöllner & Pannek [2016] reported that fifteen patients with NDO treated with mirabegron for a period of at least 6 weeks, showed significant reduction of the frequency of bladder evacuation per 24 h (8.1 vs 6.4, P=0.003), and of incontinence episodes per 24 h (2.9 vs 1.3, P=0.027). Furthermore, urodynamic studies revealed improvements in bladder capacity (from 365 to 419 ml), compliance (from 28 to 45 ml/cm H_20) and detrusor pressure during storage phase (45.8 vs 30 cm H_20). At follow-up, 9/15 patients were satisfied with the therapy.

In a prospective, multicenter, randomized, double-blind, placebo-controlled study on the efficacy and safety of mirabegron 50mg, in 66 patients with NDO suffering from spinal cord injury or multiple sclerosis [Krhut J, et al, 2018] demonstrated a significant increase of volume at the first detrusor contraction (P = 0.00047) and an improvement in bladder compliance (P = 0.0041) in the mirabegron

group compared with the placebo-treated group, whereas the increase in cystometric capacity did not reach statistical significance (P = 0.061). There was a clear tendency to reduced urine leakage (P = 0.056) in the mirabegron group. There were significant changes in all the patient-reported outcomes, favoring the mirabegron group. The incidence of drug-related adverse events was 3.13%.

Welk et al. [2018] reported the results of randomized, double-blind, placebo-controlled study to assess the effects of mirabegron conducted in Canadian patients with neurogenic LUT dysfunction due to spinal cord injury (SCI) or multiple sclerosis (MS). Patients were randomized to mirabegron 25 mg (or an identical placebo) for 2 weeks at which point a dose escalation to mirabegron 50 mg (or an identical placebo) was maintained for 8 weeks. Urodynamics were performed before and after treatment. The primary outcome measure was maximum cystometric capacity (MCC). Sixteen (9 SCI and 7 MS) patients were randomized to mirabegron and 16 (10 SCI and 6 MS) to placebo. At study completion, there was no significant difference in MCC between mirabegron and placebo (MM 305 vs 369 mL, P = 0.20). There was no significant difference in volume at first neurogenic detrusor overactivity (NDO, MM 167 vs 137 mL, P = 0.14) and peak pressure of NDO (MM 69 vs 82 cmH2 O, P = 0.25). There was no significant difference in pad weights or voiding diary parameters. There was a significantly lower symptom burden among those treated with mirabegron (total neurogenic bladder symptom score MM 29 vs 34, P = 0.047).

Due to the limited number of patients and the retrospective nature of these studies, prospective, placebo-controlled studies are required to confirm the beneficial effects of mirabegron on NDO and low compliance bladder suggested by these studies.

Efficacy and safety in children with NDO or OAB

There are some off-label studies to investigate efficacy and safety of mirabegron in children with NDO or OAB.

In their off-label study, Blais *et al*. [2016] gave mirabegron to 58 children with OAB who had shown suboptimal responses to intensive behavioural therapy and medical therapy (with at least two antimuscarinics) or had suffered intolerable adverse effects. Median age at mirabegron initiation was 10.1 years and the drug was given for a median of 11.5 months. Median bladder capacity improved from 150ml to 200ml (p<0.001). Continence improved in 52 of 58, with 13 being completely dry. Median PPBC improved from 4.0 to 2.0 (p<0.001). Eight patients reported mild or moderate side effects. Absence of a placebo group is a limitation of the study.

Fryer et al. [2020] reported their retrospective review of 70 children (50 females), median age 15 [range 8-16] years, commenced Mirabegron 25 mg (n = 29) or 50 mg (n = 41). 37 (53%) were still receiving treatment at 6 months: monotherapy n = 30, and combination therapy n = 7 (Solifenacin n = 4, Desmopressin n = 2, both n = 1). For patients on monotherapy, 6 of 17 (35%) had improvement in NE, 11 of 19 (58%) in DI, 12 of 20 (60%) in frequency, and 8 of 21 (38%) in urgency symptoms. For patients receiving combination therapy, 2 of 6 (33%) had improvement in NE, 2 of 4 in DI (50%), 2 of 4 (50%) in frequency, and 4 of 6 (67%) had improvement in urgency. Reasons for treatment discontinuation (entire cohort) were: ineffectiveness (n = 28), worse symptoms (n = 4) and/or adverse reactions (n = 7), including dry mouth (n = 2), headaches (n = 4), dizziness (n = 1), nausea/vomiting (n = 3), increased seizures (n = 1), and rash (n = 1).

Baka-Ostrowska et al. [2021] reported their open-label, multicenter, baseline-controlled, Phase III study to evaluate the efficacy and safety of mirabegron in children and adolescents (aged 3 to <18 years) with neurogenic detrusor overactivity (NDO) using clean intermittent catheterization. Participants received once daily mirabegron at an adult dose equivalent of 25 mg. Dose was increased to 50 mg equivalent unless there were safety/tolerability concerns. Overall, 86 participants (55 aged 3 to <12 years, 31 aged 12 to <18 years) received treatment; 68 were included in efficacy assessments. A statistically significant increase in maximum cystometric capacity from baseline to Week 24 was observed (87.20 ml, 95% confidence interval: 66.07, 108.33; p < .001); this increase was apparent from Week 4. Significant increases in bladder compliance, bladder volume until first detrusor contraction, average volume per catheterization, maximum daytime catheterized volume and number of dry days per week. Significant decreases in detrusor pressure and number of leakage episodes per day were also observed. Mirabegron was well tolerated in this population with a profile aligned with that in adults.

Park et al. [2019] retrospectively studied clinical and urodynamic parameters in 66 children (under 18 years of age) with spina bifida who were treated for neurogenic bladder with mirabegron 50 mg mirabegron daily for at least 6 weeks either in addition to or instead of antimuscarinic therapy. In both groups post-treatment, incontinence significantly improved. In addition, MCC and compliance significantly increased post-treatment. Six patients reported side effects (constipation, 4.5%; headache, 3.0%; and hypertension, 1.5%) and three patients discontinued treatment.

These off-label studies suggest that the efficacy and safety of mirabegron for treating OAB or NDO in pediatric patients. Prospective, placebo-controlled studies are necessary to confirm these findings.

2.2. Vibegron

Vibegron (MK-4618) is a β_3-AR agonist, potently activates human β_3-AR with an EC_{50} value of 1.1 nM, and vibegron is also highly selective over β_1- and β_2-adrenoceptors versus β_3- adrenoceptors across multiple species (**Table 4**). In contrast to mirabegron, vibegron did not show any stimulating or inhibitory effects on cytochrome P450 enzymes, suggesting a low risk of drug–drug interaction [Edmondson et al., 2016].

The efficacy and safety of vibegron were demonstrated in a phase III study conducted in OAB patients in Japan [Yoshida, Takeda, et al., 2018]. A total of 1232 patients were randomly assigned to one of the four 12-wk treatment groups: vibegron (50mg or 100mg once daily), placebo, or imidafenacin (0.1mg twice daily). The primary endpoint was change in the mean number of micturitions/d at wk 12 from baseline. The secondary endpoints were changes from baselines in OAB symptom variables (daily episodes of urgency, urgency incontinence, incontinence, and nocturia, and voided volume/micturition). Patients taking vibegron 50mg and 100mg orally for 12 wk had significant improvements over the placebo in the primary and secondary endpoints. The proportions of patients with normalization of micturition, resolution of urgency, urgency incontinence, and incontinence were significantly greater than placebo. Vibegron significantly improved QoL with high patient satisfaction. Incidences of drug-related adverse events with vibegron 50mg and 100mg were 7.6%, 5.4%, similar to placebo (5.1%), and less than imidafenacin (10.3%).

A 1-year, multicenter, open-label, non-controlled Phase III trial conducted in Japan confirmed long-term safety and efficacy of vibegron 50mg once daily in OAB patients [Yoshida, Kakizaki, et al., 2018]. After a 1-week observation phase, patients were treated with vibegron for 52 weeks. When the efficacy was insufficient after an

8-week treatment with 50 mg, the dose was increased to 100 mg and maintained for an additional 44 weeks. Among a total of 169 patients receiving one or more doses of vibegron, 118 (69.8%) received vibegron 50 mg for 52 weeks, and the dose was increased to 100 mg in 51 (30.2%) patients. The incidence of drug-related adverse events was 18.1% (21/116) in the vibegron 50 mg group and 11.8% (6/51) in the vibegron 100 mg group. Most frequent drug-related adverse events were dry mouth (3.0%), residual urine volume increased (3.0%), constipation (2.4%) and cystitis (1.8%). Statistically significant changes in overactive bladder symptom variables (daily means of micturitions, urgency episodes, urgency incontinence episodes, incontinence episodes and night-time frequency) from baseline were observed at week 4 and maintained until week 52. The condition of patients who did not respond well to vibegron 50 mg was much improved by increasing the dose to 100 mg. Vibegron improved the quality of life, and the proportion of patients' satisfaction after the treatment with vibegron was high.

A post-hoc analysis of the Japanese Phase III trial to evaluate the efficacy of vibegron on urgency urinary incontinence (UUI) in patients with OAB demonstrated that vibegron, significantly reduced the number of UUI episodes/day and significantly increased the voided volume/micturition in patients with OAB including those with severe UUI, with the response rate exceeding 50%, suggesting that vibegron can be an effective therapeutic option for OAB patients with UUI [Yoshida et al, 2020]. Vibegron administration, OAB duration ≤37 months, mean number of micturitions/day at baseline <12.0 and mean number of UUI episodes/day at baseline <3.0 were identified as factors significantly associated with normalization of UUI.

Another post-hoc analysis of the Japanese Phase III trial also showed that the efficacy of vibegron on nocturia in patients with OAB [Yoshida et al., 2019]. a total of 669 patients with nocturia (≥1 nocturnal void) were included. At week 12, the frequency of nocturnal voiding was reduced from baseline by 0.74 and 0.78, respectively, for the vibegron 50 and 100 mg groups; the reductions were significant when compared with the placebo group ($P < 0.05$ and $P < 0.001$, respectively). The mean volume of nocturnal voids and the volume of the first nocturnal voiding were significantly greater in the vibegron groups than in the placebo group. The vibegron groups showed significant correlations of hours of undisturbed sleep with the changes in the frequency of nocturnal voiding and in the volume of the first nocturnal voiding. Vibegron treatment, no previous treatment with anticholinergics, ≥12 voids per day and hours of undisturbed sleep <180 min significantly contributed to a reduction in the frequency of nocturnal voiding.

Micheson et al., [2019] reported the results of an international, phase IIb, randomized, double-blind, placebo- and active comparator-controlled, two-part superiority trial (2011-2013) in OAB-wet or OAB-dry patients aged 18-75 yr (NCT01314872); Part 1: once-daily oral vibegron monotherapy (3 [V3], 15 [V15], 50 [V50], or 100 [V100] mg), tolterodine extended release 4mg (TER4), or placebo for 8 wk, or combination V50/TER4 for 4 wk and then V50 for 4 wk; part 2: V100/TER4, V100, TER4, or placebo for 4 wk. Overall, 1395 patients were randomized. From baseline to week 8, V50 and V100 significantly decreased average daily micturitions (primary endpoint; least square mean difference [95% confidence interval], -0.64 [-1.11, -0.18]; p=0.007 and -0.91 [-1.37, -0.44]; p<0.001, respectively) and the number of urge incontinence episodes (-0.72 [-1.11, -0.33] and -0.71 [-1.10, -0.32], respectively; both p<0.001) versus placebo. All vibegron doses were well tolerated. The incidence of dry mouth was higher with TER4 than with vibegron monotherapy.

Following this Phase IIb studies, an international Phase III trial (EMPOWUR) confirmed the safety and efficacy of Vibegron 75mg once daily in patients with OAB [Staskin et al., 2020]. Adult patients with OAB with 8.0 or more micturitions per day were randomized 5:5:4 to 75 mg vibegron, placebo or extended-release 4 mg extended-release tolterodine. Up to 25% of patients could have dry OAB (less than 1.0 urge incontinence episode per day). Patients completed 7-day voiding diaries at baseline and weeks 2, 4, 8 and 12. Of 1,518 randomized patients 90.4% completed the trial. At 12 weeks micturitions decreased by an adjusted mean of 1.8 episodes per day for vibegron vs 1.3 for placebo (p <0.001, co-primary end point) and 1.6 for tolterodine. Among incontinent patients urge incontinence episodes decreased by an adjusted mean 2.0 episodes per day for vibegron vs 1.4 for placebo (p <0.0001, co-primary end point) and 1.8 for tolterodine. Moreover, vibegron was statistically significantly superior to placebo for key secondary measures of number of urgency episodes, volume per micturition and proportion of incontinent patients with a 75% or greater reduction in urge incontinence episodes (all p <0.01). Among vibegron treated patients 1.7% discontinued treatment because of adverse events vs 1.1% for placebo and 3.3% for tolterodine. Incidence of hypertension was 1.7% for vibegron and for placebo.

The long-term safety, tolerability, and efficacy of vibegron 75 mg in adults with OAB were evaluated in the 40-week Phase III EMPOWUR extension study [Staskin et al., 2021]. Patients who completed 12 weeks of once daily vibegron 75 mg or tolterodine 4 mg extended release in EMPOWUR continued double-blind treatment; patients who completed 12 weeks of placebo were randomly assigned 1:1 to receive double-blind vibegron or tolterodine. The primary outcome was safety, measured by incidence of adverse events. Secondary outcomes included change from baseline at week 52 in average daily number of micturitions and urgency episodes (OABwet) based on 7-day diary data. Of 506 patients randomized 505 received ≥1 dose of medication, and 430 (85%) completed the study. A total of 12 patients (2.4%) discontinued owing to adverse events. The most common adverse events with vibegron/tolterodine (>5% in either group) were hypertension (8.8%/8.6%), urinary tract infection (6.6%/7.3%), headache (5.5%/3.9%), nasopharyngitis (4.8%/5.2%) and dry mouth (1.8%/5.2%). Improvements in efficacy end points were maintained for patients receiving vibegron for 52 weeks; least squares mean change from baseline to week 52 in micturitions was –2.4 for vibegron vs –2.0 for tolterodine; in urge urinary incontinence episodes –2.2 vs –1.7 (p <0.05); in urgency episodes –3.4 vs –3.2; and in total incontinence episodes –2.5 vs –1.9 (p <0.05). Among patients with overactive bladder wet 61.0% receiving vibegron experienced ≥75% reduction in urge urinary incontinence episodes after 52 weeks of treatment vs 54.4% with tolterodine, while 40.8% vs 34.2% experienced a 100% reduction.

A subpopulation analysis from EMPOWUR assessed the efficacy and safety of vibegron in patients aged ≥ 65 and ≥ 75 years demonstrated that once daily vibegron 75 mg showed rapid onset and robust efficacy versus placebo and was generally safe and well tolerated, consistent with results from the overall population [Varano et al., 2021]. Of the 1463 patients with evaluable efficacy data, 628 patients were aged ≥ 65 years, and 179 were aged ≥ 75 years. After 12 weeks, patients treated with once daily vibegron 75 mg in both age subgroups showed significant improvements from baseline versus placebo in all three symptoms of OAB: daily micturitions (≥ 65 years, $P < 0.0001$; ≥75 years, $P < 0.05$), UUI episodes (≥ 65 years, $P < 0.001$; ≥ 75 years, $P < 0.0001$), and urgency episodes (≥ 65 years, $P < 0.01$; ≥ 75 years, $P < 0.01$). Significant reductions from baseline versus placebo in daily micturitions, UUI episodes, and urgency episodes were observed beginning at week 2 for pa-

tients aged ≥ 65 years treated with vibegron. In patients aged ≥ 65 years, 50.0% of those receiving vibegron versus 29.8% receiving placebo experienced a ≥ 75% reduction in UUI episodes at week 12 (P < 0.0001). Rates of cardiovascular-associated AEs were low for patients receiving vibegron (<2% of patients in either age subgroup) and similar rates in patients receiving placebo. In patients aged ≥ 65 years, hypertension was reported by 1.2%, 3.1%, and 2.9% of patients receiving vibegron, placebo, and tolterodine, respectively; in patients aged ≥ 75 years, hypertension was reported by 1.3%, 3.3%, and 2.1%, respectively.

In the 12-week EMPOWUR trial, treatment with vibegron was associated with significantly greater and clinically meaningful improvement in OAB-q and PGI scores compared with placebo, consistent with improvements in OAB symptoms [Frankel et al., 2020].

Assessment. Vibegron has a documented beneficial effect in the treatment of OAB and seems to have an acceptable side effect profile.

2.3. New developments

Thiagamoorthy et al. [2015; 2016] reviewed "novel and putative" β3-AR agonists for management of OAB, including solabegron, ritobegron, TRK-380, AJ-9677, BRL37344, and CL-316243. There seems to be a number of β_3-AR agonists in the pipeline some of which are under development. However, it is uncertain which, if any, will come to market and be available for the management of OAB.

Solabegron

Solabegron (GW427353) had an EC_{50} value of 1.9 nM in human bladder strips pre-contracted with KCl, whereas isoprenaline had an EC_{50} value of 8.3 mM (**Table 4**) [Uehling et al., 2006; Tyagi et al., 2009]. In a Phase II multicenter, randomized, proof-of-concept trial in 258 women with wet OAB, the drug produced a statistically significant difference in percent change from baseline to Week 8 in incontinence episodes over 24 hr (primary outcome) when compared with placebo (P = 0.025) and was well tolerated [Ohlstein et al., 2012]. Two additional Phase II dose-ranging study with a new formulation have been completed but results have not yet been disclosed (NCT03475706, NCT03594058).

Ritobegron

The selectivity of ritobegron (KUC-7483) for β_3-AR was 301 and 32 times higher than that for β_1- and β_2-adrenoceptors, respectively (**Table 4)** [Maruyama et al., 2012]. In its first Phase III study, ritobegron did not significantly improve the mean number of micturitions per 24 hr compared to placebo. A long-term safety and efficacy study was subsequently withdrawn, and ritobegron does not seem to have been developed further [Thiagamoorthy et al., 2015; 2016]

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3. DRUGS ACTING ON MEMBRANE CHANNELS

3.1. Calcium antagonists

Calcium channels play an important role in the regulation of free intracellular calcium concentrations and thereby contribute to the regulation of smooth muscle tone [Berridge 2008]. Two major groups of calcium channels include the voltage-gated [Caterall et al., 2003] and the store-operated channels [Leung et al., 2008]. While both can contribute to the maintenance of smooth tone in general, store-operated calcium channels apparently contribute

only to a limited if any extent to the regulation of bladder smooth muscle tone [Schneider et al., 2004]. On the other hand, various types of voltage-operated calcium channels have been implicated in the regulation of bladder smooth muscle including Q-type [Frew and Lundy, 1995]) and L-type channels [Wuest et al., 2007]. The latter appears to be of particular importance as inhibitors of L-type channels have repeatedly been shown to inhibit bladder contraction in vitro with tissue from multiple mammalian species, including humans [Frazier et al., 2007]. However, the relative importance of L-type channels may be somewhat less in humans than in other mammalian species [Wuest et al., 2007]). In confirmation of the role of L-type calcium channels, it has been shown that knock-out mice lacking a crucial subunit of this channel exhibit a markedly impaired bladder contractility [Wegener et al., 2004].

While these in vitro data suggest a possible role for calcium channel inhibitors, particularly those of L-type channels, in the treatment of DO and incontinence, only limited clinical studies are available in this regard. One urodynamic study compared the effects of intravesical installation of the calcium channel inhibitor verapamil, the muscarinic receptor antagonists oxybutynin and trospium and placebo to patients with urgency or urgency incontinence. While the two muscarinic receptor antagonists significantly increased bladder capacity, verapamil treatment was not associated with relevant changes in bladder function [Frölich et al., 1998]. In a clinical study of limited size the calcium channel inhibitor nimodipine (30 mg per day) did not significantly improve the number of incontinence episodes as compared to placebo [Naglie et al., 2002]0). It should be noted that despite a long-standing and wide-spread use of calcium channel inhibitors in the treatment of cardiovascular disease, there are no major reports on impaired bladder contractility as a side effect of such treatment. The reasons for the discrepancy between the promising in vitro and the lack of clinical data are not fully clear, but it may relate to pharmacokinetic properties of the currently used drugs which may insufficiently either reach or penetrate bladder tissue in therapeutically administered doses. At present, there is no clinical evidence to support a possible use of calcium channel inhibitors in the treatment of bladder dysfunction **(Table 2).**

Gabapentin and pregabalin are typically utilised for neuropathic pain [Wiffen et al., 2017; Wiffen et al., 2013]. One potential mechanism of action is through the high affinity binding to $\alpha 2\delta$-1 subunits of the voltage-gated calcium channel [Thorpe and Offord, 2010]. Therefore, some studies have been performed to assess its efficacy in OAB. In a randomised double blind, double dummy placebo-controlled trial of patients with OAB, Gabapentin and solifenacin were compared to placebo utilising flexible dosing regimens [Chua et al., 2018]. Both gabapentin (up to 300mg three times daily) and solifenacin (5 or 10mg) improved mean number of micturitions and urgency episodes compared to placebo but gabapentin was statistically better than solifenacin in improving nocturia. Adverse events were less with placebo and gabapentin compared to solifenacin. In those with neurogenic detrusor overactivity gabapentin was able to improve voiding diary and urodynamic parameters, notably maximum cystometic capacity, volume at first desire to void, volume at first involuntary contraction and maximum detrusor pressure during filling cystometry when compared to baseline [Carbone et al., 2006]. A study in children also suggested that gabapentin could be used as add-on therapy to antimuscarinics and was helpful in improving symptoms in approximately 50% of cases [Ansari et al., 2011]. Finally, in a randomised double-blind placebo-controlled trial evaluated in women with OAB, pregabalin alone twice daily or TOL-ER alone once daily or in combination with normal or half strength dosing was assessed Marecak et al., 2011]. Mean voided volume was significantly greater in standard dose pregabalin / TOL-ER combination (39.5 mL) vs either pregabalin (27.4 mL) or TOL-ER (15.5 mL) alone and in general all treatments were well tolerated.

3.2. Potassium channel openers

Various types of K^+ channels exist and many of them apparently are involved in the regulation of bladder smooth muscle tone [Malysz and Petkov, 2020; Parajuli et al., 2016; Gopalakrishnan and Shieh, 2004]. The opening of K^+ channels typically leads to hyperpolarization of cells and, in the case of smooth muscle, to relaxation. Therefore, various compounds targeting different types of K^+ channels have been tested in vitro, in animals and in patients as possible treatments for OAB/DO. This drug class has been confronted with two key challenges: Firstly, it has proven difficult to identify compounds with marked selectivity for a type of K^+ channel or even spe-

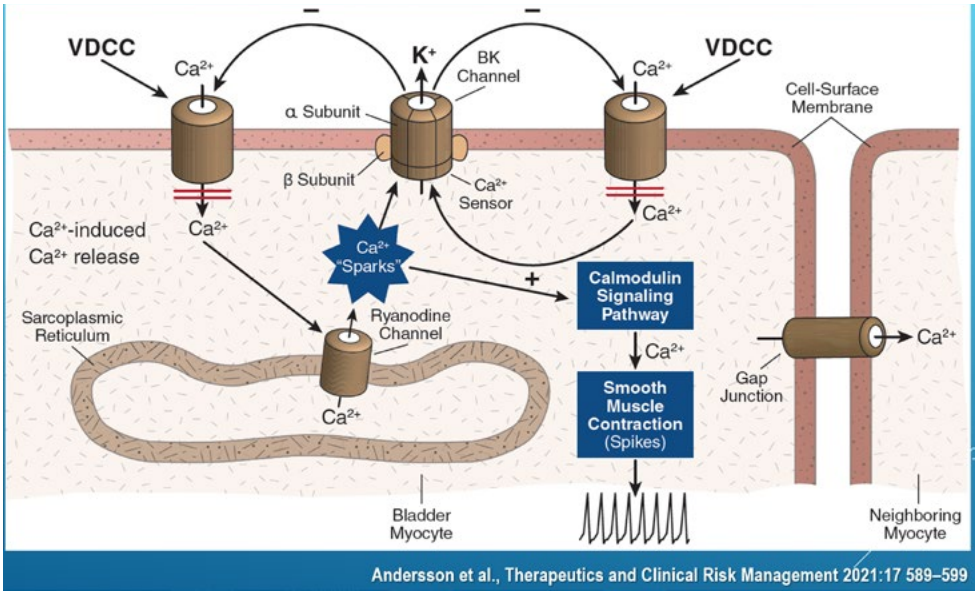

Figure 14: The Maxi K-channel. From Andersson et al., Therapeutics and Clinical Risk Management 2021:17 589–599

cific channel within a family. Second, K^+ channels are also involved in the regulation of smooth muscle and cardiomyocyte function; drug candidates for the treatment of OAB/DO should exhibit efficacy a concentrations/doses that largely lack effects on blood vessels and the heart. Such considerations have sometimes led to clinical proof-of-concept studies that used possibly suboptimal drug doses to avoid cardiovascular side effects. Overall, only few K^+ channel openers with promising animal data have been tested clinically.

an opener of ATP-sensitive K+ channels, has been tested in a phase II study with a daily dose of 25 mg administered for 12 weeks as compared to placebo [Chapple et al., 2004]. Based on >90 patients per arm, ZD0497 showed no relevant benefit for the primary endpoint, mean voided volume, any of the secondary endpoints number of micturitions and incontinence episodes.

Flupirtine has been marketed as a centrally acting, non-opioid analgesic for more than 30 years and is believed to largely act by modulating KCNQ type (K_v7) K^+ channels. Based on positive effects in several animal models has been tested in a phase II study that had planned to be administered 400 mg/day to be uptitrated to 600 mg/day for 12 weeks in comparison to placebo and tolterodine. However, the study was halted prematurely due to unexpected frequent hepatotoxicity of the compound [Michel et al., 2012]. At time of discontinuation, 189 (74, 76 and 39 on placebo, flupirtine and tolterodine, respectively) had at least one efficacy assessment during treatment (full analysis set), but only 88 (38, 32 and 18) had reached the 8-week assessment point without major protocol violations (per protocol set). In the latter, flupirtine was more effective than placebo ($p = 0.03$) for the primary endpoint of urinary frequency but less effective than tolterodine. Due to the small sample sizes upon premature discontinuation, these data are not conclusive. While flupirtine is obviously unsuitable as a treatment for OAB/DO due to its liver toxicity, other agents acting on KCNQ channels remain under investigation.

One type of large conductance, voltage and calcium activated K+ channel, known as big potassium (BK) or Maxi-K channel is expressed highly on urinary bladder smooth muscle cells and regulates bladder function **(Fig 14)**. Modulation of this channel with gene therapy has recently been explored and reviewed [Petkov, 2014]. URO-902 is a 6880-base-pair naked plasmid DNA incorporating a DNA sequence synthesised from mRNA that encodes the human BK channel alpha subunit [Andersson et al., 2021]. In phase 1 studies women with OAB, gene therapy was administered either by direct bladder injection or bladder instillation [Rovner et al., 2020]. No participants withdrew due to AEs (n=34) and no AEs prevented dose escalation. Most AEs were mild and not likely related to the therapy. In the instillation study, there was a trend towards a reduction in involuntary detrusr congractions on urodynamics and mean UUI episodes vs placebo. Furthermore, in those with direct injected gene therapy into the bladder significant reductions vs placebo was seen in urgency episodes ($p=0.036$) and number of voids 1 week post injection ($p=0.044$).

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4. α-ADRENOCEPTOR (AR) ANTAGONISTS

The smooth muscle of the bladder base and proximal urethra contains predominantly α-ARs, and contraction of the bladder base and urethra is mediated by α_1 ARs [Andersson, 2021]. There are at least three subtypes of α_1 ARs, designated α_{1A} , α_{1B} , and α_{1D} . The smooth muscle contraction within the human lower urinary tract is mediated largely by the α_{1A} subtype, and the α_{1D} subtype within the detrusor also has a role in contraction.

The use of α1-AR antagonists in the treatment of male lower urinary tract symptoms (LUTS) has been well-studied, and α1-AR antagonists are effective for treating voiding symptoms in men with bladder outlet obstruction (BOO) from BPE, thereby improving bladder emptying and improving urinary incontinence from either bladder overactivity or overflow [McVary et al., 2011].

Epidemiology studies conducted in Europe and in North America have estimated that between 9.7% and 27.2% of men are affected by OAB [Irwin et al., 2011]. Diagnosing OAB in men can be complicated by the presence of the voiding symptoms caused by BOO from BPH. Current European guidelines suggest using oral OAB meds in combination with an α-blocker when symptom relief is insufficient with either drug alone [Oelke et al., 2013].

Several studies in men have shown that antimuscarinics combined with α1-blockers can improve the bladder storage symptoms caused by OAB. Chapple et al randomized 652 men ≥40 years of age with persistent bladder storage symptoms and on a stable dose of α-blocker for ≥1 month to either 4 mg of tolterodine ER and α-blocker (n=329) or placebo and α-blocker (n=323) [Chapple et al., 2009]. After 12 weeks of treatment, men receiving tolterodine ER and α-blocker had significantly greater improvements over men receiving placebo and α-blocker in micturitions/day (-1.8 vs -1.2, p=0.0079), urgency episodes/day (-2.9 vs -1.8, p=0.0010), International Prostate Symptom Score (IPSS) storage subscale (-2.6 vs -2.1, p=0.0370), and OAB-q symptom bother scale (-17.9 vs -14.4, p=0.0086). There were no clinically meaningful changes in either postvoid residual volume or maximum urinary flow rate. The authors concluded that the addition of tolterodine ER to α-blocker therapy further improved bladder storage symptoms. Similarly, Kaplan et al randomized 398 men ≥45 years of age to either 5 mg of solifenacin plus 0.4 mg of tamsulosin (n=203) or placebo plus 0.4 mg of tamsulosin (n=195) [Kaplan et al., 2009]. The primary end point was mean change in micturitions/day after 12 weeks of treatment, and secondary end points included mean change in urgency episodes/day and total IPSS. After 12 weeks, men receiving solifenacin plus tamsulosin saw decreased daily micturitions and urgency episodes; however, only the decrease in urgency episodes reached statistical significance (-2.18 for solifenacin and tamsulosin vs -1.10 for placebo and tamsulosin, p<0.001). On the I-PSS the only significant between group difference was at week 12 in total storage symptoms (-3.15 for solifenacin and tamsulosin vs -2.40 for placebo and

tamsulosin, p<0.006). The authors concluded that while α-blockers may adequately manage voiding LUTS in men, storage LUTS may be improved with the addition of solifenacin. The intermediate-term and long-term impact of combination therapy remains largely unknown because supporting literature is absent. This becomes even more important in light of the high discontinuation rates seen with anticholinergic therapy [Gomelsky et al. 2018].

Recent studies have shown that using β-3 agonists and α-blockers in men with LUTS can improve bladder storage symptoms caused by OAB. Kaplan et al reported on the results of a phase 4 study of 676 men who, after completing a 4-week run-in period of 0.4 mg tamsulosin daily, then entered a 12-week, randomized, double-blind, treatment period where patients received either 25 mg mirabegron or placebo add-on therapy [Kaplan et al., 2020]. At 4 weeks, doses were titrated to either 50 mg mirabegron or placebo. The primary end point was the mean change in micturitions/day, and secondary end points included mean volume voided, mean change in urgency episodes/day, and IPSS score. The study found that tamsulosin plus mirabegron was superior to tamsulosin plus placebo in reducing the mean number of micturitions/day (-2.00 vs -1.62, p=0.039). As for secondary end points, statistically superior results with tamsulosin and mirabegron were seen in mean volume voided/micturition and number of urgency episodes/day, but no significant change was seen in IPSS. The authors concluded that the addition of mirabegron to tamsulosin improved the hallmark symptoms of OAB, urinary frequency and urgency. Ishikawa et al investigated the efficacy and safety of vibegron in men already receiving either α-1 blockers or tadalafil, a PDE5 inhibitor, for men with BPO from BPH and persistent bladder storage symptoms [Ishikawa et al. 2021]. Vibegron 50 mg was administered for 12 weeks to 42 men who were already on either α-1 blockers (n=22) or tadalafil (n=20). The primary endpoint was change in the OAB Symptom Score after 12 weeks of treatment. Of the men on α-1 blockers, 8 men were on silodosin (8 mg/day), 10 men were on naftopidil (50 or 75 mg/day) and 4 men were on tamsulosin (0.4 mg/day). Compared to baseline, the total OAB Symptom Score did significantly decrease after 12 weeks with this combination treatment (6.21 ± 3.12 vs 4.38 ± 2.46; p<0.001). Also, Qmax and PVR did not change after 12 weeks of vibegron use, and no patient discontinued vibegron because of AEs.

Oral OAB drugs are often used with caution in men with LUTS, becaused of the perceived risk of developing AUR. Yet, the risk of AUR from the combination of an α-blocker and an OAB drug (antimuscarinic or β-3 agonist) is very low. Urinary retention was reported in 1.8% of men taking tolterodine ER and α-blocker, which was the same rate reported in men taking placebo and α-blocker. Of the men that took 5 mg solifenacin and tamsulosin, 3% reported urinary retention. Also, urinary retention was seen in 1.7% of men taking both mirabegron and tamsulosin. Furthermore, the increase in PVR seen with combination therapy was low and not clinically significant, and Qmax was not impacted by the addition of either anticholinergics or β-3 agonists [Kim et al. 2017].

There have been several studies evaluating whether better efficacy and/or tolerability is obtained with use of the highly subtype selective α-blockers for male LUTS. Chapple et al. conducted a multicenter double-blind, placebo and active-controlled parallel group study comparing silodosin, tamsulosin, and placebo [Chapple et al. 2011]. A total of 1228 men ≥50 years of age with an IPSS of ≥13 and a Qmax between 4-15ml/s were selected at 72 sites in 11 European countries. The men were entered into a 4-week placebo run-in period. A total of 955 patients were randomized (2:2:1) to either silodosin 8 mg (n=381), tamsulosin 0.4 mg (n=384), or placebo (n=190) once daily for 12 weeks. The primary end point was change in total score of IPSS. The overall efficacy of silodosin was not inferior to tamsulosin. Only silodosin showed a significant effect on nocturia over placebo (p = 0.013). Also, although both silodosin and tamsulosin showed significant improvements in IPSS storage symptoms compared to placebo (p=0.002), there was no difference between the two. With respect to QOL at 12 weeks, there was no difference between the two α-blockers. Discontinuation rates due to treatment emergent AEs were low in all groups (2.1%,1.0%, and 1.6% with silodosin, tamsulosin, and placebo, respectively). Yet, a major advantage of silodosin is its lack of cardiovascular side effects. Unlike tamsulosin, silodosin has no clinically relevant effect on blood pressure during orthostatic testing. Yamanishi et al evaluated the urodynamic effects of silodosin in 29 men with severe LUTS from BPH [Yamanishi et al., 2010]. After 12 weeks of silodosin treatment, detrusor overactivity (DO) resolved in 40% of patients with DO at baseline, the amplitude of the largest DO contraction decreased from 85.3±35.3 cm H_2O to 37.4±42.9 cm H_2O (p=0.0003), and the bladder volume at initial DO increased from 285.34±112.8 ml to 380.6±136.87 ml (p=0.0003).

Naftopidil is an α-1 blocker with affinity for α_{1D} receptors which are largely concentrated in the bladder within the detrusor smooth muscle, the detrusor vasculature, the urothelium, afferent and efferent nerve terminals and intramural ganglia [Andersson and Gratzke, 2007]. The use of naftopidil in men with LUTS has been shown to improve OAB symptom scores (OABSS) in a study designed to compare efficacy between morning and evening dosing [Sakai et al., 2011]. Naftopidil significantly decreased the OABSS from 7.8±2.6 to 5.0±2.5 in the morning group (p<0.0001) and from 8.6±2.9 to 5.8± 3.3 in the evening group (p<0.0001). Interestingly, there was no significant difference in the incidence of AEs between morning and evening dosing of naftopidil. Matsukawa et al sought to determine the pre-treatment factors related to the improvement of OAB symptoms after α-1 blocker monotherapy in patients with BPE and OAB [Matsukawa et al., 2019]. They did a post-hoc analysis of an open-labeled study comparing silodosin 8 mg daily (n=157) and naftopidil 75 mg daily (n=157). Patients were divided into 2 groups based on the OABSS urgency sub-score after treatment: the good responder group included patients with an OABSS urgency sub-score of <2 at week 12 and the poor responder group had an OABSS urgency score of ≥2 at week 12. The proportion of patients with UUI at baseline was significantly higher in the poor responder group compared to the good responder group (77.4% vs. 55.3%, p < 0.001). In multivariable logistic regression analysis, use of naftopidil, higher OABSS-UUI score, and larger PVR were significant pre-treatment factors related to failure in OAB symptom improvement with α1-blocker monotherapy.

Little has been published on the use of α1-blockers in the treatment of women with LUTS. Low et al randomized 100 women with LUTS to either terazosin 4 mg daily or placebo [Low et al., 2008]. The primary end point was improvement on the IPSS QOL of 2 or <. Of the women receiving terazosin, 80% responded compared to 55% of the women receiving placebo, p <0.02. Recently, Kim et al performed 2 meta-analyses on the use of α1-blockers in the treatment of female LUTS [Kim et al., 2019]. The first analysis compared bladder symptom scores, Qmax and PVR before and after α1 blocker therapy in 8 prospective, open-label studies, and 5 RCTs. The second analysis compared the same variables in 4 RCTs that compared α1 blockers and placebo. The first meta-analysis showed that, women treated with α1 blockers had an improvement in bladder symptoms of 5.85 points (p<0.00001), an increase in Qmax of 3.67 mL/sec (p<0.00001), and a decrease in PVR of 28.46 mL (p<0.00001). In the second meta-analysis, α1-

blockers demonstrated greater symptom relief relative to placebo with a mean difference in symptoms of 1.60 (p=0.004); however, there were no differences in Qmax or PVR between α1 blockers and placebo. Although the authors found that α1-blockers are effective for treating women with LUTS, they stressed that the effect of α1-blockers in this population should be assessed according to underlying cause.

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5. PHOSPHODIESTERASE (PDE) INHIBITORS

Drugs stimulating the generation of cAMP are known to relax smooth muscles, including the detrusor [Andersson, 1999; Andersson and Wein, 2004]. It is also well established that drugs acting through the NO/cGMP system can relax the smooth muscle of the bladder outflow region [Andersson and Arner, 2004]. Use of PDE inhibitors to enhance the presumed cAMP- and cGMP-mediated relaxation of LUT smooth muscles (detrusor prostate, urethra) should then be a logical treatment approach to increased outflow resistance as found in BPH/BPO (Andersson et al., 1997; 2011¸ 2017). There are presently 11 families of PDEs **(Fig 15**), some of which preferentially hydrolyse either cAMP or cGMP [Uckert et al., 2006, Rahnama'i et al., 2013] (Figure 15).

As a basis for PDE inhibitor treatment of BPH/LUTS, Uckert et al. [2006] investigated human bladder tissue, revealing messenger RNA for PDEs 1A, 1B, 2A, 4A, 4B, 5A, 7A, 8A, and 9A; most of these PDEs preferably inhibit the breakdown of cAMP. In vitro, hu-

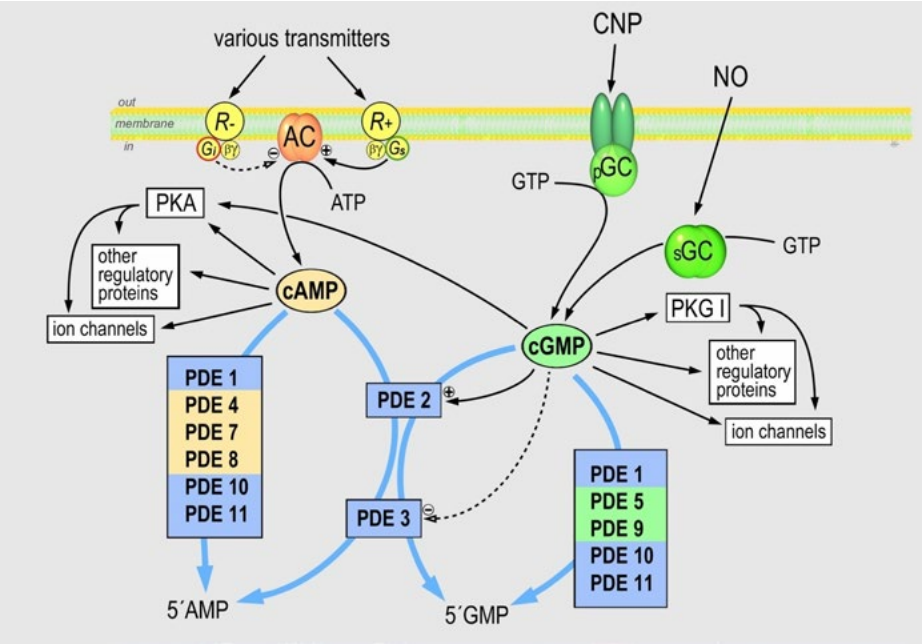

Figure 15: The family of phosphodiesterases

man detrusor muscle responded poorly to sodium nitroprusside, and to agents acting via the cGMP system [Truss et al., 2000]. However, significant relaxation of human detrusor muscle, paralleled by increases in cyclic nucleotide levels, was induced by papaverine, vinpocetine (a low affinity inhibitor of PDE 1), and forskolin (stimulating the generation of cAMP), suggesting that the cAMP pathway and PDE 1 may be important in regulation of detrusor smooth muscle tone [Truss et al., 2001]. Significant dose-dependent relaxations were also induced by human cAMP analogues [Truss et al., 2001]. With these studies as a background, Truss et al. presented preliminary clinical data with vinpocetine in patients with urgency/urgency incontinence or low compliance bladders, and not responding to standard antimuscarinic therapy [Truss et al., 2000]. This initial open pilot study suggested a possible role for vinpocetine in the treatment of OAB. However, the results of a larger RCT in patients with DO showed that vinpocetine only showed statistically significant results for one parameter [Truss et al., 2001]. Clinical studies with PDE 1 inhibitors other than vinpocetin (which may not be an optimal drug for elucidation the principle) do not seem to have been performed.

PDE 4 (which also preferably hydrolyses cAMP) has been implicated in the control of bladder smooth muscle tone. PDE 4 inhibitors reduced the in vitro contractile response of guinea pig [Longhurst et al., 1997] and rat [Kaiho et al., 2008] bladder strips, and also suppressed rhythmic bladder contractions of the isolated guinea pig and rat bladder [Gillespie and Drake, 2004; Nishiguchi et al., 2007]. Xin et al. [2014] found that that selective pharmacological inhibition of PDE4 increases the frequency of Ca^{2+} sparks and their functionally coupled BK channels, which lead to the attenuation of DSM excitability and contractility and suggested that PDE4 isoforms might be valuable therapeutic targets for the treatment of overactive bladder. In rats with bladder outlet obstruction, Balog et al. [2019] demonstrated that roflumilast (PDE 4 inhibitor) particularly in combination with tadalafil (PDE 5 inhibitor) effectively decreased non-voiding contractions and smooth muscle disruption. Linhares et al. [2020] evaluated in vitro the effect of the combination of the b-AR agonist, BRL 37344, with tadalafil or rolipram (PDE 4 inhibitor) in rats with and without chronic L-NAME treatment. They found that the inhibitory effects of rolipram, but not tadalafil, were enhanced by BRL 3744, and suggested that PDE4 inhibition when associated with $ß_3$-AR stimulation, could represent a potential treatment for overactive bladder.

Several selective PDE 4 inhibitors have been tested clinically for various inflammatory disorders (particularly skin diseases and asthma) [Li et al., 2018] but none seems to have been tested on LUT disorders. Considering the promising preclinical experiences, PDE 4 inhibition with or without combination with other drugs may be a worth further exploration, but clinical studies are needed.

Oger and co-workers showed that PDE5-inhibitor sildenafil-induced relaxation of human detrusor smooth muscle involved cGMP-, cAMP- and K(+) channel-dependent signalling pathways, with a minor contribution from NO [Oger et al., 2010]. In combination with the alpha-blocker doxazosin, sildenafil reduced adrenergic tone of prostatic and cavernosal smooth muscle and their combination provided a significant benefit when targeting relaxation of both tissues [Oger et al., 2008].

In-vivo, several studies have indicated a role for PDE5-inhibitors in the regulation of micturition function. Systemic vardenafil reduced both non-voiding contractions and bladder afferent nerve firing in unanesthetized, decerebrate, spinal cord injury rats, indicating potential mechanisms by which PDE5-Is improve storage symptoms in SCI patients [Behr-Roussel et al., 2010]. The effect of vardenafil on OAB-symptoms could be related to a cGMP-dependent RhoA/ROCK signaling inhibition, as shown in spontaneously hypertensive rats (SHR) [Morelli et al., 2009a; Morelli et al., 2009b]. Using the same animal model, bladder hypoxia was significantly reduced by acute vardenafil treatment [Morelli et al., 2009b]. Thus, besides relaxing muscular wall, PDE5 inhibition may positively affect urinary bladder blood perfusion. In the same respect, tadalfil was shown to increase prostate tissue oxygenation in SHR and human vesicular-deferential artery is characterized by a high expression and activity of PDE5, which was inhibited by tadalafil in vitro; these results

suggest another possible mechanism through which PDE5i exert beneficial effects on LUT symptoms [Morelli et al., 2011; Cellek et al., 2014].

NO has been demonstrated to be an important inhibitory neurotransmitter in the smooth muscle of the urethra and its relaxant effect is associated with increased levels of cyclic GMP [Andersson and Arner, 2004]. However, few investigations have addressed the cAMP- and cGMP-mediated signal transduction pathways and its key enzymes in the mammalian urethra. Morita et al. examined the effects of isoproterenol, prostaglandin E_1 and E_2, and SNP on the contractile force and tissue content of cAMP and cGMP in the rabbit urethra [Morita et al., 1994]. They concluded that both cyclic nucleotides can produce relaxation of the urethra. Werkström et al.[2006] characterized the distribution of PDE 5, cGMP and PKG1 in female pig and human urethra, and evaluated the effect of pharmacological inhibition of PDE-5 in isolated smooth muscle preparations. After stimulation with the NO donor, DETA NONO-ate, the cGMP-immunoreactivity (IR) in urethral and vascular smooth muscles increased. There was a wide distribution of cGMP- and vimentin-positive interstitial cells between pig urethral smooth muscle bundles. PDE-5 IR could be demonstrated within the urethral and vascular smooth muscle cells, but also in vascular endothelial cells that expressed cGMP-IR. Nerve-induced relaxations of urethral preparations were enhanced at low concentrations of sildenafil, vardenafil and tadalafil, whereas there were direct smooth muscle relaxant actions of the PDE-5 inhibitors at high concentrations. Fibbi et al. [2009] confirmed that the highest expression and biological activity of PDE5 was found in bladder. However, a consistent PDE5 expression and activity was also found in prostatic urethra. In contrast, the prostate gland showed the lowest PDE5 abundance and cultures derived from this tissue were less sensitive to vardenafil. Using a different animal model associated with C-fibre afferent activation, it was shown that the NO/cGMP signalling pathway is involved in the regulation of the micturition reflex, with an action that seems more predominant on the sensory rather on the motor component of the micturition reflex [Caremel et al., 2010]. In obstructed human and rat bladder, He et al. [2020] found an upregulation of NOS isoforms, PDE5 and PDE4A. Obstructed bladder tissue exhibited reduced relaxation responses to sodium nitroprusside but an exaggerated PDE5 inhibition effect. The authors suggested that upregulation of PDE5 could contribute to the lack of effect on Qmax for BPH/LUTS patients treated with PDE5 inhibitors. Agis-Torres et al. [2018], demonstrated a rich PDE4 and PDE4A expression in nerve fibers of the smooth muscle layer of pig and human bladder outflow region. The orally active PDE 4 inhibitor, rofumilast, approved for the treatment of severe chronic obstructive pulmonary disease, produced a much more potent smooth muscle relaxation than that induced by tadalafil. They concluded that PDE4 inhibition and subsequent increased neuronal cAMP facilitates NO- and H_2S-mediated bladder neck inhibitory neurotransmission. Rofumilast also improved bladder function in rats with diabetic [Ding et al., 2019] and obesity-related [Ding et al., 2017] bladder dysfunction. In mice. Ito et al. [2019] showed that ow-dose sildenafil increased bladder compliance, increased pelvic nerve afferent activity, and augmented the bursting activity of the external urethral sphincter. suggested that actions of the PDE5 inhibitor on afferent traffic and sphincter control may contribute to its beneficial actions to restore storage and voiding efficiency in LUT dysfunction. Sildenafil was also shown to selectively inhibit ATP release from nerve terminals innervating detrusor smooth muscle and the urothelium in rats with spinal cord injury [Chakrabarty et al, 2019].

PDE5 degrades cGMP and can thus stop the NO-mediated relaxation of smooth muscle. NO activates its intracellular receptor, soluble guanylate cyclase (sGC), to promote accumulation of cyclic GMP (cGMP), causing smooth muscle relaxation. Inhibitors of PDE5 thus increase tissue cGMP levels and have been approved for treatment of BPH/LUTS suggesting a key role for NO-sGC-cGMP pathway as the key target of PDE5 inhibitor therapy. However, refractoriness to PDE5 inhibitors can develop and alternatives to upregulate cGMP production need to be sought. When NO binds to sGC, it activates its catalytic domain to convert GTP to cGMP, which in turn activates protein kinase G (PKG), phosphorylating multiple downstream proteins. This process can be inactivated by inflammation or oxidative stress associated with different risk factors for BPH/LUTS such as e.g., aging and obesity but can be circumvented by small molecule sGC activators and stimulators which are not structural analogues of cGMP but induce its production in the absence of NO [Monica and Antunes, 2018]. This may be a promising way for treatment for BPH/LUTS patients refractory to PDE5Is.

The observation that patients treated for erectile dysfunction with PDE5 inhibitors had an improvement of their LUTS, has sparked a new interest in using these drugs also for treatment of both LUTS and OAB. After the report in an open study that treatment with sildenafil appeared to improve urinary symptom scores in men with ED and LUTS [Sairam et al., 2002], this observation has been confirmed in several well designed and conducted RCTs.

A number of RCTs are available comparing the effect of PDE5 inhibitors alone to placebo and the combination of alpha-blockers and PDE5 inhibitors vs alpha-blockers alone [Gacci et al 2016; Andersson et al., 2017, Monica and De Nucci, 2019; Pattanaik et al., 2019; Sebastianelly et al 2020]. In these studies, different PDE5 inhibitors and different doses were administered. PDE5-inhibitors significantly improve IPSS and IIEF scores, but not Qmax when compared to placebo. PDE5-inhibitors are generally shown to be safe and well tolerated [Ma et al., 2020].

As discussed above and in several reviews [Andersson et al., 2011; Giuliano et al., 2013; Cellek et al., 2014; He et al., 2020] the mechanism behind the beneficial effect of the PDE inhibitors on BPH/LUTS/OAB and their site(s) of action largely remain to be elucidated. The actions may be multifactorial and He et al. [2020] summarized plausible mechanism as 1) relief of SM tone in prostate and bladder, 2) relaxation of blood vessels so as to increase LUT perfusion and oxygenation, 3) decreasing the activity of afferent nerves in the LUT to modulate the micturition reflex, 4) anti-proliferation effect on bladder and prostate, 5) blunting of intraprostatic inflammation, and 6) anti-fibrotic effect on the bladder.

Improvement of bladder blood flow to the LUT has been suggested [Cellek et al., 2014], and this has been supported by studies in animals with chronic bladder ischemia [Nomiya et al., 2013].,

Currently, tadalafil is the only FDA approved PDE-5 inhibitor for treatment of male LUTS even of e.g, sildenafil and and vardenafil have been shown to be effective. However, there are several other drugs belonging to the same class that are used for treating erectile dysfunction, including avanafil, udenafil, microdenafil, gisadenafil [Gacci et al., 2014], and there are no reasons to believe that they should not be effective in relieving male LUTS. To what extent new molecules with ability to inhibit PDE-5 [Sawant et al., 2015] will be developed for future clinical application remains to be seen.

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6. DRUGS ACTING AT THE CNS

6.1. Antidepressants

Some antidepressants have been used in the treatment of urgency urinary incontinence. There is increasing evidence that chronic psychological stress can result in the development of bladder storage symptoms such as urinary frequency, urgency, and urinary incontinence (Chess-Williams et al., 2021). Pro inflammatory cytokines and chemokines are released during periods of chronic stress. In the brain and spinal cord, pro-inflammatory cytokines influence the regulation of micturition pathways by corticotropin-releasing factor (CRF) and its receptors, while peripheral cytokines can directly affect bladder function, thereby causing detrusor overactivity and afferent nerve hypersensitivity. In view of the role of CRF in stress-induced urinary dysfunction, Wrobel et al. (2017) showed that a CRFR-1 antagonist can prevent the development of depressive behaviors induced by stress in a rat model of bladder overactivity. The two most common antidepressants studied in the treatment of bladder overactivity are imipramine and duloxetine.

6.1.1. Imipramine

Imipramine is a tricyclic antidepressant that blocks muscarinic receptors and inhibits norepinephrine reuptake, both of which enhance detrusor smooth muscle relaxation. Also, imipramine inhibits the re-uptake of noradrenaline and serotonin in adrenergic nerve endings to enhance the contractile effects of noradrenaline on urethral smooth muscle [Maggi et al., 1989; Hoebeke et al., 2000], but its mode of action in DO has not been established [Hunsballe and Djurhuus, 2001]. Although antimuscarinics and beta-3 agonists are currently considered the drugs of choice in the treatment of OAB and urge urinary incontinence (UUI), imipramine has been shows to have in vitro and in vivo effects on the detrusor muscle to improve bladder overactivity [Creed and Tulloch, 1978]. Yet, the early data on the clinical effects of imipramine use alone in adult UUI has been conflicting. Most of these studies attesting to an improvement were either small, poorly designed, and/or uncontrolled [Castleden et al., 1986; Cole and Fried, 1972].

Imipramine has been used in combination with antimuscarinics and alpha-blockers as a treatment for refractory neurogenic detrusor overactivity (NDO) in adults with neurogenic bladder. Natalin et al evaluated prospectively the combination of doxazosin 4 mg at

night, oxybutynin 5 mg BID, and imipramine 25 in the morning [Natalin et al., 2010]. Patients were included if they had poor efficacy with oxybutynin 15 mg/d for at least 3 months and they had NDO demonstrated on urodynamics. There were 17 men and 10 women, and the median follow-up was 15 months (range, 6–38 months). Of the 27 patients, 10 had spina bifida, 5 had MS, 5 had SCI, 4 had vascular brain injury, and 3 had myelitis. After 60 days of triple drug therapy, urodynamics were performed and the mean cystometric capacity (MCC) increased from 200 to 300 cc (p<0.001), and bladder compliance increased from 6 to 20 ml/cm H_20 (p<0.001). Also, 3-day bladder diaries, performed every 6 months, showed decreases in urgency episodes/day and number of voids/day (p<0.001). Adverse events included dry mouth in 37% and constipation in 37%. The authors concluded that triple therapy of oxybutynin, doxazosin, and imipramine may be an effective, easily employed, and well-tolerated treatment option for refractory NDO. Similarly, Cameron et al. [2009] performed a retrospective a retrospective chart review and identified 77 subjects (54 men and 23 women) that were either on antimuscarinics and/or imipramine and alpha-blockers. The etiology of the neurogenic bladder dysfunction was SCI in 49 (64%) or spina bifida in 13 (17%) subjects. Patients underwent urodynamics at baseline and on average 10 months after starting the combination therapy. MCC increased from 160 to 251 ml in the 2 drug group (p=0.002) and from 156 to 263 ml in the 3 drug group (p=0.0006). In addition, bladder compliance increased from a mean of 11.3 to 56.3 ml/cm H2O (p=0.0008) in the 2 drug group and from a mean of 7.2 to 69.6 ml/cm H2O (p<0.0001) in the 3 drug group. There were also improvements in incontinence, vesicoureteral reflux, NDO and detrusor sphincter dyssynergia. The authors concluded that the addition of imipramine and/or an alpha-blocker should be considered in patients with neurogenic bladder in whom anticholinergics alone fail.

In children, imipramine has been known to have favorable effects in the treatment of nocturnal enuresis with success rates up to 70% in some controlled trials [Caldwell et al., 2016]. In a review of 64 tricyclic trials for nocturnal enuresis in 4071 children, Caldwell et al. [2016] concluded that imipramine treatment reduced enuresis by one wet night per week. Although a fifth of the children became dry while on treatment, this effect was not sustained after treatment stopped. Specifically, 96% of children were wet at follow-up after ceasing imipramine versus 97% for placebo. There is evidence that tricyclics combined with anticholinergics may be more effective that tricyclic monotherapy. Specifically, there were about two fewer wet nights per week for children taking imipramine plus oxybutynin compared with imipramine monotherapy. Furthermore, AEs from imipramine use in children include dizziness, headache, mood changes, gastrointestinal complaints, and neutropenia. The authors concluded that there was evidence that tricyclics are effective at reducing the number of wet nights during treatment for nocturnal enuresis in children, but tricyclics do not have a sustained effect after treatment stops, with most children relapsing.

It is well established that therapeutic doses of tricyclic antidepressants, including imipramine, may cause serious toxic effects on the cardiovascular system (orthostatic hypotension, ventricular arrhythmias). Imipramine prolongs QTc intervals and has an antiarrhythmic (and proarrhythmic) effect similar to that of quinidine [Bigger et al., 1977; Giardina et al., 1979]. Children seem particularly sensitive to the cardiotoxic action of tricyclic antidepressants [Baldessarini, 1985].

6.1.2. Duloxetine

Duloxetine hydrochloride is a combined norepinephrine and serotonin reuptake inhibitor **(Fig 16).** Although duloxetine has been well studied in the treatment of SUI, it was shown to increase bladder capacity in a cat acetic acid model through both motor efferent and sensory afferent modulation [Katofiasc et al., 2002]. Wrobel et al. [2020] found that the tested animals presented symptoms of depression, detrusor overactivity, inflammation, and disturbances in neurotrophic factors. Duloxetine improved all changes and the authors suggested that duloxetine may have a potential to become a new treatment option for patients with OAB co-existing with depression.

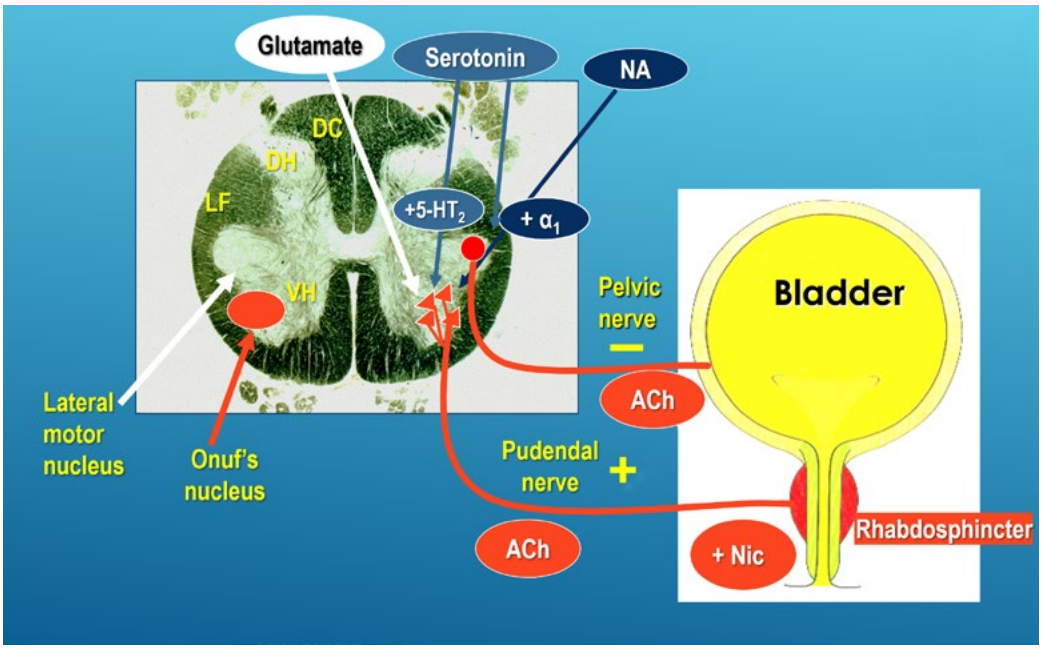

Figure 16: Site of action of duloxetine

Clinical duloxetine use was studied by Steers et al with a 12-week, randomized, placebo-controlled trial evaluating the efficacy and safety of duloxetine women with OAB [Steers et al., 2007]. The study was conducted at 30 sites in the US, Canada, and Australia. A total of 306 women were randomized to either duloxetine at 80-mg/day for 4 weeks and then increased to 120-mg/day for 8 weeks (n=153) or placebo (n=153). These OAB patients underwent urodynamics, and the testing had to demonstrate either DO or urgency which limited bladder capacity to < 400 mL. The primary end point was the mean change from baseline in the number of voids/24 h. Secondary end points included UUI episodes/24 h and scores on the Incontinence Quality of Life questionnaire (I-QOL). After 12 weeks, the number of voids/day was reduced by 1.81 voids in women receiving duloxetine and by 0.62 voids in women receiving placebo, p<0.001. Also, the number of UUIE/day was reduced by 1.12 leaks in women receiving duloxetine and by 0.29 leaks in women receiving placebo, p=0.04. In addition, the I-QOL scores improved by 8.37 points in women receiving duloxetine and by 4.87 points in women receiving placebo, p=0.035. However, nausea was reported in 30.7% of women receiving duloxetine compared to 4.6% of women receiving placebo, p<0.001. Other AEs in those receiving duloxetine included dizziness in 14.4%, insomnia in 13.1%, and fatigue in 10.5%, and all these rates were significantly higher with duloxetine compared to placebo. Study discontinuations due to AEs was 28.1% in those receiving duloxetine compared to 5.2% in those receiving placebo, p<0.001.

Di Rezze et al. [2012] studied the efficacy and tolerability of duloxetine in the treatment of OAB in patients affected by remitting-relapsing MS and secondary progressive MS. They found a statistically significant improvement in bladder disorder, as measured by OAB-Q after duloxetine treatment compared with both basal levels and placebo

In summary, despite the efficacy demonstrated in the Steers RCT with duloxetine over placebo in improving void/day, UUIE, and I-QOL, treatment emergent AEs and discontinuations due to AEs were more common with duloxetine compared to placebo. As such, the safety profile of duloxetine in this study was identical to the safety profile established in women with SUI [Dmochowski et al. 2003]. No further quality studies on the use of duloxetine for OAB have been published. As such, there is no current clinical utility of duloxetine for the treatment of OAB.

6.2. Baclofen

Gamma-amino-butyric acid (GABA) is a ubiquitous inhibitory neurotransmitter in the CNS that can inhibit the micturition reflex in several points along its central pathway [de Groat, 1997; Pehrson et al., 2002]. Experimental data suggest the GABAergic system as an interesting target for bladder dysfunction therapy. Baclofen intrathecally attenuated oxyhemoglobin induced detrusor overactivity, suggesting that the inhibitory actions of GABA(B) receptor agonists in the spinal cord may be useful for controlling micturition disorders caused by C-fiber activation in the urothelium and/or suburothelium [Pehrson et al, 2002]. In spinal intact rats, intrathecal application of bicuculline induced detrusor-sphincter dyssynergia (DSD)-like changes whereas intrathecal application of baclofen induced urethral relaxation during isovolumetric bladder contractions [Miyazato et al., 2008]. After spinal cord injury (SCI), Miyazato et al. [2008] found signs of hypofunction of the GABAergic system (glutamate decarboxylase 67 mRNA levels in the spinal cord and dorsal root ganglia were decreased) and showed that activation of GABA(A) and GABA(B) receptors in the spinal cord inhibited DO as evidenced by a reduction in non-voiding contractions. GABA(B) receptor activation preferentially reduced DO prior to inhibiting voiding contractions while GABA(A) receptor activation inhibited DO and voiding contraction at the same concentration.

As a GABA agonist on GABA(B) receptors, *baclofen* has been available for clinical use for more than 60 years [Kent et al., 2020]. Administered systemically or intrathecally in animal models, it has been shown to inhibit pain, including bladder pain [see, Ness et al., 2021]. It has been used orally in IDO patients. However, its efficacy was poor, eventually dictated by the fact that baclofen does not cross the blood-brain barrier [Taylor and Bates, 1979]. ADX71441 is a selective positive allosteric modulator of the $GABA_B$ receptor ($GABA_B$ PAM), which is orally available and showed promising effects in animal models of micturition disturbances [Kalinichev et al., 2014]. Further studies of this agent would be of interest.

Baclofen is one of the most effective drugs for the treatment of spasticity following spinal cord injury, traumatic or hypoxic brain injury, and cerebral palsy (Ochs, 1993), and *intrathecal* baclofen was shown to be useful in some patients with spasticity and bladder dysfunction [Bushman et al., 1993]. Baldo et al.[(2000] found a rapid (24 hours) and persistent increment in the volume to first detrusor contraction and of the maximal cystometric whereas maximal detrusor pressure decreased. At ten days the volume to first detrusor contraction had increased from 143 ml to 486 ml. In a retrospective chart review, Del Fabro et al. [2018] found that intrathecal baclofen caused a significant reduction of symptomatic episodes of autonomic dysreflexia after spinal cord injury, even in those with additional risk factors for development of autonomic dysreflexia.

In selected patients with spasticity and bladder dysfunction, intrathecal baclofen seems to be an effective therapy.

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7. CYCLOOXYGENASE (COX) INHIBITORS

Prostanoids (prostaglandins and thromboxanes) are synthesized by cyclooxygenase (COX) from a common precursor, arachidonic acid. Prostanoids may be involved in the control of bladder function under normal and pathological conditions, including DO and OAB. Human bladder mucosa has the ability to synthesize eicosanoids [Jeremy et al., 1987], and these agents can be liberated from bladder muscle and mucosa in response to different types of trauma [Downie and Karmazyn, 1984; Leslie et al., 1984]. Even if prostaglandins cause contraction of human bladder muscle, it is still unclear whether prostaglandins contribute to the pathogenesis of unstable detrusor contractions. More important than direct effects on the bladder muscle may be sensitization of sensory afferent nerves, increasing the afferent input produced by a given degree of bladder filling. Involuntary bladder contractions can then be triggered at a small bladder volume. If this is an important mechanism, treatment with prostaglandin synthesis inhibitors could be expected to be effective. However, clinical evidence for this is scarce.

Although early clinical studies with nonselective COX inhibitors in patients with DO showed some favourable effects and symptomatic relief, the drugs were not further developed for this indication mainly due to side effects [Cardozo et al., 1980a; Cardozo and Stanton, 1980b; Palmer, 1983]. Nevertheless, combination therapy with alpha blocker and COX-2 inhibitor for male LUTS was recently receiving some attention. Jhang et al. performed a ramdomized controlled study of 82 male patients with clinical BPH, elevated serum PSA (> 4 ng/ml), and significant LUTS (International Prostate Symptom Score [IPSS] ≥ 8) randomly assigned to receive doxazosin 4 mg daily plus celecoxib 200 mg daily (study group) or doxazosin 4 mg daily alone (control group) for 3 months. The improvement in IPSS-voiding was significantly greater in the study group than control group ($p = 0.034$). The PSA level in the study group showed significant improvement after treatment ($p < 0.01$). However, prostate cancer detection rate failed to show any significant difference between the patients whose PSA levels decreased or not (6/21 = 29% vs. 5/24 = 20%, respectively, $p = 0.447$). The changes in Qmax and voided volume after combination treatment were significantly greater in patients with prostatic hyperplasia or inflammation than adenocarcinoma.

Ozdemir et al [2009] compared the efficacy and safety of a combination therapy, doxazosin 4mg plus tenoxicam 20mg, and doxa-

zosin 4mg alone for 6 weeks in 57 patients with LUTS secondary to BPH. The improvements in IPSS, IPSS-QoL, and OABSS were significantly better in patients treated with combination therapy ($P < 0.05$).

Tanaka et al. [2018] evaluated the add-on efficacy of a cyclooxygenase (COX)-2 inhibitor on the chronological changes in urinary function in patients who underwent low-dose-rate prostate brachytherapy. A total of 310 patients with prostate cancer who underwent low-dose-rate-brachytherapy were enrolled. Patients were randomized and allocated to the monotherapy group (tamsulosin alone: 0.2 mg/d) and the combination group (tamsulosin 0.2 mg/d plus celecoxib: 200 mg/d). There was not an additional effect of a COX-2 inhibitor to the action of an alpha-1 adrenoceptor antagonist on concerning the chronological changes in IPSS and OABSS. The use of a COX-2 inhibitor reduced the daytime urinary frequency and postvoid residual after seed implantation.

These findings suggest that COX-2 inhibitors in combination with an alpha blocker may increase the effectiveness of the therapy for LUTS secondary to BPH and prostatic inflammation.

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8. TOXINS

Intravesical application of toxins gives the opportunity to use potentially lethal compounds unsuitable for systemic administration to treat bladder dysfunctions. That should be used as a second line treatment, when patients do not respond to oral therapy or do not tolerate their adverse effects. However, it might be expected that progressive patient phenotyping will identify subgroups that may benefit from intravesical therapy without requiring a period of potentially ineffective oral treatment

8.1. Botulinum toxin

Botulinum toxin (BonT) is a neurotoxin produced by *Clostridium botulinum*. Of the seven subtypes of BonT, sub-type A (BonT-A) has the longest duration of action, making it is the most relevant clinically. BoNT/A is available in different commercial forms, with the proprietary names of Botox®, Dysport®, Xeomin®, and Prosigne. Although the toxin is the same, it is wrapped by different proteins which modify the relative potency of each brand. The molecular weights are different. OnabotA is a 900 kDa molecule, abobotulinumtoxinA is approximately 500 kDa and incobotulinumtoxinA, is a 150 kDa molecule [Cruz, 2014]. This was the basis for the introduction of the non-proprietary names onabotulinum toxin A (onabotA), abobotulinum toxin A (abobotA) and incobotulinum toxin A (incobotA) for Botox®, Dysport® and Xeomin®, respectively. Prosigne is the proprietary name of a BoNT/A produced in China, which currently does not have a known non-proprietary name.

The current approved method to estimate the potency of a BoNT/A brand is the mouse LD50 (lethal dose 50%); that is, the mass of toxin (expressed in ng/kg of body weight) that kills 50% of mice. More recently, a cell-based potency assay was approved specifically for onabotulinum toxin assay which uses differentiated human neuroblastoma SiMa cells and replicates all steps in BoNT/A mechanism of action.8 The assay measures the BoNT/A-dependent intracellular increase of cleaved SNAP-25. The EC50, that is, the concentration of toxin required to provoke a response halfway between the baseline and maximum response for OnabotA, is about 1–0.4 U per well [Fernandez-Salas et al., 2012]. Nevertheless, the relative potency of each brand intended for bladder application may require additional investigations, as tissue physiology may alter the effucacy and metabolism of the different BoNT/A. A study in the mice compared the capacity of 1 U of onabotA and 1 U of abobotA injected in the bladder wall to cleave SNAP25. The average number of cleaved SNAP-25 positive fibers was higher after onabotA, suggesting a conversion ratio between onabotA and abobotA around 1:1.6 [Oliveira et al., 2015]. On the other hand, studies carried in the skeletal muscle suggest that onabotA is roughly three times more potent than abobotA and equivalent to incobotA. Therefore, without specific dose finding studies for each brand estimated equivalences should be approached with caution.

Innumerous comprehensive reviews have been produced along the years [Dowson et al., 2010; Duthie et al., 2011; Mangera et al., 2011, 2014; Moore et al., 2016]. For references before 2010 the interested reader is invited to read the version of this chapter in the previous edition of this book. Most of the information available about intravesical application of BoNT/A derives from the use of onabotA (Botox®). However, in addition to sub-type A, some studies have investigated the effect of detrusor injection sub-type B, rimabotulinumtoxinB (proprietary names being Miobloc™ or Neurobloc™ according to countries). For further details see below.

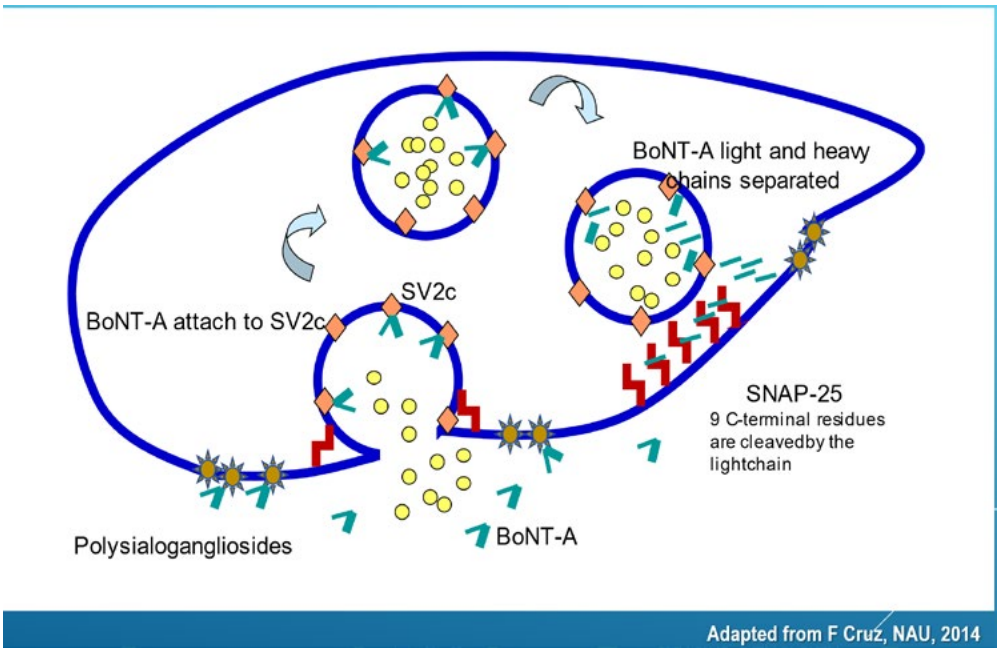

Figure 17: Mechanism of action of BoNT-A

8.1.1. Mechanism of action

This chapter will address the mechanism of action of the subtype BoNT/A, the only one with therapeutic expression in the lower urinary tract. BoNT/A consists of a heavy and a light chain linked by a disulphide bond. As the BoNT/A gene may differ in nucleotides, four A subtypes have been classified based on up to 15% variation in the amino acid composition. The amino acid sequence of the BoNT/A light chain constitutes a catalytic Zn-dependent endopeptidase domain. The heavy chain is subdivided into three portions (HN, HCN, and HCC), but only two have clear functions. The HCC is associated both with the recognition of neuronal-specific areas and toxin internalization. The HN is responsible for translocation of the light chain from synaptic vesicles into the neuronal cytoplasm. In the synaptic cleft BonT/A binds predominately to the isoform C of the synaptic vesicle protein or SV2 (SV2C) [Dong et al., 2006, Dolly, 2014] or to the FGF Receptor 3 [Jacky et al., 2013] by the heavy chain. The importance of the latter toxin acceptor is still unclear.

BoNT/A initially binds polygangliosides, resulting in an increased density of the toxin on the neuronal membrane **(Fig 17)**. This step increases the chance of heavy chain to interact with the protein acceptor SV2, predominately the isoform C (SV2C), expressed in the interior of the synaptic vesicles when they open on the neuronal surface to release the neurotransmitters [Dolly, 2014]. Then, internalization of the synaptic vesicles for recycling carriages BoNT/A into the nerve terminal (**Fig17).** Acidification occurring inside the synaptic vesicles leads to the separation of the two chains. The light chain passes into the cytosol, where it cleaves one of the attachment proteins involved with the mechanism of fusion of synaptic vesicles to the cytoplasmatic membrane necessary for neurotransmitter release. Attachment protein (SNARE or soluble N-ethylmaleimidesensitive fusion attachment protein receptor) include synaptosome associated protein 25 kD (SNAP 25), synaptobrevin (vesicle associated membrane protein -VAMP) and syntaxin. BonT/A cleaves SNAP-25 in the 9-terminal amino-acids of the C terminal of the protein rendering the SNARE complex inactive [Humeau et al., 2000; Dolly, 2014].

In the human bladder SV2 and SNAP-25 expression has been demonstrated in parasympathetic, sensory fibers and sympathetic [Coelho et al., 2010]. By immunohyscochemistry the expression is by far stronger in parasympathetic nerves. [Coelho et al., 2010].

Following BoNT/A injection in the guinea-pig bladder wall almost all parasympathetic fibers express cleaved SNAP-25 [Coelho et al, 2012a]. The evidence of such cleavage explains the inhibition of ACh release from the rat bladder during electrical stimulation [Smith et al, 2003]. In accordance, the bladder of both normal and SCI animals treated with BoNT/A exhibit less bladder contractions during electrical stimulation of spinal nerves [Ikeda et al., 2012]. Thus, impairment of acetycholine (Ach) release from cholinergic motor nerve endings in the detrusor mimic those described in the striated muscle [Humeau et al., 2000]. However, subsequent events, degeneration of cholinergic endings associated with the accumulation of non-released synaptic vesicles followed by axonal sprouting and cholinergic nerve regeneration reported in the striated muscle [de Paiva et al., 1999] could not been documented in the detrusor [Haferkamp et al., 2004].

About half of the peptidergic sensory fibers of the human bladder express SV2 and SNAP25 [Coelho et al, 2010]. Following BoNT/A injection in the bladder guinea pig they express Cleaved SNAP-25 [Coelho et al, 2012a]. BoNT/A inhibits the spinal cord release of glutamate, substance P (SP) and CGRP from sensory nerves [Purkiss et al., 2000; Aoki et al., 2005; Meng et al.,2007] as well as the release of neuropeptides at the peripheral extremities [Rapp et al., 2006; Lucioni et al, BJU Int, 2008, Ikeda, et al, 2012]. In addition, BoNT/A compromises the trafficking of TRPV1 from intracellular vesicles to the neuronal membrane, as this process is also dependent on SNARE proteins [Morenilla Palao et al. 2004, Shimizu et al, 2012] (**Fig 18**). This explains the decrease in the suburothelial immunoreactivity for TRPV1 (and by analogy P2X3) observed in the human bladder after the toxin injection [Apostolidis et al., 2005]. All these mechanisms may contribute to the observation that BoNT/A reduces firing in bladder afferents [Ikeda et al., 2012].

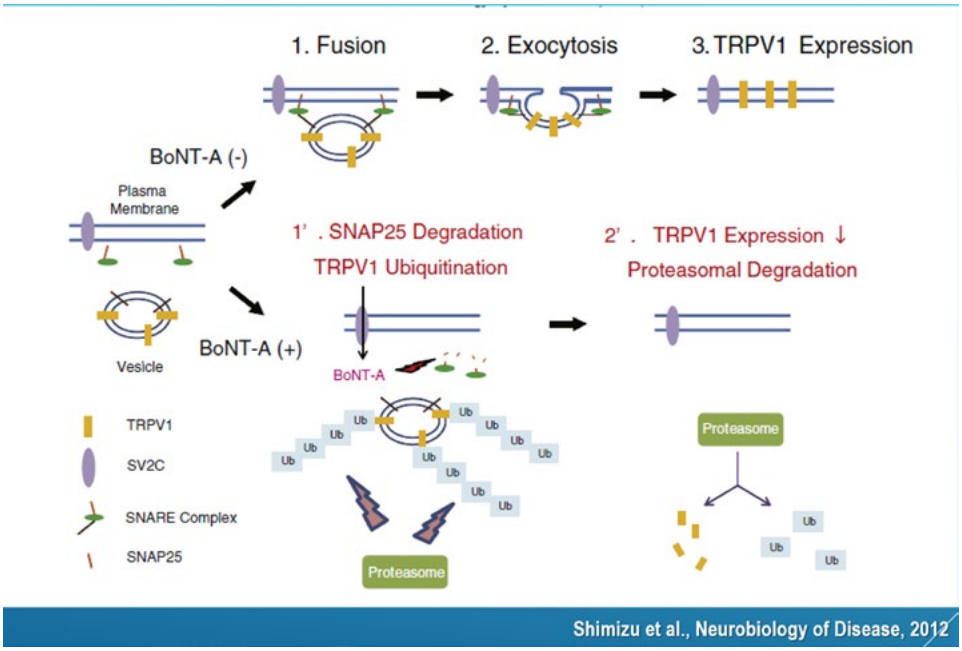

Figure 18: Schematic model of the mechanism by which BoNT-A reduces TRPV1 expression. From Shimizu et al., Neurobiol Dis. 2012 Dec;48(3):367-78

Human bladder sympathetic fibers express SV2 and SNAP-25 [Coelho et al, 2010]. This observation agrees with a decrease in noradrenaline release from the bladder tissue in rats after BoNT/A application [Smith CP et al., 2003].

In the human bladder urothelium SV2 and SNAP-25 expression could not be demonstrated by immunohistochemistry [Coelho et al., 2010]. Immunoblot analysis showed SNAP-25 but not SV2 expression in isolated human urothelial cells. [Hanna-Mitchell et al., 2013]. Another SNARE protein, SNAP 23 was identified in the human urothelial cells by the two methods [Hanna-Mitchell et al.,2013, Cruz, 2014]. BonT/A has been shown to inhibit ATP release from the urothelium in animal models of spinal cord injury [Khera et al.,2004; Vemulakonda et al, 2005, Smith et al., 2008]. BoNT/A does not alter the expression of urothelial sensory protein expression in SCI patients despite inducing a relevant clinical improvement [Chen et al, 2019].

Cleaved SNAP-25 appears rapidly after BoNT/A injection in the guinea-pig bladder, where a robust expression of the inactive protein could be detected already at 12 hours and a maximum intensity was observed at 24 hours. Almost all parasympathetic fibers, both preganglionic and postganglionic, expressed the cleaved SNAP-25 while only half of the sensory and sympathetic fibers expressed the cleaved protein at the same time point. In guinea pigs cleaved SNAP-25 expression was not observed in urothelial cells. [Coelho et al., 2012a; b].

Although all these works and many years of clinical use in multiple clinical conditions suggest a peripheral action of BoNT/A when injected in the bladder [Cruz, 2014]

some studies have proposed that BoNT/A may not be confined to nerve terminals at the injection place. Rather, it was suggested that BoNT/A activity can spread to central neurons by retrograde transport along the first-order neurons and then transferred to second order neurons contacting with the former (transcytosis). However, a study using a highly selective antibody for the cleaved protein (SNAP25-197) combined with markers for Central Nervous System neurons or glial cells contacting the first order neuron excluded that possibility [Cai BB et al, Neuroscience 2017]

Myofibroblasts form a syncytium through extensive coupling via the gap-junction protein connexin 43 and have close contacts with sensory nerves. These facts led to the hypothesis that myofibroblasts act as modulators of bladder activity [Wiseman et al., Apostolidis et al., 2006]. Nevertheless, BoNT/A does not change the expression of connexin 43, [Roosen et al, 2009] questioning an effect of the toxin through the myofibroblasts.

A decrease of the urinary and tissue levels of Nerve Growth Factor (NGF) and Brain-derived Neurotrophic Factor (BDNF) were found in some studies [Giannantoni et al.,2006; Liu et al., 2009, Pinto et al., 2010, Philippova et al, 2020] and not in others [Richter et al, 2017] As neurotrophins have paramount roles for growth, maintenance and plasticity of peptidergic sensory nerves, these findings may point toward another mechanism for BonT/A action in the bladder sensory function.

BonT/A has a long-lasting effect due to the persistence of the enzymatic capacity of the light chain to cleave SNAP-25 given by two leucines amino-acids near its C terminus [Wang et al., 2011]. In the bladder, the duration of the effect surpasses that observed in skeletal muscle. In NDO patients cleaved SNAP-25 was detected up to 11 months after BoNT/A injection [Schulte-Baukloh et al., 2007]. The mechanism for such a long persistence remains unclear. The combined impairment of pre and post- ganglionic parasympathetic neurons, urothelial cells and sensory fibers may however contribute to it.

There is no evidence that repeated injections of BoNT/A into the detrusor muscle cause inflammatory infiltrates, fibrotic activity or apoptosis within the bladder wall [Compérat et al., 2006, Apostolidis et al., 2008, Kessler et al. 2010]. Rather the reverse, one study

demonstrated that NDO patients treated with BonT/A had less fibrosis than non-treated patients [Compérat et al., 2006]. An eosinophilic infiltrate found in bladder biopsies of patients after multiple treatments did not have a clear explanation [Apostolidis et al., 2008].

8.1.2. BoNT/A injection protocols in the bladder.

For bladder injection in NDO and OAB patients, the licenced method of administration is derived from the procedures and doses described in the pivotal studies and is restricted to OnabotA. [Cruz et al, 2011; Ginsberg, 2012, Chapple et al., 2013; Nitti et al., 2013]. AbobotA and IncobotA did not receive yet a specific licence which means that their use is still off-label. The minimum interval for re-injection should be 12 weeks [Cruz et al, 2011; Ginsberg, 2012, Chapple et al., 2013; Nitti et al., 2013].

For NDO patients OnabotA 200 U diluted in 30 ml of normal saline should be distributed by 30 injections points above the trigone above the trigone (1ml saline containing 6.66 U/ml) [Cruz et al., 2011; Ginsberg, 2012]. Concerning OAB, a dose of OnabotA 100 U should be distributed by 20 intradetrusor injections of 0.5 ml each, also above the trigone [Dmochowski et al., 2010c, Chapple et al., 2013; Nitti et al., 2013]. During reconstitution the vials should be stirred but not shaken, as strong movements may break the BoNT/A molecule at the disulphide bond. The injection technique follows therefore that described in the historical descriptions of OnabotA in NDO patients [Schurch et al., 2000 a, b]. Rigid or flexible cystoscopes [Harper et al., 2003], variable brands of flexible 6 Fr injection needle of adequate length and a local anaesthetic agent (4% lidocaine whether or nor alkalinized) [Harper et al., 2003, Pereira-Silva et al, 2020] are used for injections. Colouring the fluid with methylene blue does not increase injection precision and clinical outcomes [Szczypior et al, 2019]

In NDO patients, despite the evidence of the phase 3 trials, Onabot 300 U remained in use, in particular when 200 U failed to produce the desirable effect [see Mangera et al., 2011]. Although the use of high doses might be tried off-label in selected cases one must realize that recent retrospective analysis of NDO cohorts did not find any difference in episodes of bladder evacuation or incontinence episodes in NDO patients that reduced OnabotA dose from 300 U to 200 U [Krebs et al, World J Urol, 2021]. An exception might be SCI or Myelomeningocele patients with low compliant bladders, a low percentage of whom were reported to have symptomatic improvement from a rescue treatment with Onabot 300 U [O´Connor et al, 2020].

AbobotA administration used in several institutions was applied in the bladder wall by technique similar to that licenced for OnabotA. Doses ranging between 500-1000 U of abobotA were injected in 20 above the trigone. The volume of saline at each injection site is commonly 1 ml but volumes so low as 0.25 ml per site were also used [del Popolo et al., 2008; Grise et al., 2010]. Denys et al. [2017a] compared the administration of AbobtA 750 U in 15 points (n=23) and 30 points(n=24) in NDO patients. The reduction on incontinence episodes and improvement of urodynamic parameters were similar for both methods. Two large phase III RCT used 30 injection of 0.5 ml into the detrusor muscle above the trigone to distribute abobotA 600 U, 800 U or saline [Kennelly et al, 2022].

IncobotA detrusor injection was reported in 17 NDO males in doses of 200 and 300 U (10 U/ml). The 20 or 30 injections were delivered throughout the whole bladder, including the trigone. The clinical efficacy was promising and complications were rare, justifying a larger clinical trial [Asafu.Adjei et al, 2020].

The potential advantages of injections in the trigone, the reduction in the number of injection points and, most important, the investigation of methods of administration that might allow the application and passage of BoNT/A through the urothelium have been a matter of study.

The rationale for injecting the trigone is higher density of sensory fibers in this area [Coelho et al, 2017] which makes this injection site particularly relevant for OAB and IC/BPS patients who have an important sensory component in their complains. The suggested risk of ureteral reflux after injecting bladder trigone was never demonstrated, whether OnabotA, abobotA or IncobotA was used [Karsenty et al., 2007; Citeri et al., 2008; Mascarenhas et al., 2008; Pinto et al, 2010, Asafu.Adjei et al, 2020]. A small trial randomised 22 IDO patients to receive abobotA 500 U administration in 20 injections (1ml each) sparing the trigone against 15 off the trigone plus 5 injections in the trigone [Manecksha et al., 2012]. The change from baseline of the OABSS score was greater in the trigone injected group while the mean postvoid residual volumes and clean intermittent self-catheterisation rates were similar between the two groups. One study compared 10 trigonal injections versus 40 detrusor or suburothelial injections of 100 U of OnabotA in IDO patients [Kuo, 2007a]. The 40 detrusor injections brought a more robust and lasting symptomatic improvement. The trigone-only injection protocol was the less effective and durable of the three, although the risk of urinary retention was non-existent [Kuo, 2007a].The suburothelial protocol brought intermediate results, worse than the detrusor but better than the trigone only technique [Kuo, 2007a]. In patients with BPS/IC, onabotA 100 U was injected in 10 sites in the trigone of patients with and without Hunner's lesions. This protocol was not associated with urinary retention or clinically relevant increase of PVR [Pinto, 2010, 2013]. Small RCT comparing OnabotA100 U vs placebo (saline) trigonal injections in BPS/IC patients favoured the toxin group [Pinto et al, 2018]. One study investigated the effect of detrusor plus trigonal injections of OnabotA in SCI patients. A total of 120 patients were randomised to receive 240+60 U in the detrusor plus trigone or 300 U only above the trigone. Incontinence episodes, volumes per void and detrusor leak point pressure improved in both groups although with a small but significant advantage in the group that received the toxin in the two locations [Chen et al, 2020]

The consequences of reducing the number of injection sites while increasing the dose in each injected site has been investigated under the premise that less sites facilitate the administration and may reduce UTIs. One small study in NDO patients concluded that 10 injection sites was quicker and less painful than 30 injections points to deliver OnabotA 300 U and that efficacy of the two procedures was equivalent at 24 weeks [Karsenty et al. 2005]. Interestingly, 30 injection points (30 ml of fluid in total) or 10 injection points (10 ml of fluid in total) caused a similar distribution of the fluid, as determined by MRI, covering 1/3 to 1/4 of the detrusor, respectively [Mehnert et al, 2009].

Two studies investigated further reduction in the number of injection sites in a mixed . IDO and NDO population under treatment with OnabotA ranging between 100 untill 300 U. Injection of the toxin in 1 or 3 injection sites in the posterior bladder wall used a reconstitution volume of 1ml for each 20 U. Avallone et al, [2017]. The other study divided the chosen dose by 3-4 injections at the equatorial line of the bladder of 2 ml each [Martinez-Cuenca et al, 2020]. Administration was easy and the clinical effect was good with a duration exceeding 30 weeks in both studies. However, UTIs occurred in 11.1% in the first and in 24% of the patients in the second study.

Another variable in the injection protocol is the volume of the saline used to reconstitute the toxin. Most studies used 1.0 [Cruz et al., 2011; Ginsberg et al., 2012] or 0.5 mL [Grosse et al., 2005; Schulte-Baukloh et al., 2003, Chapple et al, 2013, Nitti et al, 2013] but volumes of 0.2 mL [Kuo et al., 2004], 0.25 ml [Grise et al., 2010] or even 0.1 mL per injection site [Rapp et al, 2004]. Nevertheless, an experimental study demonstrated the amount of cleaved SNAP-25 induced by a fixed amount of OnabotA was directly related with the volume of the injection [Coelho et al., 2012a]. Thus, more controlled studies designed to compare different number and locals of injection and the volume of each injection are necessary.

BoNT/A does not cross the rat urothelium if instilled in the bladder [Coelho et al., 2012a], obliging caregivers to use bladder wall injections. Therefore, transporters or facilitators for the passage of the toxin are necessary if the injections are to be avoided. For the interested reader we recommend a thorough review of potential methodologies by Tyagi et al, [2017].

Onabot/A instillation in the bladder encapsulated in liposomes was shown to overcome the urothelial barrier in rats and cleave SNAP-25 in nerve terminals [Chuang et al., 2009]. Recently the lipossome encapsulation technology to deliver OnabotA was tested in humans. A small group of 24 patients were randomized to intravesical instillation of Lipotoxin containing 80 mg liposomes and 200 U BoNT-A or normal saline. At 1 mo after treatment, mild improvements in urinary frequency and in urgency episodes were reported in the lipotoxin group. Although no adverse events were reported, the duration of the effect was short lasting [Kuo et al., 2014]. In a RCT with IC patients, liposomal formulated OnabotA 200 U did not show any superiority over saline administration [Chuang and Kuo, J Urol, 2017].

Another form of administration investigated used hydrogel to promote a slow-release of the toxin on the urothelium. A TC-3. OnabotA mixture was assessed in BPS/IC patients. The mixture was safe, but efficacy was short lasting [Rappaport et al, 2018]

Electromotive administration (EMDA) may also help to carry the large botulinum toxin molecule across the urothelium, In 15 children with NDO due to myelomeningocele, a 10F indwelling catheter containing a silver spiral electrode was placed in the bladder, after providing a local transurethral anaesthesia with 2% lidocaine. The bladder was filled with saline and 10 U/kg of abobotA was added. A maximal current of 10 mA (100 mA increment/s) for 15 minutes was applied using abdominal pads [Kajbafzadeh et al., 2011, see also the video demonstration by Sharifi-Rad et al, 2019]. Skin erythema and burning sensation are the only side effects reported with EMDA of the toxin.

Low energy shock waves were investigated in 15 OAB patients to administer OnabotA 100 U previously instilled in the bladder in a volume of saline equivalent to half a bladder capacity. O total of 3000 shocks were delivered during 10 minutes in the supra-pubic area. An improvement in the OAB symptom Score was maintained for 2 months [Nageib et al, 2019].

In the large RCT with NDO antibiotic prophylaxis was used [Cruz et al., 2011; Ginsberg et al., 2012]. However, as many of injected SCI patients relied on some type of bladder catheterisation and presented chronic bacteriuria, the relevance of antibiotic prophylaxis was unclear. In 154 SCI patients undergoing a total of 273 treatments with onabotA bacteriuria was found in 73% (200/273) Those without clinical signs of UTI underwent injections without antibiotic prophylaxis. Following treatment, symptomatic UTI occurred in 7% (5/73) of cases with sterile urine culture and in 5% (9/200) with bacteriuria. These results suggest that routine antibiotic prophylaxis is not required prior to botulinum toxin injection in asymptomatic SCI patients [Leitner et al., 2016]. In patients non-catheterizing at treatment, however, the high risk of UTI recommends that antibiotic prophylaxis should be maintained together with an exclusion of active UTI at the moment of injection. UTI screening after each BoNT/A bladder treatment remains justifiable taking in consideration the high incidence of UTIs in in non-self-catheterizing NDO patients (Mustiple sclerosis, Parkinson´s disease).

For OAB, in large RCT (Tincello et al, 2012, Chapple et al, 2013, Nitti et al, 2013) antibiotic prophylaxis was not obligatory. In a retrospective study of 212 patients, mostly non-neurogenic, the incidence of UTIs after 335 injection cycles do not support the practice of obtaining a preprocedure urine dip in asymptomatic patients [Derisavifard et al, 2020]. However, in real life many centers maintain the use of antibiotic prophylaxis [Hamid et al, 2021]. A retrospective study in more than 100 women concluded that starting antibiotics 1 day before the injection and prolonging for 4 days decreased incidence of UTIs to 22% [Bickhaus et al, 2020].

8.1.2.1. Effect of Bont/A in NDO adult patients.

8.1.2.1.1. BONT/A in SCI and MS

After a small exploratory RCT [Schurch et al., 2005], two large phase 3 studies, as part of the Dignity program investigated the efficacy and safety of Onabot A, 200 U and 300 U against placebo in about 700 patients with NDO. Etiology included spinal cord injury below T1 or multiple sclerosis with an Expanded Disability Status Scale (EDSS) ≤ 6.5 [Cruz et al., 2011; Ginsberg et al., 2012]. Primary outcome measure was the change from baseline in week episodes of urinary incontinence at week 6 after treatment. Secondary outcome measures included the change from baseline in maximum cystometric capacity, maximum detrusor pressure during first involuntary detrusor contraction and quality of life using the I-QOL total score. Both studies yielded similar findings and indicated that 200 and 300 U provided the same effect and had the same duration of action in MS and SCI patients. Further details of the two studies are shown below and in **Fig 19.** In the study by Cruz et al, [2011] the reduction in UI during week 6 was -21.8 in onabotA 200U, -19.4 with 300U and -13.2 with placebo, with 38.0%, 39.6% and 7.6% of patients fully continent, respectively. The Ginsberg study [2012] reported -21, -23 and -9 incontinence episodes per week after 200 and 300 or placebo, respectively. Furthermore, 36% and 41% of patients in the 200 and 300 U groups, respectively, achieved dry status, contrasting with 10% in the placebo arm. Patients could request a retreatment 12 weeks after initial treatment. Median time for saline treated patients was about 90 days days and 250 to 300 days for those treated with 200 or 300 OnabotA, without differences between the two doses. No differences were found between patients with SCI or MS in terms of clinical response to OnabotA. The two doses tested improved similarly detrusor pressure and maximal cystometric capacity. The proportion of patients without IDC was around 60% after OnabotA 200 and 300 groups but only 17.4% after placebo [Cruz et al., 2011; Ginsberg et al., 2012]. Both MS and SCI patients had a significant improvement in quality of life after OnabotA treatment [see also Chancellor et al., 2013]. The improvement of I-QOL total score in MS patients was similar whether patients required or not clean intermittent catheterization (CIC) after toxin administration. Maximal detrusor pressure also decreased significantly [Ginsberg et al., 2012]

When pooled data were analysed by etiology, both MS and SCI patients treated with 200 and 300 U had a greater decrease in urinary

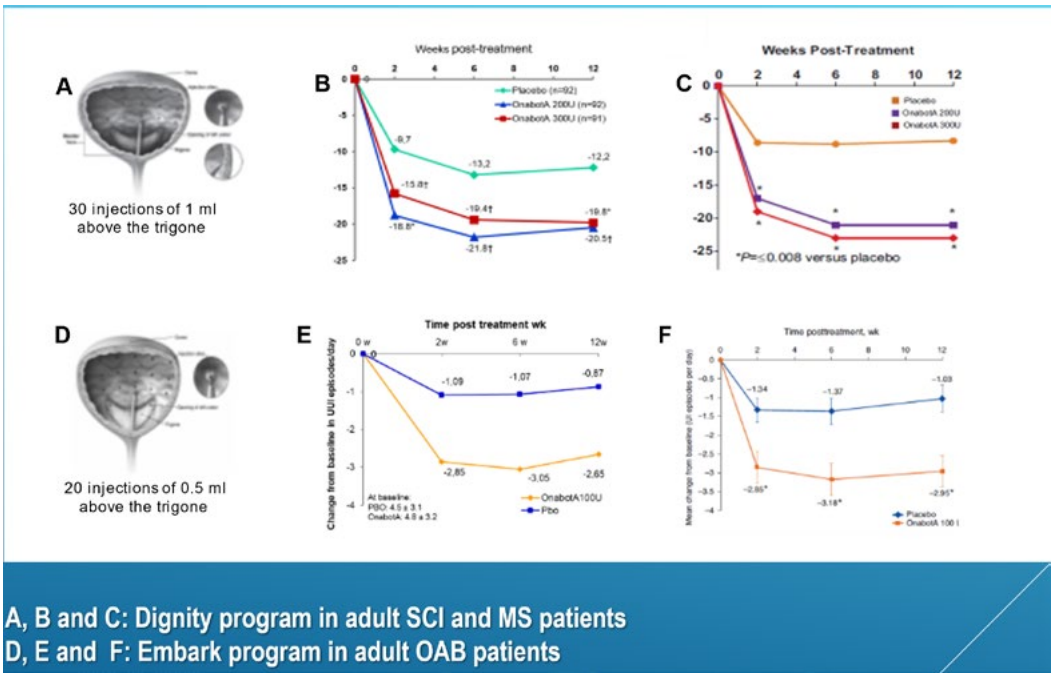

Figure 19: Distribution and effects of OnabotA injections in the detrusor above the trigone for NDO and OAB. From Cruz et al., Eur Urol. 2011 Oct;60(4):742-50, Ginsberg et al., J Urol. 2012 Jun;187(6):2131-9, Chapple et al., Eur Urol 2013, Nitti et al., Urol 2013 Jun;189(6):2186-93

incontinence episodes and more full dryness after treatment than those treated with placebo [Ginsberg et a.l, 2013]. The change in the number of voluntary voids per week was examined only in MS patients, the majority of whom did not use intermittent self-catheterization at study entrance. Following onabotA 200 U treatment, a decrease from baseline of 2 micturitions per day at week 6 and around 3 micturitions per day at week 12 was detected [Ginsberg et al., 2013].

The improvement in incontinence episodes, the proportion of patients fully dry, the urodynamic improvement and median time for re-treatment were similar in anti-cholinergic user and non-user patients [Ginsberg et al., 2013], supporting previous suggestions that SCI and MS patients might stop anti-muscarinic medication after BoNT/A injection [Reitz et al. 2004a, Grosse et al. 2005].

The symptomatic improvement brought by BoNT/A injection in the bladder does not coincide with the moment of injection. In a small open-label prospective study some improvement in urgency, nocturia and frequency could already be demonstrated at 2 days [Kalsi et al., 2008]. In large RCT with SCI and MS patients treated with OnabotA, 200 or 300U, significant decrease in the number of incontinence episodes over placebo were first detected at week 2 after injection [Cruz et al., 2011, Ginsberg et al, 2012].

Doses of OnabotA below 200 U were tested in patients with SCI below T1. Patients (n= 73) with NDO and urinary incontinence episodes received 30 intradetrusor injections above the trigone of onabotA 50 U (n = 19), 100 U (n = 21), 200 U (n = 17) or placebo (n = 16). A linear dose response for incontinence episodes/week was identified with a maximal effect detected with 200 U and no effect observed in patients treated with 50U [Apostolidis et al., 2013]. In real life practice the reduction of OnabotA dose from 300 U to 200U did not decrease clinical and urodynamic efficacy in SCI patients [Krebs et al, 2020]

Antibody formation against OnabotA were not detected during the first treatment cycle of randomised clinical trials [Cruz et al, 2011; Ginsberg et al., 2012]. However, in a large cohort of 414 patients with SCI/disease, 14 tested positive and highly positive [Tiburtius et al, 2020] and seroconversion was associated with a shorter duration of toxin efficacy (< 7 months).

A consequence of BONT/A treatment in NDO patients is the decrease in the incidence of severe urinary tract infections. In 30 SCI patients Gamé et al. [2008] observed that the number of pyelonephritis, orchitis and prostatitis in the 6 months before OnabotA 300U, 1.75±1.87 per patient, decreased to 0.2±0.41 in the first 6 month after treatment. In 17 SCI patients that received OnabotA injections for a period of 6 years, the number of urinary tract infection at the sixth year was 1.8±0.5 per year, significantly lower than at baseline, 6.7±2.1 [Giannantoni et al., 2008]. In a retrospective review of 214 NDO patients followed in 7 German centers, the rate of urinary tract infections in 12 months preceding and in the 12 months following OnabotA was 68% and 28%, respectively [Boy et al., 2008]. The reason for these findings is unclear but may lie in a decreased maximum detrusor pressure resulting in less bladder wall ischemia and vesico-ureteral reflux [Wefer et al., 2009].

Multiple Sclerosis patients represent a particular subgroup of patients in whom a careful analysis of the efficacy and safety of BoNT/A requires additional attention. First, OnabotA does not increase the risk of MS exacerbation. The annualized event rate in the phase 3 trials was 0.36, therefore in the lower range of the annualized rate known for the general MS population, that varies between 0.2 and 1.2 [Silva et al., 2015]. Second, if voluntary voiding is present before treatment the risk of de novo CIC might represent a drawback. In cohort studies that used OnabotA 300 U, while this dose was effective in improving or curing urinary incontinence, most patients had to initiate CIC [Kalsi et al., 2007; Khan et al., 2011]. The large phase 3 studies [Cruz et al., 2011; Ginsberg, 2012] showed

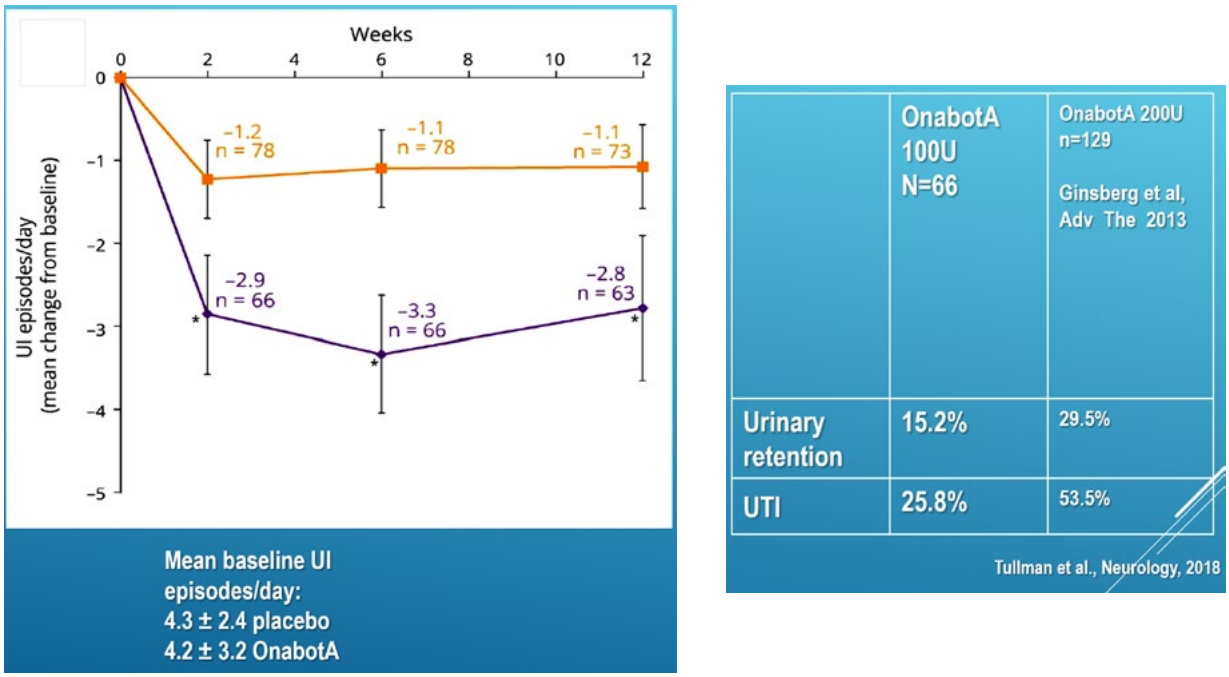

Figure 20: Onabotulinum toxin A 100 U in MS patients with spontaneous voiding is associated with a significant reduction in daily UI and less AE (AUR, UTI). From Tullman et al., Neurology. 2018 Aug 14;91(7):e657-e665

that 200 and 300 had the same efficacy in terms of continence and duration of effect. However, after 200 U about 1/3 of the MS patients started de novo CIC and after 300 U that number exceeded 40%.

Non-randomised studies suggested that OnabotA 100 U might still provide good efficacy while reducing the risk of CIC in non-catheterising MS patients [Mehnert et al., 2010]. The efficacy and safety of this strategy was confirmed by a placebo controlled randomised trial [Tullman et al, 2018, see **Fig 20**]. Injections of 1ml each were carried out in 30 places above the trigone containing onabotA (n=66) or saline (n=78). OnabotA 100U significantly improved UI episodes/day compared with placebo (-3.3 vs -1.1; P<.001) and improved all the key urodynamic parameters like maximal cystometric capacity and maximal detrusor pressure. Improvements in I-QOL total score with onabotA were 4 times higher than placebo. Median duration of effect was 11.9 for OnabotA and 2.9 months for placebo (P<.001). The risk of UTI (25.8%) and de novo CIC (15.2%) after 100 U OnabotA was approximately, half of that observed with 200 U of toxin injections [Tullman et al, 2018].

Although not officially approved for NDO, abobotA has been the object of investigation in a few small comparative clinical trials and from two large phase III trials.

The pooled results from the first treatment cycle of the first two large phase III randomized, double-blind studies are now available [Kennely et al, 2022]. The trials enrolled almost 500 SCI and MS patients with NDO and incontinence regularly performing CIC and refractory to oral medication. Treatment consisted of 30 injection of 0.5 ml into the detrusor muscle above the trigone of abobotA, in a total dose of 600 U or 800 U. One group received only saline. Injections were performed under prophylactic antibiotic. At week 2, 6 and 12 after injections mean incontinence episodes/week were significantly and similarly reduced in both abobotA groups. The reductions at week 6 were -22.7, -23.6 and -12.7 after 600 U, 800 U and saline respectively. Approximately one third of patients in both abobotA groups reported no incontinence episodes compared with only 3% after saline. A significant clinically meaningful improvements in I-QoL increase of bladder capacity and decrease of detrusor pressure occurred with both abobotA doses versus saline [Kennelly et al, 2022].

Several smaller studies had been conducted before. A total of 31 NDO patients due to spinal cord injury, myelomeningocele, trauma at birth, multiple sclerosis and myelitis to intravesical injections of abobotA 500 U or placebo [Ehren et al., 2007]. Patients in the abobotA arm had a significantly higher cystometric capacity at 6 and 12 weeks, lower maximum detrusor pressure and episodes of urinary incontinence and less consumption of antimuscarinic drugs. Efficacy and safety of abobotA were, additionally, investigated in NDO patients that had abandoned anticholinergic therapy. Two doses, 500 U (n = 39) or 750 U (n = 38) were compared [Grise et al, 2010]. Complete continence at day 30 was observed in 22 patients (56.4%) and 28 patients (73.7%) receiving 500U or 750U. The median delay in the reappearance of leakages was 168 days. Although there was a trend towards a greater improvement with 750 U, no statistically significant differences in terms of clinical and urodynamic variables between the treatment groups were found. Excellent tolerability was reported for both doses.

A single-center retrospective study investigated 750 U intradetrusor injection of abobotA in 81 consecutive patients performing CIC. Six weeks after the first injection, the success rate, defined as a combination of no incontinence episode, a number of catheterizations <8 reported in a 3-day bladder diary and the lack of detrusor overactivity, was reported in 64.2 %. Mean reinjection number was 3.9 and mean interval between reinjection was 8.8 ± 3 months. The clinical efficacy rate after each reinjection (up to fourteen) was at least 86.7 % [Peyronnet et al., 2016].

A phase IIa, enrolled 47 patients with NDO due to spinal cord injury (SCI) or multiple sclerosis (MS). Patients were treated with 15 intra-detrusor injections of abobotA 750 U or the equivalent placebo (n = 16 and 7) or 30 injections of AbobotA 750 U or the equivalent placebo (n = 17 and 7). Change from baseline in mean number of daily incontinence episode frequency at 12 weeks, for abobotA and placebo, respectively, were -3.2 and -1.7 in the 15 injections group and -3.2 and -2.6 30 injections group. Statistically significant improvements in maximum cystometric capacity, maximum detrusor pressure and volume at first contraction were reported in the toxin groups compared to placebo [Denys et al., 2017a].

Incobotulinum toxin A (IncobotA) for NDO was never object of placebo-controlled studies. A small cohort of 17 SCI patients. There were improvements in average daily pads (4.5 to 3.3), daily urinary frequency (9.4 to 4.6), daily incontinent episodes (2.5 to 0.4), CIC volumes (400 to 550 mL) and hours in between CIC (3.6 to 5.2). There were no documented adverse events. Nine of 17 patients (53%) were dry at their first postoperative visit [Asafu-Adjei et al, 2020].

8.1.2.1.2. BONT/A in other neurological conditions

In Parkinson´s disease, a retrospective review of a small cohort of 24 patients treated with OnabotA 100 U (20 injections of 5U/0.5 ml throughout the bladder including the trigone) showed improvement of LUTS in 19 and a complete resolution in 7 cases. The average post-void residual (PVR) increased significantly after the first injection from 17.6 to 125.3 mL Higher pre-injection PVR and male sex decreased the probability of symptomatic improvement and increased the risk of incomplete bladder emptying. After 49 injections, first and subsequent, 5 patients used CIC [Vurture et al, 2018]. A systematic review of 4 small cohorts published before 2018 showed that OnabotA 100 U and 200 U caused robust improvement and LUTS, including a decrease in day and night-time frequency. Although a PVR increase was concluded, no cases of urinary retention were reported [Hajebrahimi et al, 2019]

Concerning adults with myelomeningocele (MMC) A total of 125 patients under onabotA or abobotA treatment (561 intradetrusor injections in variable doses in 14 centers) were retrospectively investigated. The resolution of urinary incontinence occurred in 73.5%. All urodynamic parameters improved significantly compared to baseline, including maximum detrusor pressure (-12 cm H2O), maximum cystometric capacity (86.6 ml) and compliance (8.9 ml/cm H2O). Three cases of muscular weakness were recorded. The success rate was significantly lower in patients with poor compliance while female gender and older age were predictors of success [Peyronnet et al, J Urol, 2018].

OnabotA was successful applied to treat NDO due to transverse myelitis, the criteria for toxin application being the lack of response to oral therapy [Knight et al, 2021]. BoNT/A may also improve storage symptoms and continence in patients who did not respond satisfactory to bladder augmentation. In a small number of patients the toxin was injected both in the detrusor and in the intestinal augment [Martinez et al, 2020].

8.1.2.2. Effect of BONT/A in OAB adult patients

8.1.2.2.1. Effect of BONT/A in predominant OAB female population

The enthusiasm of investigators rapidly produced a reasonable number of pilot studies investigating BoNT/A in patients with IDO refractory to antimuscarinics. Although proper dose-escalating studies capable of defining ideal doses were lacking, investigators opted for the administration of BoNT/A in doses smaller than those initially used in NDO. That is the reason why most pilot studies used either onabot 200 U or abobot 500 U [see also Mangera et al, 2011 and 2014 for historical review] and 4 RCT trials compared onabotA 200 U against placebo [Sahai et al., 2007; Brubaker et al., 2008; Flynn et al., 2009; Tincello et al., 2012]. A small open-label trial showed that urgency, nocturia and frequency improved as soon as 4 days after Onabot 200 U in OAB patients. [Kalsi et al., 2008].

A high incidence of voiding dysfunction associated with the use of onabotA 200U in OAB patients led to the use OnabotA 100 U in one large cohort of 100 patients [Schmid et al, J Urol 2006]. Treatment remained highly effective, and incontinence and urgency sensation disappeared in 86% and 82% of patients, respectively, during an average period of 6 months. Temporary urinary retention only occurred in 4% of the cases, with additional 15% reporting moderate voiding difficulties [Schmid et al, J Urol 2006].

Following the pilot studies two large well designed dose escalating placebo-controlled studies [Dmochowski et al. 2010, Denys et al. 2012] investigated the ideal dose of onabotA in OAB. Dmochowsky et al. [2010] enrolled 313 OAB patients experiencing 8 or more urinary urgency incontinence episodes per week and 8 or more micturitions daily at baseline. Patients were randomized to 50, 100, 150, 200 or 300 U intradetrusor OnabotA, or placebo. Durable efficacy was observed for all groups treated with 100 U dose or higher but in dose response curve doses greater than 150 U contributed minimally to the symptomatic improvement. As the use of CIC was also dose dependent, 100 U offered the best balance between efficacy and safety. Denys et al. [2012] randomised 99 OAB patients to receive a single injection of either placebo or onabotA 50 U, 100 U or 150 U. A >50% improvement versus baseline in urgency and urge urinary incontinence (UUI) in 65% and 56% of patients who respectively received 100 and 150 U. Complete continence was observed in 55% and 50% patients after 100 U and 150 U. The dose of 100 U seemed to offer the best balance between efficacy and increase of PVR.

A few additional studies contributed to defined 100 U as the ideal dose for refractory OAB treatment. Cohen et al. [2009] randomized 44 OAB-dry and wet patients to receive 100 U or 150 U. No significant differences in clinical, QOL improvement or urodynamic outcome measures were noted between the two doses. Altaweel et al. [2011] randomized 11 patients for onabotA 100U and 11 patients to onabotA 200U. No clinical or urodynamic differences were detected between the 2 groups at 3 months follow-up. Urinary retention occurred in 2 patients in the 200 U and in 1 patient in the 100 U arm.

Data from four large placebo-controlled studies and one large observational study are available. Concerning randomised clinical trials, Chapple et al, [2013] and Nitti et al, [2013] enrolled around 85 to 90% women, respectively. Yokyama et al, [2020] enrolled 75% women and Tincello et al, [2012] only women. In the real-life study by Hamid et al, [2021] 85% of the patients were women. So, the following data should be extrapolated to men with precaution.

In the two pivotal phase 3 studies patients were randomized to receive 20 injections of 0.5 mL each above the trigone, containing 5 U per injection with a total of 100 U or only saline [Chapple et al., 2013; Nitti et al., 2013]. These studies enrolled patients with idiopathic wet OAB with ≥3 urgency urinary incontinence (UUI) episodes over 3 days and ≥ 8 micturitions per day and a postvoid residual less than 100 mL who were inadequately managed by anticholinergics. The co–primary efficacy end points were change from baseline in the number of UI episodes and the proportion of patients with a positive

treatment response on the treatment benefit scale (TBS) at week 12. The changes in urinary incontinence are shown in **Fig. 19**.

The Chapple et al [2013] study randomized 277 patients to OnabotA and 271 for saline injection. At baseline the average number of daily UI episodes was above 5 per day. OnabotA significantly decreased UI episodes per day (-2.95 for OnabotA versus -1.03 for placebo). Significant reductions in frequency, urgency episodes per day and nocturia were also observed. Changes in TBS indicate that patients perceived a significant improvement in their condition (62.8% for OnabotA versus 26.8% for placebo; $p < 0.001$). Clinically meaningful improvements from baseline in all I-QOL and KHQ multi-item domains indicated positive impact on quality of life.

The Nitti et al. [2013] study randomised 280 for OnabotA and 277 for saline. In average patients experienced more than 5 episodes of UI per day. At week 12 there were greater decreases from baseline in the mean daily UI in the active group ((–2.65 for OnabotA and –0.87 for Sali, , $p < 0.001$). The percentage of fully dry patients at week 12, was 22.9% after onabotA and 6.5% with saline. The other key OAB symptoms, frequemcy, urgency and nocturia also improved after OnabotA. Of interest, all changes in OAB symptoms detected at week 12 were already present at week 2. A higher proportion of OnabotA treated patients reported a positive treatment response on the TBS vs those on placebo. Large, clinically significant improvements in all I-QOL and KHQ multi-item domain scores were noted after onabotA.

A pooled analysis of these two studies [Sievert et al., 2014] confirmed the effect on incontinence (-2.8 episodes episodes per day, 100% dry or with a 50% improvement in daily incontinence in 27.1% and 60.5%), a decrease in the number of episodes of urgency (-3.30 per day) and a decrease in urinary frequency (- 2.35 per day). The median time to request retreatment was 24 weeks after onabotA and 13 weeks after placebo. Furthermore, the pooled analysis showed that the number of previous anticholinergic drugs does not influence the outcome of OnabotA treatment. The number of prior anticholinergics also did not affect the improvement caused by OnabotA in urinary urgency incontinence episodes per day and in the number of micturitions per day. The rate of satisfaction was also independent from the number of previously used anticholinergic drugs. When analysing the efficacy of onabotA by the reasons why the anticholinergic treatment was stopped, insufficient efficacy or intolerable side effects, the symptomatic improvement and patient satisfaction after OnabotA was similar in the two subgroups and comparable with the results achieved by the overall pooled population [Sievert et al., 2014]. Another post hoc analysis [Drake et al. [2015] concluded that OnabotA is effective regardless of the grade of urinary incontinence at baseline. Patients with < 2, between 2 and 5 or > 5 UUI episodes per day had, respectively, decreases in incontinence episodes of 2.7, 3.0 and 3.8, and a 50% reduction in the urinary incontinence episodes in 56.6%, 66.5% and 56.7% of the patients.

Yokoyama et al [2020] carried out a phase 3, placebo-controlled trial in Japanese patients who were inadequately managed with overactive bladder medications (anticholinergics and/or β3 -adrenergic receptor agonists). Eligible patients were randomized 1:1 to receive a single dose of either OnabotA or placebo into the 20 detrusor sites above the trigone (n = 124 each). OnabotA was reconstituted in 10 ml. In the OnabotA group, there was a significantly greater decrease from baseline in the mean number of daily urinary incontinence episodes compared with the placebo group (2.16), and significantly greater improvement for all secondary end-points that included volume voided per micturition, other symptomatic measures (urinary urgency incontinence, micturition, urgency and nocturia) and patient-reported outcomes. In addition, the percentage of patients fully dry was 19% after OnabotA and 3% after placebo.

A fourth large placebo controlled RCT was conducted in 8 centers in UK (the RELAX study) and randomised a total of 240 women with refractory DO to receive OnabotA 200 U or placebo distributed by 20 bladder wall sites above the trigone (10 U/1ml) [Tincello et al., 2012]. Primary outcome was voiding frequency per 24 h at 6 months. Secondary outcomes included urgency and incontinence episodes and quality-of-life data. A total of 122 women received onabotA and 118 received placebo. Median leakage episodes were already significantly reduced by week 6 and at 6 months were 1.67 in OnabotA vs 6.0 in the placebo group. Continence was more common after OnabotA (31% vs 12%). Significant decreases also occurred in voiding frequency (8.3 vs 9.67) and in daily urgency episodes (3.83 vs 6.33). Quality of life scores were better in the toxin group.

Hamid et al [2021] carried the first large real-world study in 504 OAB patients receiving OnabotA 100U in everyday clinical practice conditions. Rigid cystoscopy and anesthesia or analgesia with intravesical local anaesthetic liquid/gel was generally preferred. Reductions in UI episodes/day from baseline were observed as early as week 1 (-2.4 ± 3.4) and were maintained at later time points (-3.0 ± 3.9 at week 12). A proportion of 25.5% of patients became completely continent within 1 week and 41.8% at week 12. Pad/liner and diaper usage decreased from 67.7/13.9 in the month prior to baseline to 29.9/4.4 and 23.6/4.3 in the month prior to week 12 and week 52, respectively. The number of patients maintaining oral OAB medication decreased to 5.8%, 2,4% and 1,8% by week 1, 12 and 20, respectively. The median time to patient request for retreatment was approximately 7 months.

Interestingly, a sub-analysis of the dose finding study for onabotA [Dmochowsky et al. [2010] concluded that successful OAB treatment is not related with the existence of detrusor overactivity [Rovner et al., 2011]. Likewise, in a cohort of 5 male and 27 female patients with OAB and without DO, improvement in frequency and urinary incontinence was observed after treatment with onabotA, 100 and 150 U [Kanagarajah et al., 2012]. Thus, in clinical practice there is little reasoning to perform routinely invasive urodynamic tests before recommending OnabotA administration to subjects with OAB symptoms refractory to oral medication.

Studies with AbobotA in OAB are scarce. A prospective study randomised 21 female OAB patients to receive 300 or 500 U of AbobotA injected into 30 sites above the trigone [Sa-Dantas-Bezerra et al, 2018]. From baseline to 12 weeks MCC increased from 185.0 to 270.9 mL (300 U) and from 240.8 to 311.7 mL (500 U). At 12 weeks, 91% of patients were dry in both groups. At 24 weeks, episodes of incontinence had returned in 50% (300 U) and 0% (500 U). Patients were better or much better (PGI-I) in 70% (300 U) and 88.9% (500 U) at 12 w; and 50% (300 U) and 100% (500 U), at 24 w. Therefore, 500 U seems the ideal dose despite the fact that 1 woman required transient CIC.

Elderly OAB patients are a special group for BoNT/A administration. A posthoc analysis of the large phase III studies by Chapple et al., [2013] and Nitti et al., [2013] showed similar efficacy in terms of continence in the subjects below or above 65 years of age. Two studies investigated specifically the effect of the toxin in this OAB population. In one study [White et al., 2008] 21 patients (18 females and 3 males) with a mean age of 81.2 years (received onabotA 200 U in 20 bladder sites. One month after treatment 16 patients (76%)

reported more than 50% improvement in symptoms after 1 injection A significant decrease in the number of daily voids, from 11.4 ± 1.67 to 5.19 ± 0.83 and incontinence pads per day, from 4.0 ± 0.89 to 1.3 ± 0.60, occurred. Mean time to deterioration was 7.12 months. There were no treatment related complications. Liao et al. [2013] investigated the efficacy and safety of intravesical BoNT-A injections in 166 OAB frail elderly, non-frail elderly and younger patients. Frail elderly were defined as individuals >65 years who met three or more of the following criteria: unintentional weight loss, self-reported exhaustion, slow walking speed, weakness, and/or low physical activity. Incontinence improvements were similar among younger, non-frail elderly, and frail elderly patients. However, the risk of large post-treatment PVR urinary volume (>150 mL) was significantly higher in the frail elderly group. Urinary retention occurred in seven frail elderly (11.5%), four (6.3%) in non-frail elderly and one younger (2.4%) patient.

8.1.2.3. BONT/A in OAB male patients

Most trials evaluating OnabotA injections in OAB patients have included predominantly female patients. Therefore, two studies restricted to male subjects merit reference despite their retrospective design. Faure Walker [2019] used doses of 100-300 U of OnabotA in 65 men (mean age 57.1 ± 13 years), with a total of 133 treatments. Using the UDI-6 and IIQ-7 questionnaires, the degree of improvement in men was inferior to that found in women for the same baseline characteristics. Urinary tract infections (UTI) were reported after 29.0% of the treatments. Urinary retention requiring de novo clean intermittent catheterization (CIC) was observed after 42.6% of the treatments without differences between 100 U and 200 U. A low bladder contractility index could be the best predictor of CIC risk. The other study was a review 146 men (mean age 70.1±13.3 years) who were injected only with 100 U [Mateu Arrom et al, 2020]. A positive response to the treatment, assessed by the treatment benefit scale, was reported by 62.3% of men. The incidence of urinary retention, despite the higher age of the cohort, around 70 years, was only 13%. Around 2/3 of the patients had discontinued treatment by the end of followup at 1 year. A higher bladder outlet obstruction index (BOOI) was the only predictive factor for poor treatment response and risk of complications.

8.1.2.4. BoNT/A in NDO and OAB children.

8.1.2.4.1. BoNT/A in NDO children

BoNT/A has been essentially assayed in children with myelomeningocele [Schulte-Baukloh et al., 2002; 2003; Corcos et al., 2002; Riccabona et al., 2004; Kajbafzadeh et al., 2006; Altaweel et al., 2006, Austin et al, 2021]. In this age group the dose of BONT/A should be calculated according to body weight. For onabotA doses ranging between 4 U/Kg [Corcos et al., 2002] and 12 U/kg of weight up to a maximum dose of 300 U [Schulte-Baukloh et al., 2002] have been used. The maximum suggested for abobotA is 20 U/kg up to a maximum of 400 U [Altaweel et al., 2006; Akbar et al BJU Int 2007].

In the largest randomised clinical trial available so far, three OnabotA 50, 100, or 200 U doses not exceeding 6 U/kg were investigated [Austin et al, 2021]. This was a 48-week prospective, multicenter study which included 113 children (5–17 years) with NDO due to myelomeningocele, transverse myelitis or spinal cord injury inadequately managed with anticholinergics was carried out in children. Toxin was delivered via cystoscopy divided in 20 intradetrusor injections of 0.5 ml excluding the trigone, under general anesthesia/conscious sedation or instillation of local anaesthetic (for children >12 years. Injections were performed under prophylactic antibiotic. Primary endpoint was the change from baseline in daytime UI episodes (**see, Fig 21**). Similar improvements were observed in the 3 dose groups which amount -1.3 UI episodes per day at week 6 after treatment. As secondary endpoints, increases in urine volume at first morning CIC (50 U, 21.9 ml; 100 U, 34.9 ml; 200 U, 87.5 ml;) and decreases in maximum detrusor pressure (50 U, −12.9; 100 U, −20.1; 200 U, −27.3 cmH_2O) favored 200U. The proportion of patients experiencing involuntary detrusor contractions at week 6 was 50 U/61.8%; 100 U/44.7% and 200 U/46.4% also favored the highest dose. Time to request a new treatment raged between 24 and 30 weeks among the three groups. Although the improvement of UI was similar for the three doses the urodynamic changes seem to suggest that the highest dose, 200 U without exceeding 6U/kg should be preferred [Austin et al, 2021].

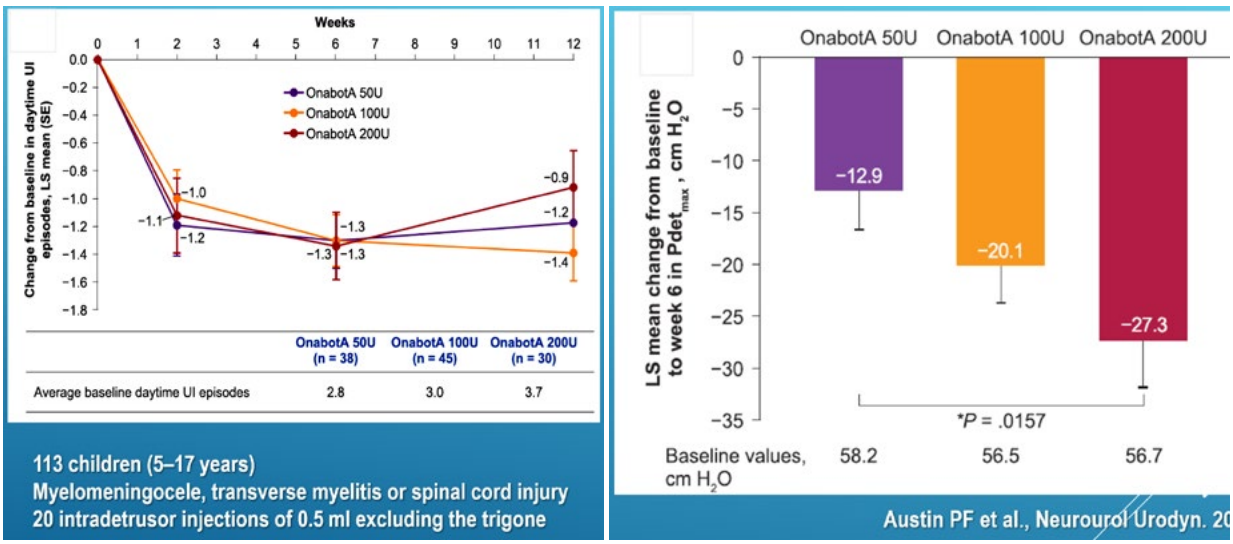

Figure 21: Onabotulinum toxin A 50, 100 and 200 U, (not exceeding 6U/kg), for the treatment of NDO in children. From Austin PF et al., Neurourol Urodyn. 2021 Jan;40(1):493-501

A systematic review made before this study [Mangera et al., 2014] had found a total of 13 studies reported on 368 children receiving BoNTA for NDO but none had a comparator arm. The only parameters reported with consistency between studies were the MCC and MDP, which decreased by between 42 to 59%.

Other studies reviewed in the previous edition of this book are now mentioned below briefly. In 19/26 children (73%) with a mean age of 6,9 years, became completely dry between clean intermittent catheterizations Interestingly vesicoureteral reflux, when present, disappeared or decreased in grade [Kajbafzadeh et al., 2006]. The success rate in terms of continence and cessation of anticholinergic medication may, however, be substantially inferior if irreversible bladder wall changes associated with longstanding detrusor overactivity are present [Altaweel et al., 2006].

As already mentioned, electromotive administration may facilitate BoNT/A administration in children [Kajbafzadeh et al, 2011]. In 15 children with myelomeningocele, electromotive administration of abobotA instilled in the bladder in a dose of 10 U/kg, proved very effective and safe. The mean volume to reflex voiding (99 ± 35 ml to 216 ± 35 ml) and maximal bladder capacity (121 ±39 ml to 262 ± 41 ml) increased substantially while maximal detrusor pressure decreased (75 ± 16 cm H2O to 39 ± 10 cm H2O). Urinary incontinence improved in 12 patients (80%) [Kajbafzadeh et al., 2011]. A small, randomised controlled trial compared AbobotA administration 10 U/Kg in 20 ml using EMDA or a classical injection protocol in 14 and 12 children with myelomeningocele [Ladi-Seyedian et al, 2020]. At 6 and 12 months the dry rate between intermittent catheterizations were 85.7% and 78.5%, respectively, higher than in the classical protocol group (66.6% and 50%).

8.1.2.4.2. BoNT/A in OAB children

To date, five case series that included a total of 135 OAB children have investigated the use of BoNT/A in children with OAB refractory to anticholinergics.

Three studies [Hoebeke et al., 2006; McDowell et al., 2011, Marte et al., 2010] with a total of 99 children of both genders received AbobotA 12 U/kg up to a maximum dose of 480 U studies [Hoebeke et al., 2006; McDowell et al., 2011] or OnabotA 12.5 U with a ceiling at 200U studies [Marte et al., 2010] in multiple bladder sites. A total disappearance of OAB symptoms was variable, between 38% [Hoebeke et al., 2006] and 66% [McDowell et al., 2011]. Time to re-injection varied from 6 months and periods exceeding 1 year.

Two more recent cohorts were identified. In one 39 patients between 5 and 16 years received OnabotA 100U, and 33 were analysed 9 months after treatment. The mean bladder capacity had a robust increase, daily voiding frequency decreased by almost 3 void per days and the mean incontinence episodes decreased from 2.72 ± 1.87 to 1.18 ± 1.13. Nocturia improved in one third of the 14 patients that had nocturia at baseline [Bayrak et al, 2017]. In another, a prospective open labelled uncontrolled study [Edwan et al, 2019], reported on the use of OnabotA 100U in 46 OAB children ageing 4-14 years. Cystometric bladder capacity increased from 194 to 244 ml. LUTS improvement was found, with robust mean decreases in daily frequency (-4.8), incontinence episodes per week (-7.9) and in nocturnal enuresis (-3.1).

Ingham et al [2019] investigated onabotA in 2 doses, 5 units/kg (with a ceiling at 150U), and 10 units/kg (with a ceiling at 300U) in 39 children with a mean age of 13.6 years. Injections were in the submucosa, 10 U per injection site above the trigone. Resolution of LUTS including incontinence after the 1st injection was observed in 11 cases and partial improvement in another 7, making 46% of the patients that got some benefice from the toxin. The mean duration of the effect was 7.6 months. At a median follow-up of 35.4 months 12 (31%) were asymptomatic and off all therapy. The dose of 5U/kg should be the one to start as the higher dose did not show a clear advantage in efficacy.

8.1.2.5. Effect of BoNT/A on quality of life

Bladder injections of BoNT/A in NDO and OAB patients increase quality of life and improve sexual function in women.

All placebo-controlled studies in NDO patients comparing 200 or 300 U [Schurch et al. 2007, Cruz et al., 2011, Ginsberg et al, 2012, Herschorn et al., 2011a,] showed strong increases in the Incontinence-QoL questionnaire score in SCI and MS patients treated with OnabotA. Interestingly, in patients non-catheterizing before treatment, I-QoL scores of those who maintained spontaneous voidings or had to initiate de novo intermittent catheterization were similar [Ginsberg et al., 2012]. Further subanalysis showed that the improvements were in the avoidance, limiting behaviour, psychosocial and social embarrassment domains of the I-QoL [Chancellor et al., 2013]. Responses to the OAB-PSTQ and to the Patient Global Assessment also demonstrated superior mean improvements from baseline in 200 U OnabotA than in placebo treated group [Chancellor et al., 2013].

The study that compared 50 U, 100 U and 200U in NDO children captured the Treatment Benefit Scale and concluded that at week 6 at least 75% of the children across the 3 groups were greatly improved or improved [Austin et al, 2021]

In a study that investigated OnabotA 100 U in non-catheterizing MS patients a strong improvement in I-QoL score, similar to those observed with 200 U, was reported [Tullman et al, 2018]. However, in MS patients voiding spontaneously but maintaining incontinence after a low toxin dose, the administration of a high dose (300U OnabotA) to induce retention combined with CIC might also improve quality of life if dryness between intermittent bladder emptying is achieved [Kalsi et al., 2007, Khan et al. 2011]

Concerning Abobot in NDO patients a single center, double blind, placebo-controlled study [Ehren et al. 2007] randomised 37 patients to abobotA 500 U or placebo. Patients in the AbobotA group showed greater improvement in quality-of-life parameters compared to the placebo group. Improvement in QoL were similar in a study that compared Abobot 500 U versus 750 U in a NDO population of where SCI predominate [Grise et al., 2010]. AbobotA administration of 750U in 15 or 30 points in the bladder of SCI or MS patients increased I-Qol score well above the minimum important difference, without differences between the two methods of administration [Denys et al, 2017a].

In OAB, dose-finding studies [Dmochowski et al. 2010, Denys et al., 2012] showed a sustained improvement in the King's Health Questionnaire score or in I-QoL in patients receiving OnabotA 100 U or higher doses. OnabotA 50U provided inconsistent improvements. In the large phase 3 trials [Chapple et al., 2013, Nitti et al. 2013] significant improvements in the I-QOL total score and in all the three domain scores were observed in the OnabotA 100U but not in the placebo arm. Improvements from baseline in all seven multi-item domains of the KHQ were also greater in the onabotA group. The OAB Japanese population treated with 100U OnabotA had a significant, robust improvement of role limitations and social limitations domains of the KHQ. In the treatment Benefit Scale more than 75% of the patients were greatly improved or improved along the first

12 weeks [Yokoyama et al, 2020]. The RELAX study with 200 U OnabotA [Tincello et al., 2012] showed significant improvement in ICIQ-SF and I-QoL scores. However, authors noticed that in none of the questionnaires the scores were restored to the normal value (0 for ICIQ; 100 for IQOL) [Tincello et al. 2012]. This placebo-controlled trial confirmed therefore the observations of a previous small non-controlled study [Sahai et al., 2009].

Two studies [Miotla et al, 2016, Balzarro et al, 2018] investigated the effect of OnabotA 100U bladder injection on sexual function of 68 OAB women. OAB treatments showed improvement of the sexual function captured by the Female Sexual Function Index (FSFI) questionnaire. In one study [Miotla et al, 2016] over 90% of women reported clinically relevant improvements in all six domains of the FSFI questionnaire.

In OAB children, OnabotA also improved quality of life. A significant change from baseline in the ICIQ-UI short form score was captured Edwan et al [2019]. The patients and their parent's perception of the treatment benefit on the treatment benefit scale also supported the improvement. In fact, 54% described their condition as greatly improved and 30% as improved.

8.1.2.6. Repeated BoNT/A injections

8.1.2.6.1. Repeated injections in NDO patients

Median time for NDO patients due to SCI or MS to request a retreatment was around 300 days after onabotA 200 or 300 U but only 92 days after placebo [Cruz et al., 2011]. Therefore, for patients who respond to BoNT/A a programme of reinjections is inevitable.

Long-term efficacy and safety of repeated onabotA injections was systematically investigated by extension studies of to large phase 3 trials [Cruz et al, 2011, Ginsberg et al, 2012]. Patients on placebo were initially ramdomized to onabotA 200 U or 300 U but further down in the study, following the licensing of 200 U, all patients were converted to this dose. Patients were treated based on their request and fulfillment of prespecified qualification criteria (≥12 weeks since previous treatment and at least 1 episode of incontinence in last 3 days). The final results of patients followed during a 4-year period (from an initial cohort of 392 cases) are available [Kennelly et al., 2017]. Percentage of responders remained high across the six treatments, between 70% and 80%. OnabotA 200U consistently decreased incontinence episodes/day at week 6 across six treatments, reductions ranging from -3.2 to -4.1. More than 80% of the patients achieved a ≥50% and 43 to 56% achieved full dryness. I-QoL total score regularly exceeded 2 times the minimum important difference. Overall, the median duration of each treatment was 9 months. Breaking down the duration, in 52% it was between 6 and 12 months, in 22% was than 6 months and in 26% exceeded 12 months. Further analysis of the patients who completed the 4 year study shows that some patients required 8 re-injections while others requested only 2. Patients who requested less treatment had a trend to have less baseline episodes of incontinence per day. Nonetheless, the daily episodes that were observed in week 6 after each treatment indicated a similar efficacy of OnabotA regardless of the number of injections requested. [Kennely et al, 2015]. This is an interesting point as it may suggest that patient preference for retreatment was not motivated by a different degree of toxin efficacy.

An additional post-hoc analysis of this cohort stratified patients by three responses: <50% (n = 33), 50-74% (n = 23), and 75-100% (n = 139), [Denys et al, 2017b]. The majority of the patients (83.1%) experienced a ≥50% UI reduction after the first treatment and the mean percent reduction in UI remained consistent in subsequent treatments in these groups. However, in those in the low initial response (<50%) one third achieved ≥50% UI reduction in all subsequent treatments. Therefore, as a practical message, a low UI reduction after first treatment does not necessarily predict low response after subsequent treatments.

Real-life studies assessed the persistence of NDO patients in a long-term treatment program with botulinum toxin injection. . A cohort of 199 patients with spinal cord lesions treated with abobotA 500 U to 1000 U was analyzed retrospectively, after 8 years of repeated injections. The intervals of between injections remained constant. Urodynamic improvements, patient satisfaction with treatment and number of pads or other protective devices required were also constant after treatments [Del Popolo et al., 2008]. Intervals exceeded 12 months in 19.5% of the patients, ranged between 10-12 months in 40.2%, was < 10 months in 30.5% and < 6 months in only 10% of the patients [Del Popolo et al., 2008].

In a MS cohort with 137 patients treated with onabotA 300 U, 99 (72%) returned for a second treatment. For third to sixth treatments only 47, 25, 14 and 5 patients returned, respectively. The median interval 2^{nd} , 3^{rd}, 4^{th}, and 5^{th} re-injections ranged between 12 and 13 months. The outcome in terms of continence did not differ among treatments [Khan et al., 2011].

Three studies [Dominique et al, 2019, Baron et al, 2019, Hebert et al., 2020] representing a total of of 375 patients followed for 10 years in real life conditions suggest that around 50% of the patients will abandon the BoNT/A program. Elderly patients, above >50 years, have a higher discontinuation rate than younger, < 50 patients [Hebert et al., 2020]. The most common cause of discontinuation is treatment failure, either primary or secondary, caused by the appearance of adverse events or progression of the neurological disease [Baron et al, 2019]. This latter explanation is particularly relevant for in MS patients. The worsening of the motor capacities will confine a significant number of MS patients to a wheelchair or a bed. Under these circumstances patients might prefer other methods for urine containment. This particular group of MS patients was never well investigated as wheelchair or bed bound cases were excluded from large phase 3 trials. In addition, a significant number of SCI patients may opt for bladder augmentation or urinary diversion.

Long-term success of repeated OnabotA injections was also investigated in 10 children (average age at first injection 11.2 years) with neurogenic detrusor overactivity who had received at least three BTX-A detrusor injections [Schulte-Baukloh et al, 2005]. The relative changes in comparison with the baseline value after the first versus the fifth injection showed a persistent increase in the reflex volume (81% versus 88%) and a progressive decrease in maximal detrusor pressure (7% versus 39%). The results after the third injection were generally similar to those after the fifth injection. No evidence of drug tolerance was detected. Concerning AbobotA [Akbar et al, 2007], 19 patients with myelomeningocele were treated with repeated injections for 3 or more years (20 units/kg, not >400 units). Urodynamic parameters improved and no tolerance developed.

8.1.2.6.2. Repeated injections in OAB patients

Patients participating in the two pivotal phase 3 studies were invited to participate in a long-term, 3 years extension study to determine the efficacy and safety of repeated OnabotA 100 U injections for the management of OAB. The final data were reported by Nitti et al. [2016]. From the initial 839 patients enrolled, 829 received 1 or more treatments and 430 (51.3%) completed the 3.5-year study period. At baseline the mean episodes of UI per day was 5.6 and the I-QOL total score was low. The decrease of UI episodes ranged

between -3.1 and -3.8 episodes per day whether patients received 1 to 6 treatments. The median duration of effect, calculated as the time to requalify to a retreatment was 7.6 months. The duration of effect was 6 months or less in 34.2% of the participants, between 6 to 12 months in 37.2% and greater than 12 months in 28.5% [Nitti et al., 2016]. Improvements in I-QOL scores were consistently 2 to 3 times the minimally important difference, and improvements in KHQ role limitations and social limitations domain scores were 5 to 6 and 3 to 4 times the minimally important difference, respectively. Of importance, 72.9% of patients who achieved or exceeded the minimally important difference for I-QOL after the first treatment maintained the score for all subsequent treatments. However about one third of those who did not achieve that outcome in the first treatment did so in subsequent treatment cycles [Ginsberg et al, 2017].

An open-label extension study of the controlled trial of onabotA 200 IU versus placebo [Tincello et al, 2012] also offered a 5-year extension study period [Owen et al, 2017]. A total of 155 had two and 59 had three injections. Time to symptom return for receiving a second and third injection was 84 and 180 days, respectively and the median inter-injection intervals were 266 and 372 days (range: 134, 1283). No statistically significant differences in symptom outcomes were observed after repeated injections. Although this study used a non-licenced dose of onabotA, it also confirmed the consistent efficacy and duration of action of the toxin [Owen et al, 2017].

Real life studies offer contradictory results concerning persistence on OnabotA OAB program. In a facility with access to flexible cystoscopies and a careful follow-up up to 90% of the patients remained in the program, 93 % would recommend the treatment to a friend and 81% accepted the necessity of a life-long treatment [Malde et al., 2015]. On the other hand, Mohee et al [2013] found that 66.3% of patients discontinued therapy at 36 months. The main reasons for abandonment were UTIs and the need for CIC. In a single-centre retrospective study [Marcelissen et al., 2017] the persistence on treatment among 128 women with at least 5-year follow-up after their first injection and a mean follow-up 97 (60-125) months was only 30 % at the last follow-up visit. Of the 70 % who discontinued treatment, 27 % had insufficient effect and 43 % had tolerability issues. Most patients discontinued treatment after the first (79 %) and second (19 %) injections [Mohee et al., 2013; Marcelissen et al., 2017]. A high rate of adverse events related to the use of high doses of toxin contributed to the low persistence on treatment.

8.1.3. Adverse events after bladder injections of BoNT/A and predictors of response

Most common adverse events related to bladder injection of BoNT/A are urinary tract infection (UTI) and urinary retention requiring CIC.

In studies with a SCI population performing CIC at baseline, the pooled data of the two larger phase 3 trials showed that the incidence of UTI/bacteriuria was similar, around 50%, across placebo, OnabotA 200 U and 300 U treated patients [Cruz et al, 2011, Ginsberg et al 2012, Ginsberg et a.l, 2013]. A low incidence of UTIs was also observed in an AbobotA phase 2a study that enrolled only SCI patients [Denys et al, 2017a] and across the three groups of two recent large clinical trials, which received AbobotA, 600U and 800 U or saline [Kennelly et al, 2022].

In the MS population voiding spontaneously before BoNT/A administration, the rate of UTI was highest in the onabotA 300 U arm (saline 32%, 200U: 58.5%, 300U: 70%) in the study by Cruz et al. [2011] whereas the incidence of UTI was similar, around 50%, after 200 and 300 onabotA doses in the study by Ginsberg et al. [2012]. However, very few complicated UTIs were reported. The incidence of UTI was directly correlated with the dose dependent increase of PVR and necessity of de novo CIC. In MS patients not catheterizing at baseline, Cruz et al., [2011] found an incidence of CIC of 12.2% after saline, 29.5% after 200U, and 42.2% after 300U. In a similar population of MS patients, Ginsberg et al. [2012] reported an incidence of de novo CIC of 10% after placebo, 35% after 200 U and 42% after 300 U. The period of time during which CIC was required after administration of OnabotA 200U was long, >36 weeks in about half of the MS patients [Ginsberg et al., 2013]. In long-term studies with NDO patients most commonly reported AEs were again urinary tract infections and urinary retention. Eventually influenced by patient selection, de novo CIC rates in long-term studies with MS patients decreased progressively as treatments were repeated [Kennelly et al, 2017]. The risk of urinary retention and de novo CIC in MS patients non-catheterising before treatment may be substantially decreased by using a lower dose of the toxin. Using 100U of OnabotA in non-catheterising MS patients de novo CIC (15.2%) and the rate of UTI (25.8%) was half of that observed with 200 U of toxin injections [Tullman et al, 2018].

In OAB, the dose finding study conducted by Dmochowski et al. [2010] showed that the proportion of patients with post treatment PVR of 200 ml or greater was dose dependent. Patients requiring CIC were 0%, 3,6%, 9,1% 12,7% 18,2% and 16,4 after placebo or 50, 100, 150, 200 and 300 U OnabotA injections, respectively, while UTI occurred in 16,3%, 33,9%, 44%, 48.1% and 34.5% patients, respectively.

In OAB large phase 3 trials which used OnabotA 100 U the risks of UTI and urinary retention were low. Chapple et al. [2013] reported an incidence of UTIs during the first treatment cycle of 24.1%. Only 8.8% of patients had an increase of PVR exceeding 200 ml, and 6.9% of the patients initiated CIC. Nitti et al [2013] reported an incidence of UTIs of 15.5% a PVR above 200 ml of 8.7% and de novo CIC of 6.1%. When pooled together and analysed by decades, the incidence of UTIs below the age <40 years was 10%, between 50-60 years 11.8% and >70 was 16.8% [Cruz et al 2017]. Concerning CIC the incidence in the same age groups was 1.1%, 5.3% and 7.2%, respectively, with a mean duration of 3, 88 and 86 days [Cruz et al, , 2017]. In 3 -year extension of these two phase 3 trials, which registered 6 treatment cycles, UTI incidence ranged between 14.4%-17.0% and CIC was necessary in 1%-4.0% The median duration of CIC ranged from 3.1 to 8.3 weeks [Nitti et al., 2016]. In the phase 3 study carried out in Japan, the incidence of UTIs and CIC at week 12 after injection was 13% and 6%, respectively while a PVR > 200 ml was noticed in 6% of the patients at week 2 [Yokoyama et al, 2020]. The studies that investigated the reduction in the number of injection points in the detrusor to facilitate BoNT/A administration still observed a relatively high incidence, 11-24% of UTIs [Avallone et al, 2017, Martínez-Cuenca et al, 2020].

In real life studies with OnabotA 100 U numbers of UTIs show great disparity. Hamid et al [2021] reported 1% UTIs and 0.4% of patients initiating CIC in a total of 504 OAB patients after one single treatment. In retrospective analyses of 103 OAB patients followed for 4 years the incidence of urinary retention was 25% and among patients who did not require catheterization the incidence of UTIs was 20% [Liberman et al, 2018]. In a real-life study with onabotA with 299 patients, mostly women, the incidence of CIC was 2.7% after the first treatment and 3.2% after the second and third treatments. No significant predictors of CIC initiation were found [Kennelly et al, 2018].

Three studies using OnabotA 200 U reported their adverse events. In the RELAX study, UTI occurred in 31% and voiding difficulty

requiring CIC occurred in 16% of cases [Tincello et al., 2012]. In a long-term extension of this study the numbers decreased substantially, due the selection of patients that agreed to continue on treatment [Owen et al, 2017]. In a smaller RCT, CIC was required in 37.5% of [Sahai et al., 2007]. In another small RCT comparing OnabotA 200U vs placebo PVR increased above 200 ml in 43% of the women in the BONT/A group and UTI developed in 75% of these women [Brubaker et al., 2008].

Faure Walker et al [2017] and Mateu Arrom et al [2020] injected only men. The first using OnabotA 100 U and 200 U reported a rate of urinary retention leading to CIC above 40% and an incidence of UTIs among those without retention of 29% among 37 men. The second reported 13% of urinary retentions and 3% of UTIs requiring antibiotics. The reason for the different incidence of adverse events between the two studies is unclear but should have to do with different criteria for male selection and for the definition of UTI and urinary retention.

A thorough investigation showed that formation of toxin-neutralizing antibodies against OnabotA was a rare event in large NDO phase 3 trials [Cruz et al, 2011, Ginsberg et al, 2012]. During long-term extension of these trials, among 388 NDO patients only 1 patient developed antibodies against OnabotA [Kennelly et al, 2013]. The overall incidence of toxin neutralizing antibody formation in large OAB trials was 0.4% [Nitti et al., 2016]. In children treated with AbobotA increment of antibodies against abobotA was shown to be a rare and transient event that was not boost by repeated injections [Kajbafzadeh et al, 2010].

Transient muscle weakness has been reported in some studies with NDO patients. After AbobotA application anecdotal generalised muscular weakness was reported [Wyndaele and Van Dromme, 2002]. Akbar et al., [2007] and Del Popolo et al., [2008] among a total of 243 NDO patients reported 8 cases of hypostenia after abobotA 1000 U injection. In a phase IIa RCT with abobotA 750 U, 3 cases of muscle weakness episodes were reported in two tetraplegic and one paraplegic patient among 15 NDO patients who received the toxin in 15 injection sites [Denys et al., 2017a]. Cruz et al. [2011], among 183 patients treated with OnabotA 200 U or 300 U reported 1 case of muscular weakness in an SCI patient treated with OnabotA 300 U. The reason for the seemingly less cases of transient muscle weakness among OnabotA-treated NDO patients is unclear but might be related with an incorrect ratio conversion and/or to the larger size of the OnabotA molecule which limits its diffusion. Anyway, the recent data of the AbobotA 600 U and 800U trials in NDO patients did not report cases of generalised weakness [Kennelly et al, 2022].

In large OAB trials generalised muscular weakness was not reported after OnabotA 100 U administration [Chapple et al, 2013, Nitti et al, 2013]. Even in geriatric OAB population the administration of OnabotA 100 or 200 U did not cause muscular weakness as investigated by the strength of handgrip test [Wiedemann et al., 2020]

Episodes autonomic dysreflexia in SCI patients during injection were rare. Cruz et al, [2011] reported 2 cases in 183 injected patients and Ginsberg et al. [2012] 7 events in 167 injected patients. Kennelly et al [2022] reported 1 case in more than 500 patients treated.

There is no evidence that repeated BoNT/A injections cause detrusor atrophy or bladder wall fibrosis. Whether onabotA or abobotA were used, repeated injections in NDO patients in the short to medium term did not decrease bladder compliance which would presumably be the case if fibrosis were to develop [Reitz et al., 2007; Del Popolo et al., 2008]. Histological inspection of injected bladders did not show inflammatory changes, fibrosis, or dysplasia after repeated treatments and independently of the neurogenic or non-neurogenic origin of the detrusor overactivity [Haferkamp et al., 2004; Compérat et al., 2006; Apostolidis et al., 2008].

The capacity to predict the response of OAB patients to BoNT/A injections was recently the object of a systematic review that identified 17 studies reporting predictive factors for poor response published between 2006 and 2020 [Abrar et al, 2020]. These were cohort studies with predominantly level 3 evidence. Factors including male gender, frailty, comorbidity, increasing age, smoking, baseline leakage episodes, and various urodynamic parameters (bladder outlet obstruction index (BOOI), high pretreatment maximum detrusor pressure, and poor bladder compliance) were proposed as predictors of nonresponse. In predicting CIC use, factors identified were male gender, the presence of comorbidities, increasing age, number of vaginal deliveries, hysterectomy, and urodynamic parameters (bladder capacity, postvoid residual volume, projected isovolumetric pressure value, bladder contractility index, and BOOI). Female gender, males with their prostates in situ, and CISC were suggested to increase UTIs after BoNT/A.

Hematuria may occur after toxin injection in the bladder wall of OAB or NDO patients but in most of the times is mild in nature and does not require any active treatment [Ginsberg et al, 2013, Sievert, et al, 2014, Cruz and Nitti, 2014].

8.1.4. Clinical comparisons of different BoNT/A brands and switch between them

The doses indicated for each brand of botulinum toxin type A cannot be used interchangeably. Moreover, inappropriate storage of the vials, incorrect toxin reconstitution, or incorrect technique of administration, including the type of needle used may contribute to differences outcomes [Karsenty et al., 2014]. A 5-fold variation of the number of neurons expressing cleaved SNAP-25, the end-product of botulinum toxin A activity, after 1 injection of a fixed dose of OnabotA was recently shown in experiments conducted in bladder rodents [Oliveira et al., 2017].

A study compared two different brands of BonT/A, Onabot A 200 or 300 U against the Chinese BoNT/A Presigne in the same dosage. Improvement in MCC was significantly greater with OnabotA (Botox) versus Prosigne (+103.3% vs. +42.2%). Continence was achieved by week 12 in 16 OnabotA recipients (76.2%) and in 10 Presigne recipients (47.6%) [Gomes et al., 2010].

A retrospective case-control study investigated the clinical and urodynamic outcomes in 211 NDO patients [Peyronnet et al, 2017] treated in three consecutives eras with onabotulinum toxin 300 U (2004-2006; 80 patients), abobotulinum toxin 750 U (2007-2011; 78 patients) or onabotulinum toxin 200 U (2011-2014; 53 patients). Patients treated with abobotulinum toxin 750 U had higher success rate compared to those who received onabotulinum toxin 200 U (65.4% vs. 41.5%). In contrast, there were similar success rates in abobotulinum toxin 750 U and onabotulinum toxin 300 U groups (65.4% vs. 65%) but with a trend towards longer interval between the first and the second injection in the onabotulinum toxin 300 U group (12.4 vs. 9.3 months).

A randomized, double-blind, non-inferiority study compared IncobotA vs OnabotA detrusor injections in patients with NDO due to SCI or MS performing CIC [Gianantoni et al, 2021]. A total 28 patients received IncobotA 200U and 29 OnabotA 100 U in 30 points. At

week 12, there was no difference in the number of urinary incontinence episodes/day between the two groups. Total score of I- QoL questionnaire, Visual Analog Scale Scores and urodynamics also did not show differences between the two groups. Adverse effects were similar for both treatments.

Ravindra et al. [2013] reported a retrospective brand comparison in OAB patients. Initially they received onabotA 200 U. Later, due to non-clinical reasons BoNT/A was changed into abobotA 500 U. Under onabotA (n = 101) or abobotA periods (n = 106) patients had similar reductions in frequency, nocturia and daily incontinence episodes. The duration of the effect was similar. However, under abobotA patients had almost twice the rate of symptomatic urinary retention requiring CIC (42% versus 23%).

Switch between brands at the moment is being made on empiric grounds. In particular, the lack of effect of a treatment with a particular brand should not be seen as a compulsory reason for switching to another brand. A sub-analysis of the NDO patients included in the OnabotA pivotal studies who experienced <50% reduction in urinary incontinence episodes following the first onabotA treatment, about 1/3 had a positive response in subsequent injections [Denys et al., 2017b].

Nevertheless, the charts of 57 patients who underwent a switch to AbobotA after failure of OnabotA 200U or 300 U in centers were retrospectively reviewed. After the first injection of AbobotA (mostly 750-1000 U) a significant decrease in number of urinary incontinence episodes per day was observed in 52.63% of patients and all patients experienced a reduction in maximal detrusor pressure (-8.1 cmH20). MCC significantly increased by a mean of 41.2 ml and the proportion of patients without involuntary detrusor contractions increased significantly (from 15.79% to 43.9%). After a median follow up of 21 months, 87% of responders to the switch were still treated successfully with abobotA [Bottet et al, 2018]

The switch may eventually work whatever is the first toxin administered. Peyronnet et al. [2015] reviewed the charts of 58 NDO patients who received either OnabotA or abobotA for the management of NDO. A toxin switch was carried out in 29 patients, whereas the other 29 patients received a reinjection of the same toxin at the same dose. The success rate was higher in patients who switched toxin (51.7% vs 24.1%). Patients who switch from abobotA to OnabotA and those who switch from OnabotA to abobotA had similar success rates (52.9% vs 50%)..

8.1.4.1. Comparison between BoNT/A and other NDO and OAB treatments

BoNT/A has been compared only rarely with other NDO and OAB oral treatments as it is assumed that the toxin introduction should follow the failure of first line pharmacotherapy with antimuscarinics and beta3 agonists.

In SCI patients with NDO, Silva-Ferreira et al [2018] compared oxybutynin 5mg TID or OnabontA 300 U in 78 SCI patients who were under CIC in the last 12 months. Urinary incontinence which was around 8 episodes per day in both groups at baseline, decreased to 5±2 and 3±1 at the end of treatment in the oxybutynin and OnabotA groups, respectively. Also, oxybutynin, in contrast to toxin, could not reduce maximal detrusor pressure to levels below 40 cm H20, indicating an inferior capacity of the antimuscarinic to protect the upper urinary tract.

In OAB, the first large comparison was the Anticholinergic Versus Botulinum Toxin A Comparison Trial (ABC trial) [Visco et al., 2012] **(Fig 22)** that included 249 women with OAB who had 5 or more episodes of urgency urinary incontinence in a 3-day bladder diary. 6-month participants were randomly assigned to one intradetrusor injection of 100 U of onabotA plus daily oral placebo daily or oral anticholinergic medication (solifenacin, 5 mg initially, with possible escalation to 10 mg and, if necessary, subsequent switch to trospium XR, 60 mg) plus one intradetrusor injection of saline. The mean reduction in episodes of urgency urinary incontinence per day, the primary outcome, was similar, 3.3 in the onaboA group and 3.4 in the anticholinergic group. Complete continence was more frequent in the OnabotA than in the anticholinergic group, 27% vs 13%, re-

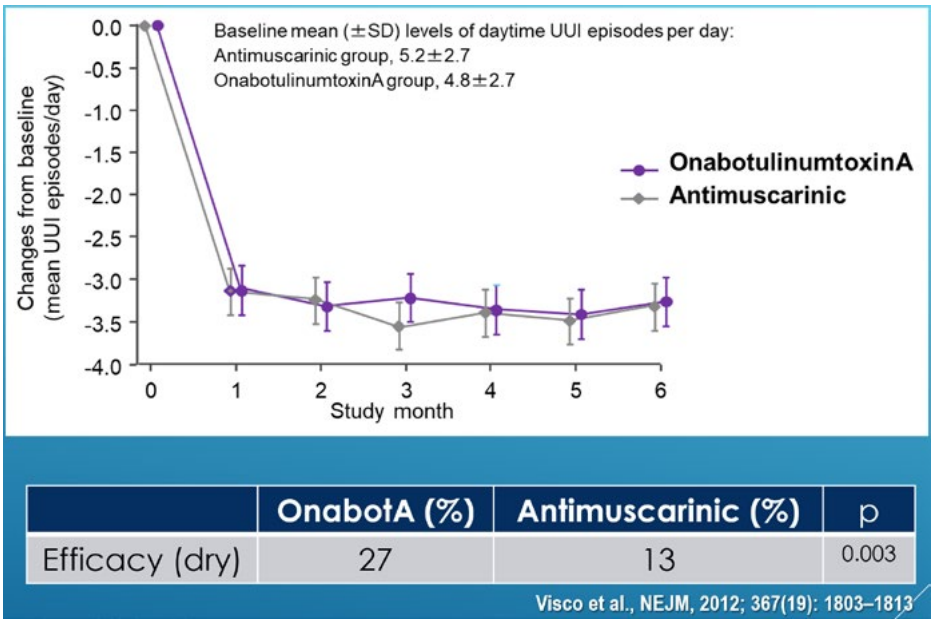

Figure 22: Comparison between Botulinum Toxin A and antimuscarinics. The ABC trial. From Visco et al., NEJM, 2012; 367(19): 1803–1813

spectively. The toxin group had higher rates of catheter use at 2 months (5% vs. 0%, P = 0.01) and UTI (33% vs. 13%) than the anticholinergic group. The latter on the other hand had a higher rate of dry mouth (46% vs. 31%, P =0.02) [Visco et al., 2012].

In contrast, other studies concluded for the superiority of OnabotA over antimuscarinics and beta 3 agonists to improve or resolve OAB wet.

In a study with OAB wet patients, placebo (injection plus oral placebo, n = 60), OnabotA 100 U injection plus oral placebo (n = 145), or oral solifenacin plus placebo injection (n = 151) were compared after 12 weeks [Herschorn et al, 2017]. Co-primary endpoints were change from baseline in urinary incontinence episodes/day and the proportion of patients with 100% reduction in urinary episodes at week 12 after injection. Overall, patients had 4.9 urinary incontinence episodes per day at study entrance. At week 12, mean reduction from baseline was significantly greater with either OnabotA (-3.2) or solifenacin (-2.6) versus placebo (-1.3). In a post-hoc analysis the reduction in urinary incontinence episodes/day was significantly greater with onabotA than with solifenacin. The proportion of patients with 100% reduction in urinary incontinence episodes at week 12 was significantly better for onabotA (33.8%) and solifenacin (24.5%) compared with placebo (11.7%) [Herschorn et al, 2017].

Drake et al, [2017] carried out a network meta-analysis to compare the relative efficacy of onabotA 100 U, and mirabegron and anticholinergics in all licensed doses in OAB adults using 56 RCTs. At a time-point of 12 weeks, patients treated with the toxin had, on average, the greatest reductions in urinary incontinence episodes, urgency episodes, and micturition frequency, and the highest odds of achieving dryness.

The Rosetta study compared OnabotA 200 U against sacral neuromodulation (SNM) (interStim) in refractory OAB wet patients at 6 months [Amundsen et al., 2016] and 2 year [Amundsen et al., 2018] follow-up. The proportion of randomised patients suitable for SNM implant was identical in the two arms. At baseline the OnabotA group (n=190) had 5.4 and the SNM (n=174) had 5.2 episodes of urinary incontinence per day. A 6-months [Amundesen et al, 2016], OnabotA 200 U resulted in a significantly greater mean daily reduction in UUI episodes over 6 months, which averaged 1 episode/day. A significantly greater number of patients experienced a complete resolution (20% vs 4%) or 75% reduction of UUI episodes (46% vs 26%) with OnabotA 200 U treatment than with SNM InterStim. UTIs were more frequent in the onabotA group (35% vs 11%) and the need for CIC was 8% and 2% at 1 and 6 months in the onabotulinumtoxinA group. Neuromodulation device revisions and removals occurred in 3% [Amundsen et al., 2016]. The advantages of onabotA, where no longer observed at 2 years follow-up [Amundsen et al, 2018]. No difference in the decrease of urinary incontinence episodes was found and no differences in incontinence cure or improvement at ≥75% or ≥50% were present at 2 years, although satisfaction and treatment endorsement were higher for the toxin [Amundsen et al, 2018]. Recurrent UTIs remained higher after OnabotA (24% vs 10%) and 6% of the patients required CIC after a second injection. SNM revision and removals occurred in 3% and 9% of the patients, respectively [Amundsen et al, 2018]. Older women with multiple comorbidities and decreased functional and health related quality of life had decreased treatment response and satisfaction with onabotA compared to SNM [Richter et al, 2017].

A survey in 50 OAB patients, with a mean age of 61 years, showed that 74% prefer OnabotA and only 26 % chose SNM as first treatment option. In those who preferred OnabotA 54 % disliked the thought of a foreign body in the back, 45.9 % made the option due to a short waiting list and 43.24 % made the choice based on the quicker onset of benefit. In the SNM group 61.5 % were averse to the potential need for repeated injections and 46.1 % chose SNM to avoid the risk of urinary retention associated with the toxin [Balchandra and Rogerson, 2014].

SNM may be useful in OAB non-responders to OnabotA. In a small cohort with 20 patients 14 (70%) received a definitive implant. One year after implantation, 11 patients were satisfied with SNM [Smits et al, 2013]. The opposite may also be true according to a retrospective multicentre analysis of 62 OAB women who had received either onabotA or abobotA injections after failure of SNM [Baron et al, 2020]. The percentage of success, either resolution or > 50% reduction of urinary incontinence or frequency, was 43.4% after the first injection. CIC was necessary in 36.8%. Overall, 42 patients (55.2%) stopped injections during follow-up [Baron et al, 2020].

8.1.5. Cost-effectiveness of BoNT/A in NDO and OAB.

Economic aspects of BonT/A are a concern due to the price of the drug and the need for repeated cystoscopies, very often performed under general anaesthesia and under close monitoring to detect and treat eventual episodes of autonomic dysreflexia. Nevertheless, in UK, in a cohort of 101 patients with detrusor overactivity, 63 of whom of neurogenic origin, BonT/A treatment was shown to be cost-effective in both NDO and OAB cases [Kalsi et al, 2006]. Costs were based on the resources used by typical patients in UK and in the cost-effectiveness of 200-300 U BoNT/A (Botox) compared with standard care [Kalsi et al., 2006]. In Germany a multicenter cost analysisin 214 NDO patients showed that onabotA treatment halved costs for incontinence aids and for urinary tract infection treatment. In patients using incontinence aids, mean costs per patient decreased from €2 to €1 per day, whereas the mean cost of drugs to treat UTIs per patient decreased from €163 to €8 per year [Wefer et al., 2009].

An assessment of costs, from a US payer perspective, extending up to 3 years, was made for 3 interventions, sacral neuromodulation, BoNTA, and augmentation cystoplasty in patients refractory to antimuscarinics. The initial treatment cost was $22,226, $1,313, and $10,252 for sacral neuromodulation, BoNTA, and augmentation cystoplasty respectively. Three years after initiating treatment, the cumulative cost was $26,269, $7651, and $14,337 respectively. Sensitivity analyses revealed that sacral neuromodulation persisted as the most costly intervention [Watanabe et al., 2010]. Also, in NDO patients, break-even point for BoNT/A and augmentation cystoplasty costs may be reached at five years. However, BoNT/A may be substantially more cost-effective if the duration of effect of each injection is superior to 5 months or if the complications associated with augmentation cystoplasty overtake 40% of the patients [Padmanabhan et al., 2011].

For OAB, a study in US over 2 years, concluded that if patients receive 15.6 and 14.3 months of selective and non-selective anticholinergics, respectively, and 2.2 OnabotA injections, the toxin is cost effective, a finding that may change BoNT/A treatment faster into a first line option [Shepherd et al, 2018]. In the Rosetta trial, OnabotA versus SNM , the authors performed a 2-year within-trial assessment of costs and modeled theoretical 5-year costs [Harvie et al, 2020]. The 2-year costs were higher for SNM than onabotA and estimated 5-year costs were still higher for SNM. Harvie et al [2020] concluded that in the US, SMN in its current form is less cost-effective than the toxin in the treatment of refractory OAB.

8.1.6. BONT/A in IC/PBS.

BoNT/ cleaves SNAP-25 in sensory fibers [Coelho et al., 2012a] which inhibits the transmission of noxious sensory input from the bladder [Vemulakonda et al., 2005; Rapp et al., 2006; Lucioni et al., 2008]. Moreover BoNT/A decreases the urinary levels of NGF and BDNF which may contribute to decrease the sensitization of bladder sensory fibers and decrease pain felt by patients during bladder filling [Pinto et al., 2010, 2014]. However, the impact of the findings described below is limited by the fact that most studies are single center, with a small number of patients included, and using different techniques for toxin administration, whole bladder versus trigone. Studies with comparators are scarce. Only one used saline and others maintained in the active arm other forms of treatment which may act as confounders for the outcome.

The first three small pilot studies showed conflicting results. Two, that included a total of 28 patients treated with OnabotA 100 U and 200 U injections in the bladder, including the trigone, reported pain improvement in a large proportion of patients as well as amelioration of urinary symptoms for 3-5 months [Smith and Chancellor, 2004, Giannantoni et al., 2006; 2008]. Importantly, 9 patients experienced moderate to severe voiding difficulties [Giannantoni et al., 2006; 2008] . A third study could not demonstrate any effect of onabotA in 13 IC/PBS patients treated with OnabotA 100–300 U in the bladder [Davies et al., 2006].

Taking in consideration that most of the bladder nociceptors course in the trigone, Pinto et al. [2010] restricted 100 U onabotA injections to the trigone, in 10 sites (10 U/ 1 ml each. Twenty-six women with positive findings at cystoscopy and biopsy were enrolled. All patients reported subjective improvement at 1- and 3-month follow-up in pain, daytime and nighttime voiding frequency, O'Leary-Sant score and QoL. Bladder volume to first pain and maximal cystometric capacity more than doubled. Treatment remained effective in >50% of the patients for 9 months. Retreatment was equally effective in all cases, with similar duration of the effect up to four consecutive treatments [Pinto et al, 2013]. No cases of urinary retention were reported and at urodynamics PVR and bladder contractility index were not impaired [Pinto et al., 2010, Pinto et al, J Urol, 2013]. Interestingly, the improvement in pain may be similar in patients with and without Hunner´s lesions. Kuo and Chancellor [2009] did not find a significant difference in pain intensity between the 2 populations after OnabotA in the whole bladder plus hydrodistention. The symptomatic outcome of trigonal injections of OnabotA 100 U was similar, whether patients had or not Hunner´s lesions [Pinto et al, 2014].

One randomized study compared onabotA 200 U (n=15) or 100 U (n=29) followed by hydrodistention 2 weeks later against hydrodistention only (n=23). The 44 patients that received OnabotA, received the toxin in 40 suburothelial sites, including the trigone [Kuo and Chancellor, 2009]. All participants remained on pentosan polysulphate throughout the study. This and the preliminary hydrodistention inevitably work as a confounder for the results. Nevertheless, the IC/PBS symptom score significantly decreased in all three groups, while pain reduction and urodynamic improvement were only observed at 3 months in the arms that received OnabotA, without any relevant differences between the two doses. A successful result at 12 and 24 months was reported in 55% and 30% of OnabotA treated patients, respectively, compared with only 26% and 17% in the control group [Kuo and Chancellor, 2009].

Three placebo-controlled trials were identified. A multicenter, randomized, placebo-controlled trial randomized 60 patients in a 2:1 ratio to hydrodistention plus 20 suburothelial injections of BoNT-A 100 U) or the equivalent amount of saline above the trigone [Kuo et al, 2016]. A decrease in pain, the primary endpoint, occurred at week 8 (-2.6 ± 2.8 vs. -0.9 ± 2.2) but urinary symptoms captured in a bladder diary, like frequency and nocturia, did not change. The overall success rates were 63% (26/40) in the OnabotA group and 15% (3/20) in the saline group. One case of urinary retention occurred in the OnabotA group [Kuo et al, 2016]. Trigonal only injections of OnabotA 100 U or saline, not associated with any other form of potential treatment, was compared in 10 and 9 IC/PBS women, respectively [Pinto et al, 2018]. A significant greater reduction in pain intensity was achieved with OnabotA (-3.8 ± 2.5 vs -1.6 ± 2.1). The proportion of patients who achieved a 50% or greater reduction in the pain visual analog scale was 60% for onabotA vs 22% for placebo. Important numerical reductions in voiding frequency were also observed with the toxin. UTI developed in 3 patients who received onabotA and in 2 who received saline. No cases of urinary retention occurred [Pinto et al, 2018]. Another small placebo- controlled trial compared periurethral injections of onabotA 50U (n=9) versus saline (n=11) [Gottsch et al, 2011]. The rationale was to investigate the contribution of periurethral somatic afferents to pain. The solution, 2 ml, was injected in the region of the bladder neck, at the 3 o'clock and 9 o'clock positions. No differences between the onabotA and saline were observed at 3-month follow-up in terms of symptoms [Gottsch et al, 2011].

Two metanalyses were identified. One investigated the different treatment options for IC/PBS and concluded that BoNT/A has the highest probability of being the best therapy available at the moment to treat IC/PBS patients [Zhang et al, 2017]. The second meta-analysis identified 12 randomised controlled trials with heterogeneous quality and methodologies. Nevertheless, significant benefits from BoNT/A injections were detected in pain, day-time urinary frequency and Interstitial Cystitis Symptom Index and Problem Index. A clinical insignificant increase in PVR was identified [Giannantoni et al, 2019].

8.1.7. BoNT/A in the Prostate

Apoptosis was reported in rats, dogs, and humans after OnabotA injection in the prostate that affected both the epithelial and stromal components [Doggweiler et al., 1998; Chuang et al., 2005; Chuang et al., 2006a, Silva et al., 2009a]. These findings levered the investigation of BoNT-A for the treatment of benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH). Following ultrasound guided OnabotA 200 U injections consistent decreases in prostate volume, improvement in LUTS were reported. [Maria et al., 2003, Kuo 2005b, Chuang et al., 2005; Chuang et al., 2006b,c Guercini et al., 2005, Silva et al, 2008]. Among 21 frail men on chronic indwelling catheter for at least 3 months, who were not candidates for surgery, 17 (81%) resume spontaneous voiding after OnabotA 200U [Silva et al. 2008]. The duration of prostate atrophy after the single injection of 200U of BoNT-A was found to be about 18 months [Silva et al., 2009b].

A multicenter, double-blind, randomized phase II clinical trial of onabotA 100 and 300 U concluded that both doses caused a 30% improvement from baseline to 3 months in American Urological Association symptom index and/or maximum urinary flow rate [Crawford et al., 2011]. Some serious adverse events were reported, including 3 cases of urosepsis injection. [Crawford et al., 2011]. However, no sexual adverse events were reported [Silva et al., 2011].

These findings were not reproduced, however, in two large RCTs. One enrolled patients with IPSS > 12 and a peak flow rate (Qmax) between 5-15 ml/s [Marberger et al., 2012]. A total of 380 men met the inclusion/exclusion criteria, were randomized (ITT population),

and received treatment via the transperineal (n = 63) or transrectal (n = 311) routes with either placebo (n = 94) or OnabotA 100 U (n = 95), 200 U (n = 94), or 300 U (n = 97).The other [McVary et al., 2014] enrolled 427 men with IPSS score > 14 and Q max between 4 to 15 ml/s. All received initially a sham procedure to exclude cases with a high placebo response during the run-in phase. Then a total of 315 patients were randomized 1:1 to receive a single intraprostatic treatment of OnabotA 200U or placebo. Although in both studies a substantial decrease in IPSS score and increase in Qmax occurred in the OnabotA 200 U groups, the changes were not significantly different from those observed in the saline arm, indicating that they arose from a considerable placebo effect associated with the injection procedure.

The population enrolled in the Marberger et al. [2012] and McVary et al [2014] trials may vary from those usually referred to minimal invasive BPH procedures. As a matter of fact, 51% of the men enrolled in first, although having moderate to severe LUTS had never received treatment with licensed drugs for BPH/LUTS. An exploratory post hoc analysis in the subgroup of patients who had received alpha-blockers showed a significant reduction from baseline in IPSS in the OnabotA 200-U group versus placebo [Marberger et al. 2012]. In the McVary et al. study [2014], 78.3% of the patients were not on alpha-blockers or 5-ARI at the moment they were enrolled in the study. From 313 patients only 68 (21.7%) were currently on treatment, while all the others had meanwhile abandoned oral pharmacotherapy.

Due to these weaknesses, other studies were conducted. A non-inferiority randomized clinical trial compared in BPH patients dissatisfied with oral pharmacotherapy prostatic injection of onabotulinum toxin type A 200 U (n=64) against optimized medical therapy (n=67), that is, any possible drug combination for treatment of BPH/LUTS. The group submitted to toxin injection stopped oral medication 30 days after the procedure [Robert et al., 2018]. Total IPSS at the end of treatment was similar in the two arms, allowing the conclusion that OnabotA is not inferior to optimized medical therapy, in men with BPH/LUTS refractory to initial oral pharmacotherapy. Interestingly, in the onabotA group only 1 episode of acute urinary retention occurred. In contrast, 6 cases were observed in the optimized medical treatment group. A smaller study [[Totaro et al, 2018] randomized 20 consecutive patients to receive intraprostatic OnabotA 200-300 U injection (n = 10) or saline (n = 10). A total volume of 6-8 mL was injected into the transitional zone. At 3 months of follow-up IPSS and PVR were significantly reduced by 55,3%, and 80,6% in the OnabotA arm, respectively. Qmax was increased by 68%. BOOI (bladder outlet obstruction index) decreased by 54%. PROs analysis revealed that 90% of patients treated with OnabotA reported a subjective symptomatic relief and treatment satisfaction and no adverse effects were observed [Totaro et al, 2018].

A curious randomised trial compared intraprostatic injection of OnabotA 200 U against TURP in BPH-patients refractory to oral therapy for more than 6 months [El-Dakhakhny et al., 2019]. The toxin was diluted in 3 mL saline with 1 mL injected in each lobe by transperineal route. At end of the study, 92 patients were available for analysis, 46 in each arm. The IPSS score significantly decreased in all patients with a non-significant difference between the groups. The Qmax increased, whilst PVR and serum PSA significantly decreased after toxin injection. The toxin did not deteriorate erectile function when compared with TURP. Patients who showed deterioration at 12 months were re-evaluated and underwent TURP. Intraprostatic OnabotA spared TURP in >70% of patients [El-Dakhakhny et al., 2019].

By analogy to the rationale of BoNT/A use in IC/PBS, the impairment of prostatic nociceptive fibers by the toxin may be useful to treat pain in patients with chronic prostatitis/chronic pelvic pain syndrome. One randomised clinical trial investigated the effect of intra-prostatic injections of BoNT/A in men 60 men ≥18 years with chronic prostatitis/chronic pelvic pain syndrome refractory to medical therapy [Falahatkar et al, 2015]. Intraprostatic injection of BoNT-A (100 or 200 U of OnabotA according to the prostate volume) or normal saline were carried out by transurethral route. In the toxin group, but not in the placebo group, a marked improvement of pain scores evaluated at the 1-, 3- and 6-month was observed. Also, NIH-CPSI total and subscale scores, the AUA symptom score as well as urinary frequency had significant improvements compared with baseline values. Only two patients developed mild transient gross haematuria, which was managed conservatively [Falahatkar et al, 2015]. Future studies will help to clarify the potential of intraprostatic BoNT/A in chronic prostatitis/chronic pelvic pain syndrome.

8.1.8. BoNT/A in the external urethral sphincter

Patients with external sphincter dyssynergia are frequently put on a program of CIC to empty their bladder. However, some might have difficulty in performing the manoeuvre. An alternative can be to weaken the urethral sphincter in order to facilitate voiding. In the late eighties Dykstra et al, [1988] reported the effect of BoNT/A injection in the rabdosphicter of 10 neurogenic patients with voiding dysfunction. The urethral pressure profile decreased an average of 27 cm. water and post-void residual urine decreased by an average of 146 ml in 8 patients. The toxin effects lasted an average of 50 days. Later, a retrospective study reviewed the charts of 68 patients that received 100 to 200 U of OnabotA in 4 mL divided in equal doses into the four quadrants of the external sphincter [Smith et al, 2005]. Patients reported significant improvement in their detrusor sphincter dyssynergia with decreased postvoid residual urine volume and improved flow. Catheterization to treat urinary retention was required in 41 patients at baseline and only in 7 after OnabotA injection. Post void residual urine volume decreased from 240 ml to 88 ml and maximal voiding pressure decreased from 81to 52 cm H2O. Cases of stress urinary incontinence were rare. Similar results were reported in children [Franco et al, 2007]. A Cochrane review [Utomo et al, 2014] concluded that all available studies were small, of limited quality, and carrying a high risk of bias. Therefore, the evidence of that intraurethral BoNT/A injections improve some urodynamic measures after 30 days in patients with functional bladder outlet obstruction and neurogenic bladder dysfunction should be interpreted with caution. The necessity of reinjection at very short interval (around 3 months) was found a significant drawback. After this review, a retrospective study of 42 neurogenic and 53 non-neurogenic (detrusor underactivity) patients with voiding dysfunction injected with 100 U onabotA into the urethral sphincter was identified [Jiang et al, 2018]. Satisfactory outcomes were reported in 58 (61.1%) patients. However less than half of the patients catheterized or doing CIC could voiding freely. Six cases developed strss urinary incontinence. An open bladder neck during video-urodynamic at voiding was the only predictor for successful outcome. Patients with non-neurogenic voiding dysfunction had a significantly longer therapeutic duration than those with neurogenic voiding dysfunction (9.55 ± 4.18 vs 7.44 ± 2.91 months).

8.1.9. BONT/B protocols in the bladder

Some humans repeatedly injected with BONT-A may show resistance to the toxin. One possibility is the formation of neutralizing antibodies. Although this event is very rare in the case of bladder injections, a minimum interval of 3 months between two BoNT/A injections is generally recommended to decrease its occurrence. If re-

sistance appears, the replacement of BONT-A serotype by BONT-B was investigated [Dykstra et al., 2003; Pistolesi et al., 2004; Reitz et al., 2004b, Hirst et al. 2007]. Empiric doses of BoNT/B were used as there is no ratio conversions for the two serotypes and between BoNT/B brands.

In 3 patients with spinal NDO, bladder injection of 5000 UI [Pistolesi et al., 2004] or 7500 UI [Reitz and Schurch, 2004b] of BONT-B (Neurobloc ®) restored bladder function for 6 months [Reitz and Schurch, 2004b]. Interestingly, 1 patient experienced dry mouth and dry eyes that resolved within 20 days. As this side effect was not reported after bladder BONT-A application, it is possible that different toxin serotypes have some different degrees of organ affinity. Dykstra et al. [2003] carried on a dose escalation study with BONT-B (rimabotulinumtoxinB in 15 female patients with OAB. They used doses of 2500, 3750, 5000, 10,000, and 15,000 U injected at 10 sites. Only 1 patient failed to respond and a clear dose-dependent effect, was observed, with the longest response seen in those injected with 15,000 U. Two patients, both injected with 15,000 U, experienced dry mouth and general malaise. In another study involving IDO and NDO patients, in which rimabotulinumtoxinB 5000 U were used. Hirst et al. [2007] concluded that Botulinum toxin B is not an effective treatment of refractory overactive bladder due to the short duration of action, in most of the patients not exceeding 10 weeks. The short duration of action for BONT-B at safe doses may, therefore, limit the clinic usefulness of this serotype for lower urinary tract dysfunctions.

8.2. Other toxins

8.2.1. Vanilloids

The rationale for intravesical vanilloid application, capsaicin and resiniferatoxin (RTX), derives from the fact that they desensitize thin type-C sensory fibers after binding TRPV1 the specific vanilloids binding site. In patients with NDO C-fiber desensitization inactivates the sacral micturition reflex [de Groat, 1997]. This sacral reflex emerges in chronic spinal-cord lesions above sacral segments [de Groat, 1997, Cruz et al, 1997a,b] in chronic bladder outlet obstruction [Chai et al., 1998] and in OAB [Silva et al., 2002]. In all conditions an increase in neuronal and urothelial TRPV1 expression was observed in the bladder [Smet et al. 1997, Brady et al., 2004, Liu and Kuo, 2007a] which correlates with urgency sensation [Liu et al., 2007b]. TRPV1 expression decreases after intravesical application of vanilloids [Apostolidis et al., 2005; 2006].

8.2.1.1. Intravesical capsaicin.

Capsaicin was the first vanilloid to be instilled in the bladder as 1-2 mM 30% alcohol solution to treat NDO. Capsaicin was studied in 6 non-controlled [Fowler et al., 1992;1994; Geirsson et al., 1995; Das et al.,1996; Cruz et al., 1997b, De Ridder et al., 1997]. Best clinical results were found among patients with incomplete spinal cord lesions. In the unique controlled study [de Sèze et al., 1998] 10 NDO patients found a significant regression of the incontinence and urge sensation after capsaicin instillation whereas only 1 among the 10 patients who received the alcohol solution had clinical improvement. The pungency of alcoholic capsaicin solutions has prevented the widespread use of this compound and no recent studies could be identified.

8.2.1.2. Intravesical Resiniferatoxin

Intravesical RTX application in NDO patients was evaluated in five small open-label studies [Cruz et al., 1997b; Lazzeri et al., 1997; 1998, Kuo 2003] at different RTX concentrations, 10 nM, 50 nM, 100 nM and 10 μM. In selected patients an improvement or disappearance of urinary incontinence and a decrease in daily urinary frequency was reported.

In a placebo-controlled urodynamic study in SCI with NDO patients a significant increase in the volume for first detrusor contraction and maximal cystometric capacity was found in the RTX arm [Silva et al., 2005]. RTX, 600 nM was compared against OnabotA, 300U in a study involving 25 patients with NDO due to chronic spinal cord injury. Both neurotoxins were capable of significantly reducing the number of daily incontinence episodes and improving maximum bladder capacity. However, onabotA turned out to be more effective [Giannantoni et al, 2004].

Resiniferatoxin (RTX) has lower pungency [Cruz et al., 1997b], offering the possibility of its instillation not only in NDO patients who lost bladder sensation but also in OAB and PBS/IC patients. A proof-of-concept study with intravesical RTX in OAB patients with IDO showed that intravesical instillation RTX 50 nmol/L was associated with an improvement in volume to first detrusor contraction and maximal cystometric capacity. These improvements were accompanied by a decrease in episodes of urgency incontinence and of daily frequency [Silva et al., 2002]. Subsequent small open label studies confirmed these observations using either a single high (50-100 nM) or multiple low (10 nM) dose approaches [Kuo, 2003; Kuo et al., 2005a].

A specific decrease on urgency was reported in males with prostate enlargement and LUTS in a small non-controlled study [Dinis et al., 2005]. The effect of RTX on refractory OAB was then further investigated in 3 randomized or quasi-randomised clinical trials with contradictory results. Kuo et al. [2006] randomised 54 patients to receive 4 weekly instillations of a low concentration RTX solutions (10 nmol/L) or the vehicle solution, 10% ethanol in saline. At 3 months, patients feeling much better or improved amount to 42.3% and 19.2% in the RTX group and 14.2% and 7.1% in the control arm, respectively. In a quasi-randomised study [Silva et al., 2007] included 23 OAB patients in a 30-day run-in period in which medications influencing the bladder function were interrupted. In the last week of this period patients filled a 7-day bladder diary. Then, patients were instilled with 100 ml of 10% ethanol in saline (vehicle solution) and 30 days later a second 7-day diary was collected. Finally, patients were instilled with 100 ml of 50 nM RTX in 10% ethanol in saline and additional bladder diaries were collected at 1 and 3 months. After vehicle instillation, the mean number of episodes of urgency per week was 56 ± 11. At 3 months after RTX instillation the number of episodes of urgency decreased to 37 ± 6 [Silva et al., 2007]. In a third study, OAB women were randomly assigned to receive a single intravesical dose of 100 ml of either RTX 50 nM or placebo and no clinical differences were found at 4 weeks. [Rios et al., 2007].

TRPV1 involvement in pain encouraged the investigation of RTX as a treatment for bladder pain in IC/PBS [Lazzeri et al. 2000, 2004, Chen et al., 2005, Apostolidis et al., 2006; Peng and Kuo, 2007]. However, a randomized, double-blind study in 163 patients with IC/PBS, in which several doses of intravesical RTX (10 nmol/L, 50 nmol/L, and 100 nmol/L) were compared with placebo, failed, however, to show any advantage for the neurotoxin over placebo in terms of overall symptoms, pain, urgency, frequency, nocturia, or average voided volume during 12 weeks of follow up [Payne et al., 2005].

8.2.2. NX-1207.

is a new drug under investigation for the treatment of LUTS associated with BPH [Kunit and Lusuardi, 2014]. It is a new therapeutic protein of proprietary composition with selective pro-apoptotic prop-

erties [Shore, 2010]. The drug is injected directly into the directly into the transitional zone of the prostate as a single administration to induce focal cell loss in prostate tissue through apoptosis, leading to non-regressive prostate shrinkage and both short- and long-term symptomatic improvement. Two US Phase II trials have been performed [Shore, 2010]. Information about the drugs was only available in abstract form and not yet in the peer-reviewed literature. One of them was a multicenter, randomized, non-inferiority study involving 32 clinical sites with 85 subjects and two dose ranges (2.5 and 0.125 mg) and an active open-label comparator (finasteride). Allegedly, the mean AUA Symptom Score improvement after 90 days in the intent to- treat group was 9.71 points for 2.5 mg NX-1207 (n = 48) versus 4.13 points for finasteride (n = 24). Despite these data, the clinical development of this drug was suspended due to the release of negative data coming from a phase III trial run in the US.

8.2.3. PRX302

PRX302 is a modified form of proaerolysin, a highly toxic bacterial pore-forming protoxin that requires proteolytic processing by prostate-specific antigen (PSA) [Singh et al., 2007]. The safety and efficacy of PRX302 was evaluated in men with moderate to severe BPH [Denmeade et al.,2010]. The patients were refractory, intolerant, or unwilling to undergo medical therapies for BPH and had an IPSS >12, a quality of life (QoL) score >3, and prostate volumes between 30 and 80 g. Fifteen patients were enrolled in phase 1 studies, and 18 patients entered phase 2 studies. Subjects received intraprostatic injection of PRX302 into the right and left transition zone via a transperineal approach in an office-based setting. Phase 1 subjects received increasing concentrations of PRX302 at a fixed volume; phase 2 subjects received increasing volumes per deposit at a fixed concentration. IPSS, QoL, prostate volume, Qmax), IIEF, serum PSA levels, pharmacokinetics, and adverse events were recorded at 30, 60, 90, 180, 270, and 360 days after treatment. Sixty percent of men in the phase 1 study and 64% of men in the phase 2 study treated with PRX302 had >30% improvement compared to baseline in IPSS out to day 360. Patients also experienced improvement in QoL and reduction in prostate volume out to day 360. Patients receiving >1 ml of PRX302 per deposit had the best response overall. There were no deleterious effect on erectile function. Adverse eventswere mild tomoderate and transient in nature. The major study limitation was the small sample size. The promising safety profile and evidence of efficacy in the majority of treated subjects in these phase 1 and 2 studies led to a phase IIb study [Elhilali et al., 2013]. A total of 92 men with an IPSS ≥15, Qmax ≤12 ml/s and prostate volume beween 30 and 100 ml were randomized 2:1 to a single ultrasound guided prostatic injection of PRX302 (0.6 mg per grame prostate) or placebo. Benign prostatic hyperplasia medications were prohibited. The toxin decreased IPSS score by approximately 9-point and increase Qmax by 3 ml/s, both changes being statistically significant when compared to vehicle. Efficacy was sustained for 12 months. PRX302 apparent toxicity was mild, transient, and limited to local discomfort/pain and storage urinary symptoms occurring in the first few days, with no effect on erectile function. No further developments were identified.

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9. COMBINATIONS

9.1. Antimuscarinics with α1-AR antagonists

Traditionally, male lower urinary tract symptoms (LUTS) were thought to result from benign prostatic obstruction (BPO) secondary to benign prostatic enlargement (BPE). However, male LUTS can arise from prostatic pathology, bladder dysfunction, or both. Thus, diagnosing and appropriately treating men with overactive bladder (OAB) symptoms can be complex and difficult. **α_1**-AR antagonists remain the most widely used pharmacologic agents for the relief of bladder outflow resistance as they relax prostatic and urethral smooth muscle tone, which is the dynamic component of BPO. In contrast, antimuscarinics, which function by competitively blocking muscarinic receptors, are the first-line pharmacologic treatment for OAB. Given the prevalence of combined voiding and OAB symptoms, as well as the finding that the quality of life (QoL) of these patients is affected primarily by the symptoms of OAB, it is logical for this category of patients to be given antimuscarinic drugs.

Several studies have demonstrated the superior efficacy of a combination treatment of an **α_1**-AR antagonist and an antimuscarinic in alleviating symptoms of BPO and concomitant OAB, compared with either monotherapy [Saito, et al., 1999; Lee et al., 2005; Kaplan et al., 2006, MacDiarmid et al., 2006; Kaplan et al., 2013a; van Kerrebroeck et al., 2013a; b Van Kerrebroeck et al., 2013: Drake, Sokol et al., 2016; Matsukawa, Takai et al., 2017). The combination is now the treatment recommended by AUA, EAU, and NICE for men with moderate-to-severe LUTS with predominant storage symptoms.

the therapeutic benefits of combining an antimuscarinic agent (propiverine) with an α_1-AR antagonist (tamsulosin) were compared with an α_1-AR antagonist alone and reported by Saito and colleagues (Saito, Yamada et al. 1999). The rates of improvement in daytime frequency, incontinence, and urgency were greater in the combination group than in the α_1-AR antagonist monotherapy group. The post-void residual (PVR) was unchanged in both groups, and one case (1.5%) of acute urinary retention (AUR) occurred with the combined treatment. Subsequently, Lee et al. (Lee, Choo et al. 2005) compared the safety and efficacy of 8 weeks of combination therapy using propiverine and doxazosin in 211 men with urodynamically confirmed bladder outlet obstruction and OAB symptoms. Compared with doxazosin monotherapy, patients in the combination therapy group showed greater improvement in urinary frequency, average micturition volume, and storage and urgency scores on the International Prostate Symptom Score (IPSS). Patient satisfaction was significantly higher in the combination group. There was a significant increase in PVR (+20.7 mL) in the combination group, but no case of urinary retention was reported.

a large-scale, multicenter, randomized, double-blind, placebo-controlled trial (TIMES study) demonstrated the efficacy and safety of tolterodine extended release (ER) alone, tamsulosin alone, and the combination of the two in 879 men with OAB and BPO (Kaplan, Roehrborn et al. 2006). In their primary efficacy analysis, 172 men (80%) receiving tolterodine ER plus tamsulosin reported treatment benefits by week 12 (p<0.001 vs. placebo; p=0.001 vs. tolterodine ER; p=0.03 vs. tamsulosin). In their secondary efficacy analysis, patients receiving tolterodine ER plus tamsulosin experienced small but significant reductions in urgency incontinence, urgency episodes, daytime frequency, and nocturia compared with patients receiving placebo. However, tamsulosin monotherapy and placebo did not differ significantly in any diary variables at week 12. Patients receiving tolterodine ER plus tamsulosin showed significant improvements in total IPSS (−8.02 vs. placebo, −6.19, p=0.003) and QoL (−1.61 vs. −1.17, p=0.003). Although patients who received tamsulosin alone reported significant improvements in total IPSS, the differences in total IPSS among patients who received tolterodine ER versus placebo were not significant. A subanalysis (Rovner, Kreder et al. 2008) of data from the TIMES study focused on the urgency perception scale and concluded that the 217 men who received tolterodine plus tamsulosin showed significantly improved urgency variables and patient-reported outcomes. Moreover, this group of patients reported increased satisfaction with the treatment as well as a greater willingness to continue the treatment. Another subanalysis (Kaplan, Roehrborn et al. 2008) of the data examined the effects of the drugs on urinary symptoms as assessed by the IPSS. Those authors concluded that tolterodine ER plus

tamsulosin was significantly more effective than placebo in treating storage LUTS, including OAB symptoms.

On the other hand, Maruyama and colleagues (Maruyama, Kawachi et al. 2006) reported different results from their prospective, randomized, controlled study in which naftopidil (25–75 mg/day), an α_{1d}-AR antagonist, was administered for 12 weeks alone or in combination with propiverine hydrochloride (10–20 mg/day) or oxybutynin hydrochloride (2–6 mg/day) to 101 men with BPH. In their study, the IPSS and QoL indexes improved significantly in both groups, with no significant differences between the groups. Maximum flow rate (Qmax) and PVR showed improvement in both groups, again with no differences between groups. However, the median post-therapeutic PVR was significantly higher in the combination group (45.0 mL) than in the monotherapy group (13.5 mL, p = 0.021). Significantly more patients had increased PVR relative to unchanged residuals in the combination therapy (22.9%) group than in the monotherapy group (5.0%, p = 0.038). Those authors concluded that combination therapy with a low-dose antimuscarinic agent was not more effective than naftopidil monotherapy. Moreover, although they did not encounter any cases of urinary retention, the percentage of patients with increased PVR was significantly greater in the combination therapy group than in the monotherapy group.

In caution of increased PVR and aggravated voiding symptoms, combination therapy with a lower dose of an antimuscarinic and α_1-AR antagonist was tried to assess its efficacy and adverse events in men with BPO and OAB. Kang et al. (Kang, Sung et al. 2009) evaluated the efficacy and safety of tamsulosin combined with a low dose of propiverine hydrochloride (10 mg) in comparison with tamsulosin monotherapy in 119 men with prostate volume of 20 ml or greater, IPSS of more than 8, and OAB symptoms. After 3 months of treatment, both groups showed significant improvements in IPSS, QoL, voided volume, Qmax, and PVR, but only the QoL index differed significantly between the groups in favor of the combination group. No cases of AUR were recorded in this low-dose study. Those authors suggested that for patients with LUTS due to BPH and concomitant OAB, combination therapy with an alpha-blocker and low-dose anticholinergic could be a reasonable and effective initial therapeutic option.

Another study evaluated the efficacy and safety of low-dose (2 mg) tolterodine ER with an α-blocker compared with a standard-dose (4 mg) tolterodine ER with an α-blocker in 95 men with residual storage symptoms after 4 weeks of α-blocker monotherapy (Kim, Jung et al. 2016). The inclusion criteria were IPSS ≥12, IPSS QoL ≥3, and ≥8 micturition and ≥2 urgency episodes per 24 h. After 12 weeks of treatment, patients in both groups had a significant improvement in their total IPSS scores (−5.5 and −6.3, respectively), micturition per 24 h (−1.3 and −1.7, respectively) and nocturia per night (−0.4 and −0.4, respectively). Changes in IPSS, bladder diary variables, and patient-reported outcomes did not differ significantly between the treatment groups. All interventions were well tolerated. The authors concluded that low-dose tolterodine ER add-on therapy is similar to standard-dose tolterodine ER add-on therapy in terms of efficacy and safety.

The efficacy and safety of solifenacin in combination with tamsulosin have been reported in several large-scale RCTs, including the VICTOR (Kaplan, McCammon et al. 2013)and SATURN (Van Kerrebroeck, Haab et al. 2013)b trials.

The VICTOR trial (Kaplan, McCammon et al. 2013) was a randomized, placebo-controlled study assessing solifenacin 5 mg as an add-on therapy to **α_1**-AR antagonist treatment in men with residual OAB symptoms. Significant reductions in daytime frequency, the primary outcome of the study, were achieved in both the solifenacin and tamsulosin and placebo and tamsulosin groups compared to baseline, but the difference between the two groups was not significant. Solifenacin add-on significantly reduced daily urgency episodes compared to placebo, but that was the only significant efficacy difference between solifenacin and placebo. Seven patients (3%) in the solifenacin group developed retention, with three requiring catheterization, versus none in the placebo group.

The SATURN trial was a phase 2 dose-finding study evaluating the combination of different doses of solifenacin (3, 6, and 9 mg/day) with tamsulosin versus tamsulosin alone in 937 men with voiding and storage LUTS (total IPSS ≥ 13, and Qmax 4.0–15.0 ml/s with a volume voided ≥120 ml) (Van Kerrebroeck, Haab et al. 2013). There were no specific inclusion criteria regarding storage symptoms. Patients were excluded if they had a PVR >200 ml. Decreases in micturition frequency and total urgency and frequency scores and increases in void volume per micturition were significantly greater with increasing solifenacin dosages in the combination groups compared with tamsulosin monotherapy. In a post-hoc analysis, patients with at least two urgency episodes and at least eight micturitions per 24 h at baseline showed clear improvements in storage and QoL parameters with combination treatment over tamsulosin alone. The subgroup of patients with fewer storage symptoms experienced little or no additional benefit from combination therapy compared with tamsulosin monotherapy. Combination therapy was well tolerated, and adverse events were consistent with the safety profiles of each individual compound. Mean PVR volume increased with increasing solifenacin dose, but the changes were not clinically relevant and were not accompanied by an increase in the incidence of retention.

Based on the results from the SATURN trial, those authors expected to establish the most useful clinical dose of combination therapy for further evaluation in the phase 3 study (NEPTUNE) of solifenacin and tamsulosin in males with moderate to severe storage LUTS (van Kerrebroeck, Chapple et al. 2013). The study evaluated the efficacy and safety of a fixed-dose combination (FDC) tablet containing solifenacin plus an oral controlled absorption system formulation of tamsulosin (TOCAS). A total of 1334 men with LUTS/BPH who had moderate-to-severe storage symptoms (two or more urgency episodes per 24 h, eight or more micturitions per 24 h and Patient Perception of Intensity of Urgency Scale grade 3 or 4) were included. Men with ultrasound-estimated prostate weight ≥75g or PVR >150 ml were excluded. Patients were randomized to placebo, TOCAS 0.4 mg, FDC solifenacin 6 mg plus TOCAS 0.4 mg, or FDC solifenacin 9 mg plus TOCAS 0.4 mg. The primary efficacy endpoints were (1) total IPSS and (2) Total Urgency and Frequency Score (TUFS). An FDC met the success criteria if it demonstrated superiority over placebo and noninferiority to TOCAS for total IPSS and superiority to TOCAS for TUFS. After 12 weeks of treatment, reductions in total IPSS and TUFS were observed with both solifenacin 6 mg plus TOCAS (–7.0 and –8.1, respectively) and solifenacin 9 mg plus TOCAS (–6.5 and –7.6, respectively) compared with TOCAS (–6.2 and –6.7, respectively) and placebo (-5.4 and -4.4, respectively). Solifenacin 6 mg plus TOCAS met all the prespecified success criteria for both primary endpoints, and solifenacin 9 mg plus TOCAS met the success criteria compared with placebo but not compared with TOCAS. Both FDCs improved QoL and were well tolerated, with low incidences of AUR. Consequently, a once-daily FDC tablet of solifenacin 6 mg plus TOCAS 0.4 mg intended to treat both storage and voiding symptoms in men with

LUTS/BPH is licensed and available in several countries, including the UK.

Patients completing the 12-week NEPTUNE study were invited into the open-label, 40-week NEPTUNE II extension study to evaluate the long-term (up to 52 weeks in total) safety and efficacy of the solifenacin plus TOCAS combination therapy (Drake, Chapple et al. 2015). For total IPSS, significant improvements from baseline to the end of treatment compared with placebo were achieved with TOCAS (−6.2, p = 0.039), solifenacin 6 mg plus TOCAS (−7.0, p < 0.001), and solifenacin 9 mg plus TOCAS (−6.5, p = 0.006). Solifenacin 6 mg plus TOCAS was noninferior to TOCAS for total IPSS (p = 0.001); improvement was observed with solifenacin 9 mg plus TOCAS compared with TOCAS (p = 0.028), but that was not significant after multiplicity adjustment, and noninferiority was not proven. Improvements in TUFS from baseline to the end of treatment were significantly greater with TOCAS, solifenacin 6 mg plus TOCAS, and solifenacin 9 mg plus TOCAS than with placebo (−6.7, −8.1, and −7.6, respectively; all p < 0.001). Solifenacin 6 mg plus TOCAS was statistically superior to TOCAS alone on TUFS (p = 0.025), but solifenacin 9 mg plus TOCAS was not (p = 0.162). Urinary retention occurred in eight patients, and five cases required catheterization: one case (0.3%) each with TOCAS and solifenacin 6 mg plus TOCAS and three cases (0.9%) with solifenacin 9 mg plus TOCAS.

Responder and health-related QoL (HRQoL) analyses of the NEPTUNE study reported that men treated with an FDC of solifenacin 6 mg plus TOCAS consistently had significantly improved outcomes compared with both the placebo and TOCAS groups (Drake, Sokol et al. 2016). The reduction in total urgency frequency score correlated significantly with the improvement in HRQoL, as defined by the IPSS QoL score, the OAB-q symptom bother score, the overall patient global impression bladder symptoms, and the general health of the patient. The authors expected the positive HRQoL data for the FDC of solifenacin 6 mg plus TOCAS to translate into improved persistence of treatment and possibly increased confidence in prescribing the combined therapy as an initial treatment for moderate-to-severe LUTS/BPH.

More recently, a pilot study evaluated the potential influence of antimuscarinics on morphometric parameters of the prostate in patients with BPE/OAB (Sakalis, Sgas et al. 2018). All five muscarinic receptors are present in the endothelium and smooth muscle cells of small arteries (Walch, Brink et al. 2001). The human prostate expresses muscarinic receptors at densities exceeding those of α1-adrenoreceptors, with a preponderance of the M1 subtype on the prostatic epithelium and a smaller population of the M2 subtype on stromal cells (Ventura, Pennefather et al. 2002, Witte, Chapple et al. 2008). In primary epithelial and stromal cultures of enlarged prostates, M1, M3, and M5 receptors were expressed in the prostatic epithelium, and M2 and M4 receptors were found in the prostatic stroma (Obara, Arai et al. 2000). In cell cultures, carbachol, a muscarinic receptor agonist, stimulated prostatic growth of prostate cancer cells through increased DNA synthesis (Rayford, Noble et al. 1997). This mitogenic response is mediated by M3 receptors. Based on those results, the authors assessed whether solifenacin influenced the growth and vascularity of the prostate in patients with BPE/OAB. For that study, men with prostate volume >30 mL, predominately storage LUTS, urgency episodes ≥3/24 h, Qmax ≥10 mL/s, and PVR ≤100 mL were randomized to receive either tamsulosin or tamsulosin + solifenacin. After 6 months, a reduction in total prostate volume (mean –9.5%) was noted in the combination group, as opposed to an increase in the monotherapy group (+9.2%; P < 0.001). Similar changes were noted in adenoma volume (monotherapy +17.4% vs. combination –12.5%, P = 0.001) and prostate vascularity (monotherapy +149.3% vs. combination –19.8%, P = 0.001). The results of this pilot study suggest that solifenacin might affect the morphometric properties of the prostate, decreasing total prostate and adenoma volume, as well as vascularity. Further study is needed to determine the molecular mechanisms of antimuscarinics in the prostate.

As mentioned earlier, to prevent AUR and increased PVR, a lower dose of antimuscarinics was studied in combination with α_1-AR antagonists in men with BPO and OAB. However, the efficacy of low-dose antimuscarinic therapy in patients with severe symptoms of OAB should be considered. A study evaluated the safety and efficacy of high-dose anticholinergics combined with alpha-blockers as an initial treatment (Lee, Hur et al. 2017). Another study assessed the efficacy of combining two antimuscarinics (solifenacin and trospium) with alpha-blockers.

In the first study, 146 men with total IPSS ≥8, total OAB symptom scores (OABSS) ≥3, OABSS questionnaire number 2 ≥2, and prostate volume >20 mL were randomly assigned to receive 0.2 mg of tamsulosin (Group I, *n* = 44), 0.2 mg of tamsulosin plus 5 mg of solifenacin (Group II, *n* = 55), or 0.2 mg of tamsulosin plus 10 mg of solifenacin (Group III, *n* = 47) for 12 weeks (Lee, Hur et al. 2017). Men with PVR ≥200 mL were excluded. After treatment, the groups receiving both tamsulosin and solifenacin (II and III) showed improvements in storage symptoms significantly greater than those in the monotherapy group (I) in the OABSS and IPSS storage subscores. The total IPSS and IPSS voiding sub-score improved significantly in every group, and the IPSS QoL and Patient Perception of Bladder Condition (PPBC) scores also showed improvements, although not significant ones. Qmax decreased in groups II and III, but not significantly. PVR increased in the combined treatment groups, but that was not significant, either. Dry mouth developed in four (7%) and eight (17%) men in groups II and III, respectively, and one (2%) and three (6%) men dropped out in groups II and III, respectively. Two cases of AUR developed in group III, and one of those patients was withdrawn from the study. Those authors concluded that initially treating men with LUTS with a combination of tamsulosin and solifenacin significantly improves storage symptoms, but dose modification is necessary to prevent adverse events.

Another study assessed the effectiveness of combining solifenacin with trospium and tamsulosin to treat men with severe symptoms of OAB (Kosilov, Loparev et al. 2016). Men initially diagnosed with BPH (8–19 points on the IPSS, residual urine volume ≤ 100 ml) were enrolled in the preliminary stage of the study. During that preliminary stage, men with severe OAB were selected. More than 3 episodes of urinary incontinence/day, IPSS > 19, and OAB-V8 questionnaire score > 32 were considered to be severe symptoms of OAB. The included patients were randomly assigned to the main group (daily combination of 5 mg of solifenacin and 5 mg of trospium with 0.4 mg of tamsulosin) or the control group (tamsulosin 0.4 mg) for 8 weeks. The percentage of patients with severe symptoms of OAB, the first endpoint, was 44%. In the main group, the number of incontinence episodes decreased from 3.4/day to 0.9/day (p < .01), and daytime frequency decreased from 9.2/day to 5.7/day (p < .05). Changes in the parameters in the control group proved to be insignificant. Six patients from the main group (3 dry mouth, 2 hypertension, 1 unknown) and 3 from the control group (2 lack of efficacy, 1 dry mouth) stopped participating in the study. Retention was not reported. The combination of standard doses of trospium and solifenacin with tamsulosin was suggested to be an effective and well tolerated treatment option for the management of severe symptoms of OAB in men.

Besides, in a 52 week extension study (NEPTUNE II), Matsukawa et al.(Matsukawa, Takai et al. 2017) evaluated 1 year efficacy and safety of a combination therapy with an anticholinergic agent and an α1-blocker for patients with BPE and OAB, in comparison with those of α1-blocker monotherapy by conducting a urodynamic study. A total of 120 men with BPE, urinary urgency at least once per week, and an OABSS of ≥3 were randomly assigned to receive 8 mg of silodosin and 20 mg of propiverine or 8 mg of silodosin alone. Changes in parameters from baseline to 1 year after treatment were assessed using IPSS, IPSS-QoL, OABSS, and voiding and storage functions measured by UDS. In the results, although the mean IPSS and OABSS improved significantly in both groups, the combination group showed statistically significant improvement in the OABSS (–3.4 vs. –2.4 in monotherapy, $p = 0.04$), IPSS-QoL (–1.9, –1.2, $p = 0.01$), and OAB-urgency scores (–1.8, –1.2, $p < 0.01$). In storage function, both groups showed significant improvements, but the combination group demonstrated a greater improvement in terms of the disappearance of detrusor overactivity (54.5% vs. 34.2% monotherapy, $p = 0.07$) and bladder capacity (+61 mL, +33 mL, $p = 0.02$).

Those authors concluded that the long-term combination of silodosin and propiverine is a safe and effective treatment for men with BPE and OAB showing urodynamic improvement in the storage phase parameters.

Several systematic reviews and meta-analyses have compared the safety and efficacy of treatments combining anticholinergics and α-blockers with α-blocker monotherapy in men with BPH and OAB (Filson, Hollingsworth et al. 2013) (Hao, Tian et al. 2014) (Gong, Dong et al. 2015). In results from a pooled analysis of 7 placebo-controlled trials, combination therapy produced a significantly greater reduction in the IPSS storage sub-score (Δ -0.73, 95% CI –1.09 to –0.37) and voiding frequency (Δ -0.69 voids, 95% CI –0.97 to –0.41) than monotherapy (Filson, Hollingsworth et al. 2013). Combination therapy also produced a greater reduction in Qmax (Δ -0.59 ml/sec, 95% CI –1.04 to –0.14) and an increase in PVR (Δ 11.60 ml, 95% CI 8.50–14.70). The number of patients who need to be treated with combination therapy to cause 1 AUR episode was calculated to be 101 (95% CI 60–267). Those authors concluded that combination treatment with α-blockers and anticholinergics significantly improved the storage voiding parameters compared with men treated with α-blocker therapy alone. The combined treatment approach was deemed to be safe, with a minimal risk of increasing PVR, decreasing Qmax, or causing AUR. Hao et al. evaluated 18 eligible RCTs in a systematic review including 2106 subjects (52%) in the combination therapy group (antimuscarinic and α-blocker) and 1978 subjects (48%) in the α-blocker monotherapy group (Hao, Tian et al. 2014). The combination group reported significant improvements in storage IPSS (mean difference (MD) = −1.51; 95% CI −2.10 to −0.91, $p < 0.00001$), QoL score (MD = −0.53; 95% CI −0.89 to −0.17, $p = 0.004$), micturitions/24 h (MD = −1.14; 95% CI −1.84 to −0.45, $p = 0.001$), and urgency episodes/24 h (MD = −0.99; 95% CI −1.46 to −0.51, $p < 0.0001$). Q_{max} (MD = −0.05; 95% CI −0.27 to 0.17, $p = 0.64$), total IPSS (MD = −0.88; 95% CI −1.64 to −0.12, $p = 0.02$), and voiding IPSS (MD = 0.40; 95% CI −0.34 to 1.15, $p = 0.29$) did not differ significantly between groups. Worsened PVR was observed only in the combination therapy group (MD = −6.53; 95% CI 3.06–10.00, $p < 0.0002$). Gong et al. performed a meta-analysis of studies that compared tamsulosin and solifenacin combination therapy with tamsulosin monotherapy (Gong, Dong et al. 2015)]. Seven eligible articles were identified with a total of 3063 participants. Combination therapy produced significant improvements in storage IPSS (MD = −0.60; 95% CI −0.81 to −0.38, $p < 0.0001$), QoL (MD = −0.23; 95% CI −0.34 to −0.11, $p < 0.0001$), micturitions/24 h (MD = −0.70; 95% CI −0.86 to −0.55, $p < 0.0001$), and urgency episodes/24 h (MD = −0.26; 95% CI −0.48 to −0.05, $p = 0.018$). The incidence of AEs in the combined therapy group (31%) was similar to that in the tamsulosin monotherapy group (26%). AUR was seldom reported in those studies, and no clinically significant changes in Qmax were reported.

More recently, a systematic review and meta-analysis compared the effectiveness of newer medications for LUTS/BPH (Dahm, Brasure et al. 2017). Six combination therapies of anticholinergics and α-blockers were compared with ABs alone: 1. Darifenacin plus an AB versus an AB alone; 2. Fesoterodine plus an AB versus an AB alone; 3. Oxybutynin plus an AB versus an AB alone; 4. Solifenacin plus an AB versus an AB alone; 5. Tolterodine plus an AB versus an AB alone; 6. Trospium plus an AB versus an AB alone. The safety and efficacy of the combination therapies seemed to be similar among different the antimuscarinics. However, those trials often excluded participants with high PVRs, thereby excluding the patients at highest risk for urinary retention. Furthermore, the applicability of those findings to general medical practice was affected by their use of an assessment of postvoid residuals that is not part of the routine care pathway.

9.2. Antimuscarinics with 5α-reductase inhibitors

The standard first-line medical therapy for men with moderate-to-severe LUTS is an α_1-AR antagonist, a 5α-reductase inhibitor, or a combination of the two. Both α_1-AR antagonists and 5α-reductase inhibitors alleviate LUTS in men by reducing bladder outlet resistance: α_1-AR antagonists decrease smooth muscle tone in the prostate and bladder neck, and 5α-reductase inhibitors reduce prostate volume. Several trials have demonstrated the safety and efficacy of combining antimuscarinics with an α_1-AR antagonist in patients with OAB and BPO. However, post hoc analyses of the TIMES study (Kaplan, Roehrborn et al. 2006) suggested that men with smaller prostates benefit more from antimuscarinic therapy than those with larger prostates (Roehrborn, Kaplan et al. 2008, Roehrborn, Kaplan et al. 2009). Chung and co-workers conducted an open-label, fixed-dose study to assess the safety and efficacy of tolterodine ER in combination with dutasteride in men with large prostates (≥30 g) and persistent OAB symptoms who had been unsuccessfully treated with dutasteride alone (Chung, Te et al. 2010)]. At the start of the study, all patients had been on dutasteride 0.5 mg daily for at least 6 months, and α1-AR antagonist therapy had failed. All patients were given 4 mg tolterodine ER daily for 12 weeks and had discontinued taking the α1-AR antagonist before the start of the study. After 12 weeks of treatment, the frequency (–3.2/24 h, $p < 0.02$), urgency (19.2%, $p < 0.03$), number of severe OAB episodes (71.4%, $p < 0.05$), and incidence of nighttime voiding (–0.9, $p < 0.003$) had all decreased significantly from baseline. IPSS decreased with dutasteride treatment (from 19.3 to 14.3) and further decreased with the addition of tolterodine to 7.1 ($p < 0.001$). Storage symptoms decreased from 9.8 to 4.5 ($p < 0.001$). Dry mouth occurred in four (7.5%) subjects, constipation in one (2%), and decreased sexual function in two (3.9%). PVR increased by 4.2 mL, Qmax decreased by 0.2 mL/s, and no patients went into retention. The authors concluded that the combination of tolterodine and dutasteride was safe, effective, and well-tolerated in men with large prostates who had persistent OAB symptoms and LUTS secondary to BPO. Their results indicate that antimuscarinics are safe and effective when used in combination with 5α-reductase inhibitors in certain patients with OAB and BPO. Further studies are required to verify the efficacy of antimuscarinics combined with 5α-reductase inhibitors in patients with persistent OAB symptoms and LUTS secondary to BPO.

Dutasteride was evaluated in terms of OAB symptoms and bladder ischemia in men with BPE (Wada, Matsumoto et al. 2015). After 24 weeks of dutasteride treatment, the bladder vascular resistive index (RI) had decreased significantly, and the IPSS urgency score was significantly improved, from 2.3 ± 1.9 to 1.4 ± 1.4 (P < 0.01). In 20 patients with persistent urgency after dutasteride, RI was less improved than in an additional 10 patients without urgency. Post-treatment bladder outlet obstruction index scores and PdetQmax in patients with persistent urgency were significantly higher than in those without urgency after dutasteride. The authors suggested that the reduction of obstruction and improvement in bladder ischemia might play important roles in the beneficial effects of dutasteride on OAB symptoms. In another study, patients with persistent OAB symptoms after the initial administration of dutasteride were given solifenacin, and IPSS and OABSS were prospectively collected at 4 and 12 weeks (Maeda, Kikuchi et al. 2015). Solifenacin 5 mg significantly reduced the IPSS, OABSS, and OABSS Q3 at 4 (–2.0, – 2.0, –1.0; P <0.05) and 12 weeks (–3.1, –2.7, –1.3; P <0.05).

9.3. Antimuscarinic with β3-adrenoceptor agonists

Because the mechanism of action of β3-adrenoceptor agonists differs from that of antimuscarinics, they might be a useful combination treatment for patients experiencing adverse events or insufficient symptom improvement with antimuscarinics. In addition, combining an β3-adrenoceptor agonist with an antimuscarinic could improve efficacy in the treatment of OAB. Several clinical trials have demonstrated the safety and efficacy of combination therapy using antimuscarinics and β3-adrenoceptor agonists.

9.3.1. Antimuscarinics with mirabegron

SYMPHONY and relevant studies

SYMPHONY was a phase 2, randomized, double-blind, parallel-group, placebo- and monotherapy-controlled trial that evaluated the efficacy, dose-response relationship, and safety/tolerability of solifenacin combined with mirabegron in comparison with placebo and solifenacin 5 mg monotherapy in adults with OAB symptoms (Abrams, Kelleher et al. 2015). A total of 1306 patients were randomly assigned to 12 groups: placebo, 6 combination groups (solifenacin 2.5, 5, or 10 mg plus mirabegron 25 or 50 mg), and 5 monotherapy groups (solifenacin 2.5, 5, or 10 mg; mirabegron 25 or 50 mg) for a 12-week treatment period. The primary endpoint was change from baseline to end of treatment in mean volume voided (MVV) per micturition. All combinations with solifenacin 5 or 10 mg improved MVV significantly more than solifenacin 5 mg monotherapy, and a decreasing trend in the mean number of micturitions per 24 hours was observed with increasing solifenacin and mirabegron doses. Three drug combinations (solifenacin 5 mg plus mirabegron 50 mg, solifenacin 10 mg plus mirabegron 25 mg, and solifenacin 10 mg plus mirabegron 50 mg) demonstrated significant improvements compared with both solifenacin 5 mg and placebo. No severe adverse events were reported, and treatment was generally well tolerated.

In the same study population, changes from baseline to end of treatment were assessed versus placebo and solifenacin 5 mg in patient-reported outcomes (PROs) (OAB-q [Symptom Bother/total HRQoL] and PPBC) and predetermined clinically meaningful improvements in efficacy (e.g., <8 micturitions/24 h). The solifenacin 5 mg plus mirabegron 25 mg and solifenacin 5 mg plus mirabegron 50 mg groups showed significantly improved PPBC versus the placebo and solifenacin 5 mg groups ($p < 0.05$). Significant improvements in the Symptom Bother score were evident for three combinations (solifenacin 2.5 mg plus mirabegron 50 mg, solifenacin 5 mg plus mirabegron 25 mg, and solifenacin 5 mg plus mirabegron 50 mg). Significant improvements in total HRQoL were observed for the solifenacin 5 mg plus mirabegron 50 mg group versus placebo and for three combinations (solifenacin 2.5 mg plus mirabegron 50 mg, solifenacin 5 mg plus mirabegron 25 mg, and solifenacin 5 mg plus mirabegron 50 mg) versus solifenacin 5 mg ($p < 0.05$). In the efficacy responder analyses, two combinations (solifenacin 5 mg plus mirabegron 25 mg, and solifenacin 5 mg plus mirabegron 50 mg) were associated with significant improvements versus solifenacin 5mg in terms of patients achieving complete dryness and achieving ≥ 50% reduction in incontinence episodes per day. The proportion of patients achieving micturition frequency normalization at week 12 was 65.4 and 61.6% with the combinations of solifenacin 10 mg + mirabegron 25 mg and solifenacin 5 + mirabegron 50 mg, respectively, which was significantly greater than in the placebo and solifenacin 5 mg groups ($p < 0.05$). The proportion achieving a major (≥2 point) improvement in PPBC was significantly higher with solifenacin 5 mg plus mirabegron 50 mg than with placebo ($p = 0.038$) and with solifenacin 5 mg + mirabegron 25 mg and solifenacin 5 mg + mirabegron 50 mg than with solifenacin 5 mg ($p = 0.020$ and $p = 0.012$, respectively) **(Table 5)** (Abrams, Kelleher et al. 2017).

Table 5. Health-related quality of life (HRQoL) outcomes and responder analysis results for the SYMPHONY study

HRQoL parameters	n	PRO			Responder analysis (* Difference (%) vs solifenacin 5 mg, p<0.05)				Double responder; Micturition normalization (≤ 8/24hr) and one option below			Triple responder: Micturition normalization (≤ 8/24hr) and one option below	
		OAB-q Symptom Bother	OAB-q HRQoL Total	PPBC	≥10-point improvement in OAB-q Symptom Bother	≥10-point improvement in HRQoL Total	≥1-point improvement in PPBC	≥2-point improvement in PPBC	≥10-point improvement in the OAB-q Symptom Bother	≥10-point improvement in HRQoL Total	≥1-point improvement in PPBC	≥10-point improvement in the OAB-q Symptom Bother score and a ≥1-point improvement in PPBC	≥10-point improvement in HRQoL Total score and a ≥1- point improvement in PPBC
Placebo	79	-25.5	22	-1.4	73.40%	67.10%	69.20%	39.70%	43.60%	43.60%	37.70%	36.40%	36.40%
M25	75	-27.1	20.2	-1.4	84.00%	57.30%	76.70%	42.50%	36.50%	29.70%	38.90%	36.10%	30.60%
M50	76	-27.5	23.1	-1.5	78.90%	71.10%	78.90%	38.20%	41.30%	34.70%	40.00%	36.00%	29.30%
S2.5	77	-29.8	24.6	-1.5	85.70%	74.00%	68.00%	44.00%	52.10%	43.80%	40.80%	39.40%	38.00%
S5	150	-26.8	21.6	-1.3	81.30%	72.70%	72.80%	42.20%	41.80%	34.20%	37.50%	34.00%	30.60%
S10	75	-29.9	23.5	-1.5	85.30%	74.70%	*84.9%	46.60%	48.60%	44.60%	50.00%	47.20%	41.70%
S2.5+M25	144	-28	22.7	-1.4	82.60%	72.90%	74.50%	48.20%	51.40%	44.40%	47.50%	46.80%	42.40%
S2.5+M50	145	-31.7	26	-1.7	85.50%	78.60%	83.20%	52.40%	49.00%	46.20%	48.90%	45.40%	43.30%
S5+M25	139	-32	26.4	-1.7	85.60%	77.00%	77.90%	*54.4%	46.40%	42.00%	47.40%	43.70%	41.50%
S5+M50	146	-33.5	28.4	-1.8	88.40%	*84.2%	*82.6%	*54.9%	57.00%	52.10%	54.20%	51.40%	49.30%
S10+M25	78	-33.6	27.4	-1.8	88.50%	79.50%	82.90%	57.90%	61.50%	55.10%	63.20%	60.50%	53.90%
S10+M50	78	-31.4	27	-1.6	83.30%	82.10%	75.60%	50.00%	50.60%	50.60%	48.10%	45.50%	45.50%
S10 vs S5		p=0.21	p=0.41	p=0.38					p=0.40	p=0.22	p=0.10	p=0.080	p=0.16
S2.5+M25 vs S5		p=0.54	p=0.57	p=0.85					p=0.20	p=0.15	p=0.15	p=0.052	p=0.060
S2.5+M50 vs S5		p=0.016	p=0.021	p=0.024					p=0.48	p=0.15	p=0.11	p=0.12	p=0.083
S5+M25 vs S5		p=0.011	p=0.013	p=0.005					p=0.87	p=0.34	p=0.23	p=0.24	p=0.13
S5+M50 vs S5		p<0.001	p<0.001	p=0.003					p=0.009	p=0.002	p=0.003	p=0.002	p<0.001
S10+M25 vs S5		p=0.005	p=0.011	p=0.004					p=0.011	p=0.007	p<0.001	p<0.001	p=0.003
S10+M50 vs S5		p=0.056	p=0.018	p=0.26					p=0.28	p=0.047	p=0.16	p=0.13	p=0.057

HRQoL: health-related quality of life, M25: mirabegron 25 mg, M50: mirabegron 50 mg, OAB-q: Overactive Bladder questionnaire, PPBC: Patient Perception of Bladder Condition, PRO: patient-related outcome, S2.5: solifenacin 2.5 mg, S5: solifenacin 5 mg, S10: solifenacin 10 mg

Table 6. Health-related quality of life (HRQoL) outcomes and responder analysis results for the SYNERGY study

HRQoL parameters	n	PRO					Responder analysis				Double responder: at least a 50% reduction in the mean number of incontinence episodes/24 h and one option below			Triple responder: at least a 50% reduction in the mean number of incontinence episodes/ 24 h and one option below	
		OAB-q Symptom Bother	OAB-q HRQoL Total	TS-VAS	PPBC	PGI-C	≥10-point improvement in OAB-q Symptom Bother	≥10-point improvement in HRQoL Total	≥1-point improvement in PPBC	≥2-point improvement in PPBC	≥10-point improvement in the OAB-q Symptom Bother	≥10-point improvement in HRQoL Total	≥1-point improvement in PPBC	≥10-point improvement in the OAB-q Symptom Bother score and a ≥1-point improvement in PPBC	≥10-point improvement in HRQoL Total score and a ≥1- point improvement in PPBC
Placebo	400	-19.5	15.4	1.4	-0.9	8%	65.30%	56.80%	59.80%	29.50%	45.20%	39.10%	40.90%	36.10%	33.30%
M25	392	-23.9	18.9	2.2	-1.2	14%	71.20%	61.00%	65.40%	37.20%	54.00%	46.00%	48.50%	45.00%	39.10%
M50	398	-26.1	21	2.2	-1.3	15%	77.10%	68.30%	72.40%	40.70%	58.20%	52.90%	53.90%	48.40%	44.80%
S5	399	-26.4	20.2	2.3	-1.3	14%	81.20%	71.20%	71.90%	42.60%	62.60%	54.00%	56.00%	53.30%	49.20%
S5+M25	800	-31.1	24	2.5	-1.5	20%	82.80%	74.50%	75.70%	49.70%	65.20%	59.00%	59.90%	56.30%	51.60%
S5+M50	795	-32.2	24.3	2.6	-1.7	27%	84.30%	71.10%	78.40%	51.20%	68.20%	58.20%	63.80%	60.30%	52.80%
S5+M25 vs S5		p<0.001	p<0.001	p=0.077	p<0.001		p=0.224	p=0.077	p=0.065	p=0.007	p=0.381	p=0.095	p=0.210	p=0.335	p=0.416
S5+M50 vs S5		p<0.001	p<0.001	p=0.050	p<0.001		p=0.037	p=0.321	p=0.001	p<0.001	p=0.040	p=0.073	p=0.004	p=0.009	p=0.105
S5+M25 vs M25		p<0.001	p<0.001	p=0.008	p<0.001		p<0.001	p<0.001	p<0.001	p<0.001	p=0.001	p<0.001	p<0.001	p=0.001	p<0.001
S5+M50 vs M50		p<0.001	p=0.003	p=0.007	p<0.001		p=0.002	p=0.294	p=0.294	p<0.001	p=0.001	p=0.067	p<0.001	p<0.001	p=0.005

HRQoL: health-related quality of life, M25: mirabegron 25 mg, M50: mirabegron 50 mg, OAB-q: Overactive Bladder questionnaire, PGI-C: Patient Global Impression of Change, PPBC: Patient Perception of Bladder Condition, PRO: patient-related outcome, S5: solifenacin 5 mg, TS-VAS: treatment satisfaction visual analogue scale

SYNERGY and relevant studies

SYNERGY was a phase 3 study that evaluated the safety and efficacy of combinations of solifenacin and mirabegron in comparison with monotherapy and placebo in wet OAB patients with at least 3 urinary incontinence episodes in a 7-day micturition diary (Herschorn, Chapple et al. 2017). A total of 3527 patients was randomly assigned to 6 groups: placebo, 2 combination groups (solifenacin 5 mg plus mirabegron 25 mg or solifenacin 5 mg plus mirabegron 50 mg), and 3 monotherapy groups (solifenacin 5 mg or mirabegron 25 or 50 mg) for a 12-week treatment period. The co-primary endpoints were change from baseline to end of treatment (EoT) in the mean number of urinary incontinence episodes and micturitions per day. All treatment groups demonstrated a reduction in urinary incontinence episodes per day, with a greater reduction in the combination therapy groups than in the monotherapy and placebo groups (reductions of −1.34 for placebo; −1.7 and −1.76 for mirabegron 25 mg and 50 mg, respectively; −1.79 for solifenacin 5 mg; −2.04 for mirabegron 25 mg plus solifenacin 5 mg; and −1.98 for mirabegron 50 mg plus solifenacin 5 mg). However, although the combined solifenacin 5 mg plus mirabegron 50 mg group was superior to solifenacin 5 mg monotherapy for urinary incontinence episodes (mean adjusted difference of −0.2 episodes per day, p = 0.033), the solifenacin 5 mg plus mirabegron 50 mg group did not achieve a significant effect versus mirabegron 50 mg. In terms of micturitions per day, all treatment groups had greater improvements than placebo, with effect sizes for the combination groups (solifenacin 5 mg plus mirabegron 25 mg: –0.85; solifenacin 5 mg plus mirabegron 50 mg: –0.95) higher than those with solifenacin 5 mg (–0.56) and mirabegron (25 mg: -0.36; 50 mg: -0.39) monotherapies. The mean adjusted change in MVV/micturition from baseline to EoT was greater in the combined solifenacin 5 mg plus mirabegron 25 mg (34.84 ml) and solifenacin 5 mg plus mirabegron 50 mg (39.73 ml) groups than in the monotherapy and placebo groups. Improvements in the mean adjusted differences in the MVV/micturition for the combinations were significantly greater than those for monotherapy except for the comparison between solifenacin 5 mg plus mirabegron 25 mg and solifenacin 5 mg. Responder analyses showed odds ratios in favor of the combination therapies versus the monotherapies in the proportion of patients with zero UI episodes (the odds were 31–50% higher in the combination groups) and those achieving micturition frequency normalization (the odds were 30–60% higher in the combination groups). In all, 46% of patients had received previous OAB treatment. A subgroup analysis found a larger effect size in patients who had received prior OAB medication than in treatment-naïve patients in the mean number of incontinence episodes per day (except for the combined solifenacin 5 mg plus mirabegron 25 mg versus mirabegron 50 mg comparison) and in the change in the number of micturitions per day (except for the combined solifenacin 5 mg plus mirabegron 25 mg versus solifenacin 5 mg comparison).

HRQoL was evaluated using OAB-q, PPBC, a treatment satisfaction-visual analogue scale (TS-VAS), and a responder analysis (≥10-point improvement in OAB-q Symptom Bother score, ≥10-point improvement in HRQoL total score, and ≥1-point or ≥ 2-point improvement in PPBC) (Robinson, Kelleher et al. 2018). At 12 weeks, combination treatment (solifenacin 5 mg plus mirabegron 25 mg and solifenacin 5 mg plus mirabegron 50 mg) showed significantly greater improvements in OAB-q [Symptom Bother/total HRQoL] and PPBC than monotherapy, except for the comparison between solifenacin 5 mg plus mirabegron 25 mg and solifenacin 5 mg, The odds ratios significantly favored combination therapy over monotherapy in the proportion of responders with most of the predefined criteria **(Table 6)**.

BESIDE and relevant studies

The BESIDE study, a phase IIIB trial, specifically recruited OAB patients who had not responded to 4 weeks of solifenacin monotherapy (Drake, Chapple et al. 2016). A total of 2174 patients with OAB who remained incontinent despite 5 mg of solifenacin once daily during a 4-week, single-blind, run-in were randomized 1:1:1 to a double-blind daily combination (solifenacin 5 mg plus mirabegron 25 mg, increasing to 50 mg after 4 weeks) (n=727), solifenacin 5 mg (n=728), or solifenacin 10 mg (n=719) for 12 weeks. The primary efficacy endpoint was a change in the mean number of incontinence episodes per 24 h. Key secondary efficacy endpoints were changes in the mean number of micturitions per 24 h and the number of incontinence episodes noted in a 3-d voiding diary. The adjusted change in incontinence episodes per day from baseline to EoT was significantly greater in the combination group (–1.80) than the solifenacin 5 mg group (–1.53). There was also a greater reduction in mean daily micturitions (–1.59 versus –1.14) and 3-day incontinence episodes (4.25 versus 4.87) in the combination group than the solifenacin 5 mg group. The combination treatment was not inferior to solifenacin 10 mg in the key secondary endpoints and was superior to solifenacin 10 mg at improving daily micturitions. All treatments were well tolerated. These results suggest that a combination therapy of mirabegron 50 mg and solifenacin 5 mg could be an alternative to dose escalation of solifenacin in patients with insufficient response to 5 mg of solifenacin alone. The incidence of TEAEs was lowest in the solifenacin 5 mg group (33.1%) and highest in the solifenacin 10 mg group (39.4%); in the combination group, it was 35.9%. The incidence of dry mouth was highest in the solifenacin 10 mg group (9.5%), with the combination group (5.9%) similar to the 5.6% of the solifenacin 5 mg group. In a prespecified subanalysis stratified by age (≥65 yr and ≥75 yr), the combination treatment improved OAB symptoms more effectively than solifenacin monotherapy irrespective of age (Gibson, MacDiarmid et al. 2017).

The proportion of responders who became continent was 46.0% in the combination group, which was significantly higher than in the solifenacin 5 mg (37.9%) and 10 mg (40.2%) groups. Patients receiving the combination were 47% and 28% more likely to achieve zero incontinence, 51% and 25% more likely to achieve a 50% or greater reduction in incontinence episodes per 24 h, and 29% and 12% more likely to achieve normalization of micturition frequency versus treatment with solifenacin 5 mg and 10 mg, respectively. The combination group was superior to the solifenacin 5 mg and 10 mg groups in the OAB-q Symptom Bother score, total HRQoL, and PPBC (details in **Table 3**). According to the responder analysis, statistically significant odd ratios were found in favor of the combination treatment versus monotherapy in the proportion of responders with a 10-point or greater improvement in the OAB-q Symptom Bother score and total HRQoL and a 2-point or greater improvement in PPBC (MacDiarmid, Al-Shukri et al. 2016) **(Table 7)**.

Table 7. Health-related quality of life (HRQoL) outcomes and responder analysis results for the BESIDE study

HRQoL parameters	n	PRO				Responder analysis				Double responder: at least a 50% reduction in the mean number of incontinence episodes/24 h and one option below			Triple responder: at least a 50% reduction in the mean number of incontinence episodes/ 24 h and one option below	
		OAB-q Symptom Bother	OAB-q HRQoL Total	TS-VAS	PPBC	≥10-point improvement in OAB-q Symptom Bother	≥10-point improvement in HRQoL Total	≥1-point improvement in PPBC	≥2-point improvement in PPBC	≥10-point improvement in the OAB-q Symptom Bother	≥10-point improvement in HRQoL Total	≥1-point improvement in PPBC	≥10-point improvement in the OAB-q Symptom Bother score and a ≥1-point improvement in PPBC	≥10-point improvement in HRQoL Total score and a ≥1- point improvement in PPBC
S5+M50	727	-26.9	20.8	1.8	-1.5	81.70%	68.60%	76.50%	49.80%	62.20%	53.50%	58.40%	55.50%	48.00%
S5	728	-21.9	17.6	1.4	-1.2	71.70%	60.60%	69.50%	39.10%	50.10%	43.00%	49.00%	42.20%	38.10%
S10	719	-23.6	17.4	1.6	-1.3	74.60%	60.10%	71.90%	43.20%	56.50%	44.50%	53.10%	49.10%	39.50%
S5+M50 vs S5		p<0.001	p=0.001	p=0.001	p<0.001	p<0.001	p=0.001	p=0.006	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
S5+M50 vs S10		p=0.001	p<0.001	p=0.113	p=0.004	p=0.002	p=0.002	p=0.081	p=0.027	p=0.050	p=0.003	p=0.083	p=0.037	p=0.005

HRQoL: health-related quality of life, M50: mirabegron 50 mg, OAB-q: Overactive Bladder questionnaire, PPBC: Patient Perception of Bladder Condition, PRO: patient-related outcome, S5: solifenacin 5 mg, S10: solifenacin 10 mg, TS-VAS: treatment satisfaction visual analogue scale

Table 8. Health-related quality of life (HRQoL) outcomes and responder analysis results for the SYNERGY II study

HRQoL parameters	n	PRO			Responder analysis	
		OAB-q Symptom Bother	OAB-q HRQoL Total	TS-VAS	≥10-point improvement in OAB-q Symptom Bother	≥10-point improvement in HRQoL Total
S5+M50	1206	-29.5	21.3	2.7	82.90%	68.40%
M50	305	-22	16.6	2.2	70.70%	56.20%
S5	303	-24.9	18.5	2.2	72.40%	61.60%
S5+M50 vs M50		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
S5+M50 vs S5		p<0.001	p=0.010	p<0.001	p<0.001	p=0.014

HRQoL: health-related quality of life, M50: mirabegron 50 mg, OAB-q: Overactive Bladder questionnaire, PRO: patient-related outcome, S5: solifenacin 5 mg, TS-VAS: treatment satisfaction visual analogue scale

SYNERGY II

SYNERGY II was a phase 3 study of 1829 patients with wet OAB symptoms that demonstrated the safety and efficacy of a combination treatment (solifenacin 5 mg plus mirabegron 50 mg) over 12 months (Gratzke, van Maanen et al. 2018). Overall, 47% experienced ≥ 1 TEAE, and the incidence of TEAEs was slightly higher in the combination group (49%) than in the mirabegron (41%) and solifenacin (44%) groups. A total of 3.7% of the TEAEs were reported to be serious, and only one patient was considered to have possibly treatment-related TEAE (atrial fibrillation in the mirabegron group). Dry mouth was observed more frequently in the combination (6.1%) and solifenacin groups (5.9%) than in the mirabegron group (3.9%). Constipation occurred more frequently in the combination group (3.3%) than the solifenacin (2.3%) and mirabegron (1.0%) groups. Despite the longer treatment period, similar incidence rates for anticholinergic-associated AEs were observed after combination treatment. This study showed that the OAB-q Symptom Bother score and HRQoL total score improved significantly more with combination treatment than with either monotherapy at EoT **(Table 8)**. At EoT, the combination of solifenacin 5 mg and mirabegron 50 mg group was superior to the mirabegron 50 mg and solifenacin 5 mg groups in terms of changes in the number of incontinence episodes per 24 h (vs. mirabegron: adjusted mean difference [AMD]: –0.5, 95% CI –0.7 to –0.2, p<0.001; vs. solifenacin: AMD –0.1. 95% CI –0.4 to 0.1, p=0.002) and in the number of micturitions per 24 h (vs. mirabegron: AMD –0.5, 95% CI –0.8 to –0.2, p<0.001; vs. solifenacin: AMD –0.4, 95% CI –0.7 to –0.1, p=0.004).

MILAI

In Japan, Yamaguchi et al. conducted a multicenter, open-label, phase IV study (MILAI study) to assess the safety and efficacy of mirabegron in combination with solifenacin in OAB patients who had been treated with solifenacin 2.5 mg or 5 mg once daily for at least 4 weeks (Yamaguchi, Kakizaki et al. 2015). If at 8 weeks the patients showed insufficient response to mirabegron 25 mg, were agreeable to a dose increase, and the investigator judged that there were no safety concerns, the mirabegron dose could be increased to 50 mg. In the MILAI study, 223 patients were assigned to one of 4 groups: solifenacin 2.5 mg plus mirabegron 25 mg (n=35), solifenacin 2.5 mg plus mirabegron 50 mg (n=37), solifenacin 5 mg plus mirabegron 25 mg (n=58), and solifenacin 5 mg plus mirabegron 50 mg (n=93) for a 16-week treatment period. The overall incidence of drug-related TEAEs was 23.3%, and all TEAEs were mild or moderate. All treatments produced significant improvements in the OABSS total score, OAB-q-short-form (SF) score (Symptom Bother and total HRQoL score), mean number of micturitions/24 h, mean number of urgency episodes/24 h, mean number of UI episodes/24 h, mean number of urgency UI episodes/24 h, MVV/micturition, and mean number of nocturia episodes/night. In the mirabegron 50 mg groups, the mean OABSS total score, mean OABS-q SF Symptom Bother score, and total HRQoL score were further improved after the dose increased from 25 to 50 mg.

MILAI II

Previous combination studies involved add-on therapy of mirabegron 50 mg in OAB patients who did not respond to anticholinergic monotherapy (Yamaguchi, Kakizaki et al. 2015, Drake, Chapple et al. 2016) or concurrent use of mirabegron and anticholinergics (Abrams, Kelleher et al. 2015, Herschorn, Chapple et al. 2017). Alternatively, the MILAI II study demonstrated the long-term safety and efficacy of antimuscarinic add-on therapy in patients with OABS symptoms who had a suboptimal response to initial mirabegron monotherapy (Yamaguchi, Kakizaki et al. 2019). A total of 647 patients with residual OAB symptoms despite receiving mirabegron 50 mg once daily for at least 6 weeks were randomized to receive a combination of mirabegron 50 mg and solifenacin 5 mg (n=166), propiverine 20 mg (n=161), imidafenacin 0.2 mg (n=161), or tolterodine 4 mg (n=159) for 52 weeks (1:1:1:1 ratio). At week 8, the dose of anticholinergics (except for tolterodine) could be doubled, if a patient had a poor response to the study drugs. If a TEAE occurred after the dose escalation, the dose could be reduced to the original level. Overall, 80.2% of patients experienced at least one TEAE. Furthermore, 46.8% of patients experienced at least one drug-related TEAE, with similar incidences in all groups. Dry mouth (25.2%), nasopharyngitis (21.6%), and constipation (16.5%) were the most commonly reported TEAEs. Dry mouth (31.7%) in the mirabegron plus propiverine group and constipation in the mirabegron plus solifenacin group were slightly higher than found with the other regimens. No notable change from baseline was found for PVR in any group. Significant improvements in OABSS and OAB-q SF were observed at the first evaluation (week 4 for OABSS, week 12 for OAB-q SF) and were maintained throughout the entire 52-week treatment period. Significant improvements from baseline were observed in all of the efficacy parameters assessed using data from patient micturition diaries.

9.3.2. Antimuscarinic with vibegron

Vibegron is a novel, potent, and highly selective β3-adrenoceptor agonist. The efficacy and safety of vibegron were demonstrated in a phase III study conducted in OAB patients in Japan (Yoshida, Kakizaki et al. 2018, Yoshida, Takeda et al. 2018). The efficacy of vibegron in combination with anticholinergics can be predicted from the results of several studies combining anticholinergics with mirabegron, but the evidence is insufficient. One two-part phase IIb study assessed the safety and efficacy of vibegron as a once-daily treatment for OAB patients (part 1) and the safety, tolerability, and efficacy of vibegron administered with or without an antimuscarinic (part 2) (Mitcheson, Samanta et al. 2019). In part 1, patients received once-daily vibegron at 3, 15, 50, or 100 mg, tolterodine ER 4 mg, or placebo for 8 weeks or concomitant vibegron 50 mg plus tolterodine ER 4 mg for 4 weeks and then vibegron 50 mg for 4 weeks. In part 2, patients received once-daily vibegron 100 mg, tolterodine ER 4 mg, vibegron 100 mg plus tolterodine ER 4 mg, or placebo for 4 weeks. The combination of vibegron 100 mg plus tolterodine ER 4 mg decreased the least square mean (LSM) daily number of micturitions and urgency episodes from baseline to week 4 more than tolterodine ER 4 mg or vibegron 100 mg alone; the decrease was statistically significant ($p < 0.05$) versus tolterodine ER 4 mg. Among wet OAB patients, a numerically greater decrease in the LSM daily number of urgency incontinence episodes was observed from baseline to week 4 with the combination of vibegron 100 mg plus tolterodine ER 4 mg versus vibegron 100 mg or tolterodine ER 4 mg alone. Furthermore, a greater decrease in the LSM daily number of total incontinence episodes from baseline to week 4 was observed with a combination of vibegron 100 mg plus tolterodine ER 4 mg than with vibegron 100 mg alone (numerically) or tolterodine ER 4 mg alone ($p < 0.05$) **(Table 9)**.

9.4. Combined antimuscarinics

Although antimuscarinic agents are the first-choice treatment for patients with OAB symptoms, they do not always lead to the desired effects of detrusor stability and continence, especially in patients with spinal cord injury or neurologic diseases such as multiple sclerosis or meningomyelocele. When antimuscarinic treatments fail, invasive procedures such as the injection of botulinum toxin, electrical nerve stimulation, or augmentation cystoplasty are necessary.

Table 9. Change in average daily number of micturitions, urgency urinary incontinence episodes, total incontinence episodes, and urgency episodes from baseline to week 4 in the full-analysis set population

	Placebo	V100	TER4	V100+ TER4	Difference in LSM from V100	Difference in LSM from TER4
Number of micturitions	-1.2	-1.95	-1.16	-2.09	-0.23 (p=0.356)	-0.91 (p<0.001)
UUI episodes	-1.5	-1.71	-1.38	-1.77	-0.17 (p=0.492)	-0.53 (p=0.027)
Total incontinence episodes	-1.73	-1.98	-1.65	-1.98	-0.12 (p=0.626)	-0.51 (p=0.038)
Urgency episodes	-2.35	-2.52	-1.56	-2.68	-0.27 (p=0.400)	-1.27 (p<0.001)

LSM: least square mean, TER4: tolterodine ER 4 mg, UUI: urgency urinary incontinence, V100: vibegron 100 mg

Table 10. Clinical studies of combined antimuscarinic treatments

Study	Patients (n)	Initial antimuscarinics	Combined antimuscarinics	Efficacy results
Amend et al. (Amend, Hennenlotter et al. 2008)	NDO (27)	Oxybutynin 30 mg/day Tolterodine 2×8 mg/day Trospium 3×30 mg	+trospium 45–90 mg +oxybutynin 15–30 mg +tolterodine 4–8 mg	UI episodes decreased: 8.6±2.7 to 1.3±0.9 7.0±1.5 to 0.6±0.7 7.5±2.7 to 2.0±1.5
Nardulli et al. (Nardulli, Losavio et al. 2012)	NDO (12)	Oxybutynin 15 mg/day Oxybutynin 15 mg/day	+trospium 80 mg +solifenacin 10 mg	UI episodes decreased: 5.3to 0.8 4.5 to 1.0
Bolduc et al. (Bolduc, Moore et al. 2009)	NDO (19) OAB (14)	Tolterodine 4 mg	+solifenacin 5 mg +solifenacin 10 mg	UI episodes decreased: 100% in 17 pts > 90% in 14 pts 50–89% in 2 pts
Kosilov et al. (Kosilov, Loparev et al. 2014)	OAB (313)	Trospium 60 mg + solifenacin 20 mg (198) or placebo (115)		Significant decrease in UI episodes compared to placebo
Kosilov et al. (Kosilov, Loparev et al. 2014)	OAB (341)	Trospium 60 mg/day + solifenacin 20 (58) Trospium 30 mg/day + solifenacin 10 (55) Trospium 30 mg/day + solifenacin 10 (62)		Cyclic therapy with high-dose combination showed the most successful treatment without increase in side effects
Kosilov et al. (Kosilov, Loparev et al. 2016)	OAB & BPH (338)	Solifenacin 5 mg + trospium 5 mg + tamsulosin 0.4 mg vs. tamsulosin 0.4 mg		UI episodes decreased: 3.4 (0.8) to 0.9 (0.7)
Wang et al. (Wang, Jiang et al. 2017)	OAB (129)	Any antimuscarinic	+ oxybutynin ER (5–15 mg once a day)	All OAB symptom indexes decreased significantly

In patients who fail to respond or show suboptimal responses to antimuscarinic drugs but tolerate the treatment well, it has been shown that increasing the daily dose can lead to significant improvements in OAB symptoms. A significant decrease in incontinence episodes was observed after doubling the recommended daily doses of trospium chloride and tolterodine to 90 and 8 mg, respectively, in patients with persistent neurogenic detrusor overactivity (NDO) (Horstmann, Schaefer et al. 2006). Another non-invasive approach in patients with refractory NDO or OAB is the combination of two different antimuscarinic drugs, which has been demonstrated to be safe and effective in several clinical studies of patients with NDO (Amend, Hennenlotter et al. 2008, Nardulli, Losavio et al. 2012) or OAB (Bolduc, Moore et al. 2009, Kosilov, Loparev et al. 2014)a; b (Wang, Jiang et al. 2017) **(Table 10).**

Positive results were speculated to result from 1) synergistic activation of different muscarinic receptors or interactions with receptors on different parts of the bladder wall, 2) undiscovered increase in the metabolism of antimuscarinics requiring an increased dose of different antimuscarinic drugs, 3) down-regulation of subdivisions of antimuscarinic receptors under monotherapy that could produce better susceptibility in the other subdivisions when treated by the second drug.

A combined antimuscarinic regimen using tolterodine, oxybutynin, and trospium was evaluated as a non-invasive alternative by Amend and colleagues (Amend, Hennenlotter et al. 2008)] for patients who had neurogenic bladder dysfunction with incontinence, reduced bladder capacity, and increased intravesical pressure. They added secondary antimuscarinics to the existing double-dose antimuscarinics for patients who previously demonstrated unsatisfactory outcomes with double-dose antimuscarinic monotherapy. After a 4-week combined regimen, incontinence episodes decreased, and reflex volume, maximal bladder capacity, and detrusor compliance increased. Side-effects were comparable to those seen with normal-dose antimuscarinics.

Kosilov and colleagues found that cyclic therapy of high-dose solifenacin and trospium in elderly men and women with moderate or severe OAB symptoms enabled patients to maintain a longer therapeutic effect with an acceptable level of side effects (Kosilov, Loparev et al. 2014)a. They conducted another study to evaluate the efficacy of cyclic treatment with combined antimuscarinic drugs in elderly men and women with severe OAB symptoms and determined that it appeared to be effective by increasing the compliance level (76–84%). On the other hand, continuous therapy with standard doses of trospium and solifenacin resulted in low adherence and high rates of treatment withdrawal (≥ 66%), despite satisfactory clinical and urodynamic results.

The effectiveness of combination therapy with two different antimuscarinics was also evaluated in patients with severe symptoms of OAB and BPH (Kosilov, Loparev et al. 2015, Kosilov, Loparev et al. 2016). Patients in the experimental group received 2 months of treatment with a daily combination of solifenacin 5 mg, trospium 5 mg, and tamsulosin 0.4 mg. Patients in the control group received only tamsulosin. In the experimental group, the number of episodes of incontinence decreased from a moderate level of 3.4 (0.8) per day to 0.9 (0.7) per day, and most urodynamic indices normalized significantly. In the control group, changes in the urodynamic indices were not significant. The quantity of side effects did not exceed the level that is commonly found in patients receiving antimuscarinic monotherapy. Those authors concluded that a combination of trospium and solifenacin in standard doses is an efficient and safe method for managing severe OAB symptoms in patients with OAB/BPH already receiving tamsulosin (Kosilov, Loparev et al. 2016). However, in patients with OAB/BPH, the efficacy and side effects of combination therapy using different antimuscarinics should be further evaluated.

Wang CC, et al. (Wang, Jiang et al. 2017) evaluated the efficacy and safety of flexibly adding oxybutynin ER in patients with OAB refractory to monotherapy with an initial muscarinic antagonist. A total of 129 patients with persistent symptoms or partial response to 3 months of behavioral therapy and an optimized dose of one antimuscarinic agent were included. At baseline, week 4, and week 12 after the addition of oxybutynin ER (5–15 mg once a day), OAB symptom indexes, PPBC, uroflowmetry, PVR, therapeutic effect, AE, and tolerability were evaluated. Patients continuing combined antimuscarinic therapy were followed for up to 12 months. All OAB symptom indexes decreased significantly at all visits compared with baseline. A total of 32 (24.8%) and 25 (19.4%) patients reported successful therapeutic effect at weeks 4 and 12, respectively. Twenty-four (18.6%) and 44 (34.1%) patients discontinued therapy at weeks 4 and 12, respectively. However, only 31 (24.0%) patients continued the combined medication for up to 12 months. Discontinuation of the combined medication was noted in 28 (21.7%) patients due to AE and in 70 (54.3%) due to a lack of efficacy. The long-term efficacy of the combination of two antimuscarinic agents is thus limited.

9.5. α1-AR antagonists with β3-adrenoceptor agonists

Mirabegron facilitates detrusor relaxation during the storage phase of the micturition cycle and, in contrast with antimuscarinic agents, improves the storage capacity of the bladder without impairing the amplitude of the contraction during the voiding phase of the micturition cycle. In a pooled safety analysis of three phase III studies (Nitti, Khullar et al. 2013), the incidence of urinary retention was infrequent and lower in mirabegron-treated patients than in placebo and tolterodine-treated patients: placebo (n = 7; 0.5%), mirabegron 25 mg (n = 0), mirabegron 50 mg (n = 1; 0.1%), mirabegron 100 mg (n = 0), total mirabegron (n = 1; < 0.1%), and tolterodine (n = 3; 0.6%). The mean change in PVR volume from baseline to the final visit was unremarkable across treatment groups: placebo (−1.6 ml), mirabegron 25 mg (−3.0 ml), mirabegron 50 mg (−0.9 ml), mirabegron 100 mg (−0.7 ml), and tolterodine ER 4 mg (+ 0.1 ml). The proportion of patients experiencing ≥ 150 ml change in PVR volume from baseline was lower in the mirabegron groups than in the placebo and tolterodine groups: placebo (0.7%), mirabegron 25 mg (0%), mirabegron 50 mg (0.3%), mirabegron 100 mg (0.4%), and tolterodine ER 4 mg (0.8%). Although patients with a large PVR or risk of retention were excluded from those studies, as in the antimuscarinic studies of men with BPO, mirabegron can be a reasonable option for treating OAB symptoms and can be used in combination with α_1-AR antagonists in men with OAB and BPO.

Ichihara et al. (Ichihara, Masumori et al. 2015) evaluated the efficacy and safety of add-on treatment with mirabegron for OAB symptoms remaining after α1-blocker (tamsulosin) treatment for BPO. Men with urinary urgency ≥1/wk and a total OABSS ≥3 after 8 or more weeks of treatment with tamsulosin were randomly allocated to receive 0.2 mg of tamsulosin daily or 0.2 mg of tamsulosin and 50 mg of mirabegron daily. Patients with PVRs >100 ml were excluded. After 8 weeks of treatment, the change in total OABSS was significantly greater in the combination group than in the monotherapy group (–2.21 vs. –0.87, p=0.012). The changes in scores for urinary urgency, daytime frequency, IPSS storage symptom sub-score, and QoL were significantly greater in the combination group. The change in PVR was also significantly greater in the combination group, and AUR was observed in 1 patient.

Matsukawa et al.(Matsukawa, Takai et al. 2019) used a urodynamic study to compare the efficacy of fesoterodine and mirabegron as add-on therapies to silodosin in 120 men with persistent OAB symptoms despite silodosin monotherapy. Patients were randomized to receive add-on therapy with fesoterodine (4 mg/day) or mirabegron (50 mg/day) for 12 weeks. At week 12, the fesoterodine (vs. mirabegron) group showed significantly greater improvements in the OABSS-total (–2.8 vs. –1.5, p = 0.004), IPSS-QoL (–1.5 vs. –1.1, p = 0.04), and OABSS-urgency scores (–1.5 vs. –0.9, p = 0.008). Regarding storage functions, although both groups showed significant improvements, the fesoterodine group demonstrated greater improvements in the detrusor overactivity alleviation rate (52.6% vs. 28.9%, p = 0.03). Voiding functions did not deteriorate in either group; no significant inter-group differences were observed. PVRs increased significantly (by 16 mL) only in the fesoterodine group. Those authors concluded that using fesoterodine as an add-on therapy to silodosin was more effective than adding mirabegron to silodosin to improve OAB symptoms and storage functions without deteriorating voiding symptoms or functions.

9.6. α1-AR antagonists with 5a-reductase inhibitors

The Medical Therapy of Prostatic Symptoms Study (MTOPS) and Combination of Avodart® and Tamsulosin study (CombAT) demonstrated the superiority of combinations of α1-AR antagonists and 5-α reductase inhibitors over monotherapy in improving clinical outcomes and preventing symptomatic progression, AUR, and BPH-related surgery (McConnell, Roehrborn et al. 2003, Roehrborn, Siami et al. 2010). Post hoc analyses of MTOPS and CombAT data reported that combination therapy produced a significant improvement in IPSS, QoL, and nocturia (Fwu, Eggers et al. 2013, Oelke, Roehrborn et al. 2014, Roehrborn, Barkin et al. 2014). Discontinuation of 5-α reductase inhibitors after combination therapy was significantly associated with the resumption of combination therapy, progression of BPH, and need for BPH-related surgery (Lin, Liao et al. 2014). Currently, a combination of an α1-AR antagonist and a 5-α reductase inhibitor is recommended by many guidelines for men with bothersome moderate to severe LUTS, a high risk of disease progression or enlarged prostate (prostate volume > 40 mL), and high PSA. The possible disadvantage of combining α1-AR antagonists with 5α-reductase inhibitors is the increased incidence of adverse events from the concomitant effects of both classes of drugs (Fullhase, Chapple et al. 2013, La Torre, Giupponi et al. 2016). Potential side effects (e.g., ejaculation dysfunction with α1-AR antagonists or loss of libido with 5α-reductase inhibitors) might be additive and can negatively affect patient QoL, especially sexual function.

10. FUTURE POSSIBILITIES

Many potential drug targets for the treatment of OAB/DO have been explored in non-clinical and clinical research and have been reviewed elsewhere [Anderssonet al. 2018; Sacco and Bientinesi 2015]. These approaches can be grouped by route of administration such as transperineal, transrectal and transurethral (Andersson 2015) or as drugs acting peripherally or in the central nervous system, but in some cases the site of action remains unclear or.

They can also be grouped by level of evidence, for instance as negative clinical proof-of-concept data, promising animal data not yet tested clinically and targets with positive clinical proof-of-concept data. Details on some of the drugs under discussion are given below as is a critical summary of the current situation.

10.1. Drugs and targets with negative clinical proof-of-concept data

10.1.1. Prostaglandin receptor agonists and antagonists

The major prostaglandins (PG) PGD_2, PGE_2, $PGF_{2\alpha}$, prostacyclin (PGI_2), and thromboxane A_2 work on a family of receptors grouped into DP, EP, FP, IP, and TP subfamilies (Woodwardet al. 2011). Interest in prostaglandin receptors is partly based on increased urinary PGE_2 in OAB patients, but the proposed role as a biomarker of OAB has been questioned (Antunes-Lopeset al. 2014). Additional evidence comes from a demonstration of the presence of multiple prostaglandin receptors in the bladder (Ponglowhapanet al. 2010), prostaglandin receptor knock-out mice (McCaffertyet al. 2008, Molnáret al. 2021), and data with ligands of various prostaglandin receptors in animal models of OAB (Joneset al. 2009, Houet al. 2021). This section focuses on PG receptors as a drug target; enzymes involved in the generation of PGs, specifically cyclooxygenase will be covered in another section.

Intravesical installation of PGE_2 can induce detrusor overactivity (McCaffertyet al. 2008) and urine of patients with OAB contains elevated concentrations of PGE_2 (Antunes-Lopeset al. 2014).

Among the 4 subtypes of EP receptors, EP_1 and EP_3 appear to mediate detrusor contraction, whereas EP_2 and EP_4 mediate relaxation (Houet al. 2021). FP receptors also appear to mediate detrusor contraction, in some cases possibly even those of PGE_2 (Strombergaet al. 2020). PG receptors can also be found in the urothelium (Strombergaet al. 2020, Rahnama'iet al. 2010, Rahnama'iet al. 2012). They may also modulate afferent nerve activity (Schröderet al. 2004).

Based on such findings, the EP_1 receptor antagonist ONO-8539 had entered a double-blind phase II proof-of-concept study randomizing 435 patients to receive placebo or 30, 100 or 300 mg once daily ONO-8539 or 4 mg tolterodine for 12 weeks (Chappleet al. 2014). While tolterodine as positive control reduced micturition frequency (primary endpoint) by 2.18 episodes, the active treatments with all three doses reduced frequency to a similar extent as placebo (1.02, 1.53 and 1.31 as compared to 1.40). These data suggest a small if any role of EP_1 receptor inhibition in the treatment of OAB. While this does not exclude a role for other PG receptor subtypes, apparently no clinical trials for any other PG receptor modulator in OAB are ongoing.

10.2. Drugs and targets with promising animal data

10.2.1. Rho kinase and Rac1 inhibitors

Rho kinase 1 and 2 are essential enzymes in the regulation of smooth muscle contractility because of its involvement in Ca-sensitization (Frazieret al. 2008, Anjum 2018, Liet al. 2020) and also of generating the large compliance of the urinary bladder during filling (Nealet al. 2017). Inhibitors of Rho kinase such as Y 27,632, GSK 269,962 and fasudil inhibit bladder contraction in in vitro preparations from multiple species including rats, mice, guinea pigs and humans. Rho kinase is a potentially attractive target for two reasons: Firstly, rho kinase is involved in contraction elicited by a wide variety of agents including agonists at muscarinic (Frazieret al. 2008), bradykinin (Sand and Michel 2014), tachykinin (Déret al. 2019), sphingosine 1 phosphate (Anjumet al. 2017) or prostaglandin receptors (Molnáret al. 2021). Conversely, agonists relaxing bladder smooth muscle such as β_3-adrenoceptor agonists inhibit rho kinase (Cirinoet al. 2003) and combined administration of a β-adrenoceptor agonist and a rho kinase inhibitor yields greater detrusor strip relaxation (Cerneckaet al. 2015). Moreover, rho kinase

can also be activated by stretch in human bladder smooth muscle cells (Kushidaet al. 2016). Second, the expression and/or function of rho kinase are increased in pathologies associated with DO such as BOO, diabetes or in spontaneously hypertensive rats (Peterset al. 2006, Boopathiet al. 2014, Akaihataet al. 2015, Hanet al. 2015, Baeet al. 2015, Akakpoet al. 2017, Adedejiet al. 2019) and inhibition of detrusor contraction in vitro by rho kinase inhibitors is more pronounced in animal models of OAB or cystitis than in matched controls (Denizaltiet al. 2018). On the other hand, rho kinase expression is regulated in the bladder of aged subjects (Kirschsteinet al. 2014, Kirschsteinet al. 2015). Taken together, these data make rho kinase an attractive target for the treatment of OAB and cystitis.

Considering this background, the effect of rho kinase inhibitors, mostly GSK 269,962 and fasudil or hydroxy-fasudil, has been tested in rodent models of bladder dysfunction. The rho kinase parameters consistently improved cystometric parameters in a variety of OAB models including that induced by acetic acid (Wróbel and Rechberger 2017), retinyl acetate (Wróbel and Rechberger 2016, Wróbel and Rechberger 2017), corticosterone (Wróbelet al. 2018) or chronic bladder ischemia (Akaihataet al. 2018). They were similarly effective in rat models of cystitis as induced by protamine sulfate (Akinet al. 2015) or cyclophosphamide (Wróbelet al. 2017). Although the rho kinase inhibitor fasudil has been approved in some countries for clinical use in indications unrelated to the bladder, apparently no clinical studies of rho kinase inhibitors in bladder dysfunction are currently performed or have been completed.

Rac1 is a monomeric GTPase involved in similar pathways as rho kinase. Inhibitors of Rac1 such as NSC23766 and EHT1864 inhibit bladder contraction in in vitro preparations from multiple species including rats, mice and humans, and smooth muscle-specific knockout of Rac1 has similar effects (Liet al. 2020).

10.2.2. Purinergic system – P2X3 receptor antagonists

Other promising targets seem to be the purinergic [Ford and Cockayne, 2011: Ford and Undem., 2013; North and Jarvis., 2013; Andersson, 2015] and cannabinoid [Ruggieri. 2011; Hedlund, 2014; Hedlund and Gratzke 2016] systems, and different members of the TRP channel family [Everaerts et al., 2008; Andersson et al., 2010; Skryma et al., 2011; Avelino et al., 2013; Deruyver et al., 2014; Franken et al., 2014]. P2X3-receptor antagonists are currently being developed for treatment of non-bladder diseases, but clinical experiences in bladder disorders have not yet been reported.

10.2.3. Opioid receptor agonists

Opioids primarily exert their effects via opioid receptors, which are subdivided into the subtypes δ, κ and μ (Coxet al. 2015). The nociception/orphanin (NOP) receptors are also considered to be part of the opioid receptor family because of structural and functional similarities to the classic opioid receptors despite low potency of naloxone, whereas sigma receptors are not. While some studies suggest that sigma receptors may play a role in the regulation of bladder function (González-Canoet al. 2020), sigma receptors are not considered here.

Studies in guinea pigs have demonstrated a considerable expression of μ opioid receptors, whereas that of δ or κ opioid or NOP receptors was lower (Zhouet al. 2016). Studies with naloxone and other opioid receptor antagonists suggest that endogenous opioids play a role in the regulation of bladder function in health and disease and for instance may mediate bladder effects of gentle mechanical skin stimulation (Hotta and Watanabe 2015) or of sacral neuromodulation (Zhanget al. 2015, Jianget al. 2016, Bandariet al. 2017, Liet al. 2017); by acting in both ascending and descending pathways, they may also contribute to the micturition reflex (Hotta and Watanabe 2015, Fujimuraet al. 2017). This may in part involve direct effect on transmission of sacral parasympathetic nerves (Chenet al. 2015).

Tramadol is an analgesic drug that is an analgesic drug that is a weak μ-receptor agonist, but its active metabolites are stronger μ-receptor agonists and also act as serotonin and noradrenaline uptake inhibitors (Minamiet al. 2015). Tramadol has been shown to inhibit bladder overactivity in rats caused by apomorphine (Pehrson and Andersson 2003) or upon cerebral infarction (Pehrsonet al. 2003). Tramadol also inhibited micturition in conscious, freely moving rats without bladder dysfunction (Panditaet al. 2003). A published double-blind, placebo-controlled, randomized study on the efficacy and safety of tramadol in 76 patients with idiopathic DO has been retracted (Safarinejad and Hosseini 2014) and no other clinical trials appear to have been performed or ongoing. The preferential μ receptor agonist naltalimide (also known as TRK-130) has shown promise in animal models of OAB (Fujimuraet al. 2014) or cystitis (Fujimuraet al. 2017) but apparently has not progressed to clinical studies. While observations with both the weak agonist tramadol and the antagonist naltalimide are interesting, they are also puzzling as they leave it open whether an opioid receptor agonist or antagonist is more promising for the treatment of bladder dysfunction.

10.3. Drugs and targets with positive clinical proof-of-concept data

10.3.1. Neurokinin receptor antagonists

The tachykinins/neurokinins substance P, neurokinin A (also known as neurokinin α, neuromedin L or substance K) and neurokinin B (also known as neurokinin β or neuromedin K) act on NK_1, NK_2 and NK_3 receptors, respectively (Alexanderet al. 2019). There are major species differences in the recognition profile of non-peptide small molecules for all three receptors, which makes the extrapolation of data from animal experiments to humans challenging.

Neurokinins (Coveñaset al. 2003) and their three receptors are found in various parts of the CNS including those involved in micturition control (Saffroyet al. 2003). Accordingly, neurokinins are modulators of the micturition reflex at the central and peripheral level, which includes effects on afferent transmission to supraspinal sites and descending inputs to the sacral parasympathetic nucleus; these effects make it plausible that tachykinin receptor antagonists should affect micturition in pathological states with little effect on normal bladder function (Lecci and Maggi 2001). Within the bladder, tachykinins in nociceptive cells that are sensitive to capsaicin (Lecci and Maggi 2001). Thus, activation of such cells releases tachykinins, which causes neurogenic inflammation. Tachykinin receptor antagonists including aprepitant, netupitant and serlopitant have been tested in animal models of bladder dysfunction and in patients. Of note, some tachykinin receptor antagonists such as aprepitant and fosprepitant have been authorized for clinical use in combination with other antiemetic agents for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy (Alexanderet al. 2019).

In a rat cyclophosphamide/lipopolysaccharide cystitis model, aprepitant reduced bladder inflammation, reduced PGE_2 and TNF-α content and expression of NK_1, EP_1, EP_2 and $P2Y_2$ receptors (Zhanget al. 2016). Similarly, aprepitant also improved inflammation, and additionally reduced micturition frequency and bladder enlargement, and increased pain threshold; in contrast to the rat study, expression of NK_1 receptors was not altered (Liuet al. 2019). In randomized,

8-week pilot study in 125 postmenopausal women with OAB with a history of urgency incontinence or mixed incontinence (with predominantly urgency urinary incontinence), 160 mg q.d. aprepitant as compared to placebo significantly improved symptoms of OAB (Greenet al. 2006). Number of micturitions (primary endpoint) was reduced by 10.2 ± 17.9 % as compared to 3.3 ± 16.3% (mean difference -6.8 [95% CI -12.5; -1.1]. Number of urgency episodes was also reduced whereas a reduction in total or urgency incontinence episodes did not reach statistical significance with the given sample size and variability. Aprepitant was generally well tolerated and the incidence of side effects, including dry mouth, was low. While more than 200 other clinical studies with aprepitant have been or currently are performed in other indications, apparently none of them has a primary or key secondary endpoint related to bladder dysfunction, perhaps reflecting that aprepitant is vulnerable to several drug-drug interactions (Frenklet al. 2010).

Serlopitant apparently is a successor molecule to aprepitant. While no pre-clinical studies for serlopitant have been disclosed, a randomized, a 5-armed, double-blind, multicenter trial with 557 adults with OAB compared 0.25, 1 or 4 mg serlopitant, 4 mg tolterodine ER and placebo during an 8-week study (Frenklet al. 2010). Mean change from baseline of frequency (primary endpoint) was significantly greater for 0.25 (-1.1) and 4 mg (-1.1) serlopitant, and for tolterodine (-1.5) than for placebo (-0.5), but not for 1 mg serlopitant (-0.8), indicating lack of a clear dose-response relationship within the tested dose range. Tolterodine was also more effective than any serlopitant dose for the secondary endpoints of urgency incontinence and particularly for urgency episodes. Serlopitant was generally well tolerated and had a lower incidence of dry mouth (3.3%) as compared to tolterodine (8.8%; placebo 4.6%).

Another NK_1 receptor antagonist, netupitant, blocked excitatory effects on guinea pig L6 and S1 dorsal root ganglion cells (Zhanget al. 2012). Netupitant reduced contractions elicited by a substance P analog in isolated detrusor strips with high potency (mean pK_B D 9.24) without affecting contraction amplitude, as did the experimental NK_1 antagonist L-733,060 (Paleaet al. 2016). In an acetic acid model of OAB in guinea pigs, netupitant increased inter-contraction intervals without affecting the contraction amplitude (Paleaet al. 2016). Intravesical netupitant increased void volume and the interval between micturitions with no effects on bladder pressure (baseline, threshold, peak), but had little effects on wild-type mice (Girardet al. 2016). A phase II, multicenter, double-blind study compared an 8-weeks treatment with 3 doses of netupitant (50, 100, 200 mg q.d.) with placebo in adults with OAB symptoms >6 months (Haabet al. 2014). However, netupitant at any dose was not superior to placebo for change in number of daily micturitions at week 8 (primary endpoint) or secondary endpoints such as urinary incontinence, urge urinary incontinence, and urgency episodes. No further studies of netupitant related to bladder dysfunction have been reported.

In conclusion, animal models suggested that NK_1 receptor antagonists may have a role in the treatment of OAB, but at least the compounds tested clinically until now failed to exhibit superior efficacy relative to placebo and/or tolterodine. An alternative approach could be not to antagonize neurokinin receptors but to reduce neuropeptide release. Cizolirtine is a modulator of substance P and CGRP release in the spinal cord, most likely secondary to increased extracellular levels of noradrenaline and serotonin. A pilot study compared 200 and 400 mg b.i.d. of cizolirtine to placebo in 79 OAB patients (Martínez-Garcíaet al. 2009). Although the decrease in key OAB symptoms of incontinence and urgency episdoes was significantly greater in the active arms, adverse events were frequent (68% and 81% of the patients on cizorlitine 200 and 400 mg as compared to 39% with placebo) and most commonly of gastro-intestinal nature including dry mouth and vomiting. A follow-up study compared 800 mg q.d. cizolirtine with 15 mg oxybutynin and placebo in 135 OAB patients treated for 12 weeks (Zaturaet al. 2010). Cizolirtine was similar to oxybutynin and superior to placebo for endpoints such as number of daily voids and increase in mean voided volume; both were also superior to placebo in fraction of patients achieving fewer than 8 voids, complete dryness, or both over placebo. Cizolirtine caused fewer antimuscarinic but more gastrointestinal (nausea) and neurologic (headache and vertigo) adverse events than oxybutynin. Apparently, no additional studies have been or currently are performed.

10.3.2. Vitamin D3 receptor agonists

Epidemiological studies from multiple countries have reported inverse associations between circulating levels of vitamin D_3 and lower urinary tract symptoms. For instance, urinary flow rate was positively associated with vitamin D_3 levels (Chenget al. 2021). On the other hand, low levels were associated with urinary incontinence (Kilicet al. 2016) and such association was confirmed in other populations and persisted upon multivariate analysis adjusting for factors such as ethnicity or age (OR 1.8) (Vaughanet al. 2011). Moreover, low levels were observed in winter and during that season, but not in other seasons where levels were higher, were associated with higher OAB symptom scores (Yooet al. 2018).

Such associations are plausible based upon the observation that rat and human bladders express receptors for vitamin D (Crescioliet al. 2005). Considering this background, a pilot study reported that vitamin D_3 supplementation improved urgency incontinence (Marklandet al. 2019). Such data spawned research programs on synthetic vitamin D_3 analogs, among which a program on elocalcitol, formerly known as BXL-628 has reported the largest amount of data, not only on bladder and incontinence but also on prostate and BPH.

In human bladder smooth muscle cells, elocalcitol did not alter the expression of rho kinase I or II and neither did upon in vivo treatment of rats; however, treatment with elocalcitol delayed contractile responses in isolated bladder strips (Morelliet al. 2007). On the other hand, treatment with elocalcitol increased expression of L-type Ca^{2+} channels in detrusor smooth muscle (Morelliet al. 2008), which may lead to greater contractile responses based on the role of such channels in bladder contraction (Frazieret al. 2008). Elocalcitol improved bladder function in several rat models of OAB including acetic acid-induced overactivity (Shapiroet al. 2013) or BOO (Schröderet al. 2006, Strenget al. 2012). The latter study also found that a muscarinic agonist became more effective in elocalcitol-treated animals. Elocalcitol has improved bladder function in the cyclophosphamide rat model of cystitis (Shapiroet al. 2013). Another vitamin D_3 analog, maxacalcitol at 30 but not 15 µg/kg/d reduced detrusor overactivity in a retinyl acetate rat model of OAB (Wróbel and Rechberger 2016).

Against this background, a phase IIb, multi-center, double-blind proof-of-concept study has compared elocalcitol doses of 75 and 150 µg/d with placebo during a 4-week treatment in 308 women with overactive bladder and idiopathic detrusor overactivity (Digesuet al. 2012). The primary endpoint of this study was the change in bladder volume at first involuntary bladder contraction from baseline; this endpoint was not met. However, reductions in incontinence episodes and improvements in Patient Perception of Bladder Condition score were observed. Elocalcitol was well tolerated with no difference in adverse events as compared to placebo. Apparently,

no further clinical studies of elocalcitol or other vitamin D_3 analogs are ongoing in OAB or cystitis patients.

10.3.3. Cannabinoid system – exocannabinoids; FAAH inhibitors

The cannabinoid system consists of enzymes involved in the generation of endogenous cannabinoids such as *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoyl glycerol (2-AG) and of receptors on which they act (**Fig 23**). Endocannabinoids are generated after cyclooxygenase formed arachidonic acid that is further metabolized by several enzymes including transacylase and phospholipase D. The two well-defined cannabinoid receptor subtypes are CB_1 and CB_2, but the existence of additional receptors cannot be excluded (Pertweeet al. 2010, Ruggieri 2011). Activation of peripheral CB_1 receptors is typically associated with vasodilation and regulation of via inhibition of neurotransmitter release, whereas activation of CB_2 appears to induce anti-inflammatory, antinociceptive, and immunosuppressive actions (Pertweeet al. 2010, Ruggieri 2011, van Diepenet al. 2008). The inactivation of endocannabinoids involves transporters and the enzyme fatty acid amide hydrolase (FAAH). The role of the cannabinoid system in the regulation of bladder function has been explored in healthy animals and models of three diseases, neurogenic voiding dysfunction, particularly in the context of multiple sclerosis, bladder outlet obstruction and other models of OAB, and in cystitis.

Cannabinoid system in normal bladder function

Cannabinoid receptors are found both in the brain and in the periphery including the healthy and diseased bladder (Ruggieri 2011, Hedlund 2014, Hedlund and Gratzke 2016). CB_1 and CB_2 receptors have been identified in all layers of the human bladder including the urothelium (Merriamet al. 2008, Gratzkeet al. 2009, Tyagiet al. 2009, Walczak and Cervero 2011, Ochodnickyet al. 2012, Bakaliet al. 2014). CB_2 receptor expressing nerves in the suburothelium, were found to co-express TRPV1 and/or CGRP, whereas those in the detrusor also expressed the vesicular ACh transporter, indicating that they represent cholinergic neurons.

In isolated detrusor strips from rats, monkeys or humans, the endogenous agonist anandamide and the exogenous agonists CP 55,940 or cannabinor did not affect basal tone or carbachol-induced contractions (Gratzkeet al. 2009, Gratzkeet al. 2010); however, contractions induced by field stimulation were enhanced by anandamide and attenuated by CP 55,940, indicating that these agents act predominantly pre-junctionally in isolated detrusor (Gratzkeet al. 2009, Gratzkeet al. 2010). At least at some stimulation frequencies, cannabinor reduced contraction induced by field stimulation in the presence but increased it in the absence of urothelium (Gratzkeet al. 2010). Similarly, the mixed CB_1/CB_2 agonist arachidonyl-2'-chloroethyl amide did not affect basal but attenuated field stimulation-induced tension of isolated rat detrusor strips (Blahaet al. 2016). In contrast, cannabigerol, Δ9-tetrahydrocannabivarin, cannabidiol and cannabidivarin, but not cannabichromene were reported to inhibit contraction of isolated mouse detrusor induced by acetylcholine; however, none of them inhibited contraction induced by field stimulation (Paganoet al. 2015); similarly, the mixed CB_1/CB_2 agonist Bay 59-3047 was reported to inhibit ACh- or KCl-induced contraction in rat isolated bladder strips (Chenet al. 2018). Whether these differences can be attributed to species or specific compounds under investigation cannot be determined from the present data. In guinea pig bladder, methanandamide and the CB_2-selective agonist 4-quinolone-3-carboxyamide inhibited mechanosensitive afferent fiber activity in an ex vivo preparation, an effect blocked by a CB_2 receptor antagonist (Christie and Zagorodnyuk 2021). Taken together these data indicate that cannabinoids may modulate bladder function in vitro at the levels of smooth muscle, detrusor, afferent and efferent nerves, but these observations were not made universally.

In cystometric studies in rats, anandamide, CP 55,940 and cannabinor increased threshold pressure, but micturition intervals were

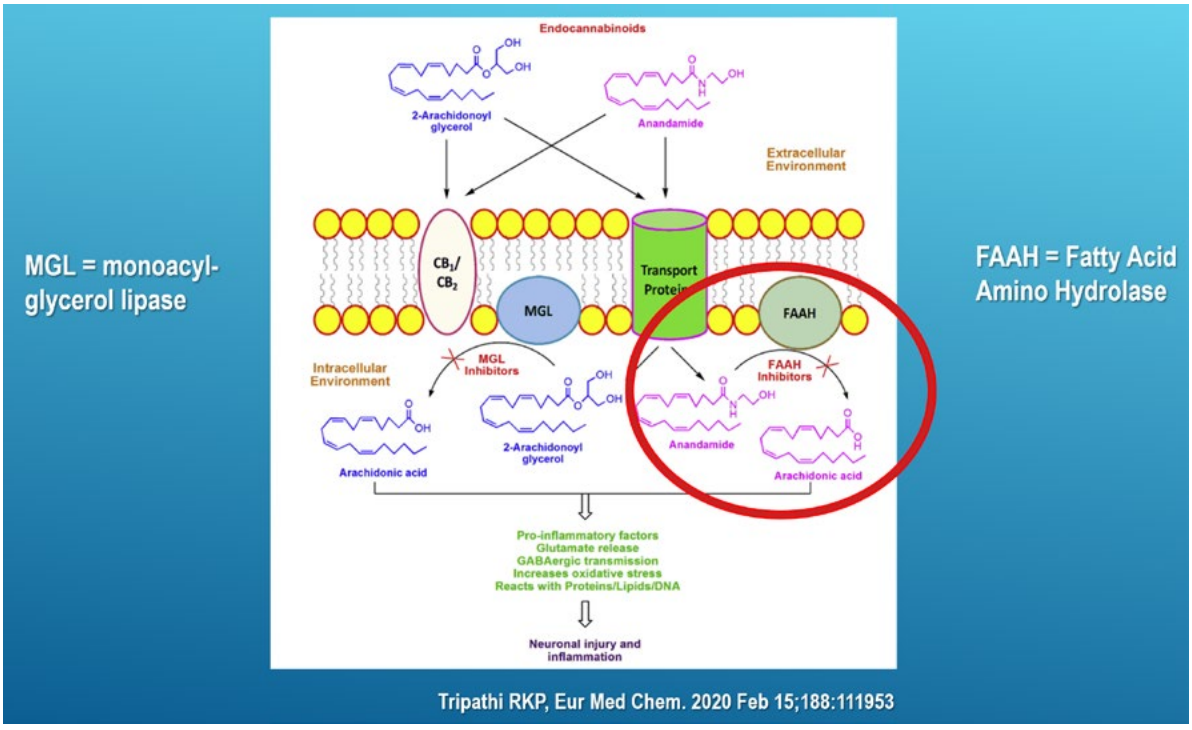

Figure 23: The cannabinoid system. From Tripathi RKP, Eur Med Chem. 2020 Feb 15;188:111953

shortened by anandamide and lengthened by CP 55,940 or a high dose of cannabinor (Gratzkeet al. 2009, Gratzkeet al. 2010). The anandamide transport inhibitor VDM11 also increased threshold pressure in rats and increased inter-contraction intervals in rats (Hondaet al. 2016). These data suggest a consistent effect of cannabinoids on threshold pressure, with effects on micturition intervals being compound specific. On the other hand, administration of the CB_1 antagonist rimonabant or the CB_2 antagonist SR 144,528 induced detrusor overactivity in healthy rats, which was counteracted by an inhibitor of fatty acid amino hydrolyse (FAAH) (Füllhaseet al. 2016). Additional evidence for a role of cannabinoids in the regulation of bladder function comes from proteomic studies comparing potential urinary biomarkers between regular cannabis users and controls (Nedumaranet al. 2017).

Multiple sclerosis

In a mouse model of spinal cord injury, cannabidiol attenuated pro-inflammatory mediators, T cell and infiltration and thermal sensitivity and failed to improve bladder function (Liet al. 2018). Nonetheless, multiple clinical studies have been performed in which patients with multiple sclerosis or other types of neurogenic voiding dysfunction were treated with cannabinoids.

Cannabinoids have been tested in randomized, placebo-controlled trials in multiple sclerosis patients. In the CAMS trial, 630 patients received 4-10 capsules (depending on body weight) of either placebo, a cannabis extract containing 1.25 mg of cannabidiol (CBD), or 2.5 mg Δ^9-tetrahydrocannabinol (THC) for 13 weeks (Freemanet al. 2006). Based on 3-day voiding diaries, placebo, extract and THC reduced number of incontinence episodes by 18%, 38% and 33%, indicating a 25% and 19% reduction relative to placebo ($p = 0.039$). Among secondary outcome parameters, pad tests were also improved by the extract and THC relative to placebo, whereas urodynamic tests and the King's Health questionnaire were not.

Several other studies assessed effects of an oromucosal spray containing a combination of 2.5 mg each of CBD and THC (nabiximols, Sativex®). Following an open-label dose finding study in which urgency, incontinence, frequency and nocturia were improved relative to baseline (Bradyet al. 2004), a 10-week, double-blind, randomized, placebo-controlled, parallel-group trial on 135 randomized subjects with MS and OAB was performed (Kaviaet al. 2010). While no difference was found between treatment groups for the primary endpoint incontinence and three of the seven secondary endpoints (urgency, I-QOL and voided volume), data in favor of active treatment was observed for frequency, nocturia, overall bladder condition and patient global impression of change. Thereafter, three non-interventional studies were reported with the same preparation: In one study, 433 patients were included of which 349 exhibited a reduction of spasticity of at least 20% after 1 month and 281 after 3 months and continued the study and reported an improvement of spasticity and bladder function (Vermersch and Trojano 2016). Another post-marketing surveillance study in 102 patients observed for 40 weeks; among the 46 patients with assessments, an improvement of IPSS relative to baseline was observed (Paolicelliet al. 2016). A third non-interventional study was small (15 patients) but primarily explore effects on bladder function (Maniscalcoet al. 2018). Treatment was associated with an improvement of the OAB symptom score from 17 at baseline to 12 and a reduction of postvoid residual from 80 to 30 ml; in contrast, various cystometric parameters were not affected.

A meta-analysis of 2 randomized (Freemanet al. 2006, Kaviaet al. 2010) and one open-label trial (Bradyet al. 2004) reported a difference in 0.35 incontinence episodes between active treatment and placebo (Abo Youssefet al. 2017). A broader meta-analysis of 9 randomized studies using various cannabinoids and endpoints found an improvement of bladder function by 0.29 standard deviations for cannabis extracts [CI 0.09; 0.50] and 0.11 standard deviations for cannabinoids [CI 0.0008; 0.20] (Torres-Morenoet al. 2018). Taken together these studies suggest a moderate efficacy of cannabis extracts and cannabinoids in bladder dysfunction associated with multiple sclerosis, but the findings were not sufficiently robust to be detected in all individual studies.

OAB

Cannabinoids have been tested in various, largely rat, models of OAB. Reduced expression of CB_1 and CB_2 receptors in the detrusor was observed in Zucker diabetic fatty rats (Blahaet al. 2016) and fructose-fed rats (Chenet al. 2018), whereas an increased expression of CB_1, but not CB_2 receptors was observed in detrusor and urothelium of BOO rats (Gratzkeet al. 2011). Irrespective of such differences in receptor expression, the tested cannabinoids improved bladder function in all studies. This was observed based on detrusor strip experiments with the mixed CB_1/CB_2 agonist Bay 59-3047 in fructose-fed rats (Chenet al. 2018), and with arachidonyl-2'-chloroethyl amide in Zucker diabetic fatty rats (Blahaet al. 2016). It was also observed in cystometric in vivo experiments in rats with acute installation of the CB_1 agonist WIN 55,212-2 or the CB_2 agonist CB65 (Kimet al. 2017) or cannabinor in BOO (Gratzkeet al. 2011), with peripheral but not intrathecal administration of the CB_1 antagonist AM 251 (Jianget al. 2017) and with CP 55,940 in acetic acid-induced bladder irritation (Bakaliet al. 2016). On the other hand, the CB_1 and CB_2 antagonists AM 281 and AM 630, respectively, diminished the severity of hyperosmolar saline-induced detrusor overactivity (Juszczak and Maciukiewicz 2015)

Endocannabinoids may also work via the GPR55 receptor. One group tested O-1602, a cannabidiol analog and agonist for GPR55, in several rat models of overactivity including spontaneously hypertensive rats (Wróbelet al. 2020), rats with corticosterone treatment (Wróbelet al. 2020) and those exposed to retinyl acetate (Wróbelet al. 2020). In all three models and in one of cystitis (see below), O-1602 reduced detrusor overactivity and improved various parameters of inflammation and oxidative damage.

In conclusion, cannabinoids improved bladder function in all tested OAB models, except when administered intrathecally, indicating that they may mainly act at a peripheral level. To which extent this involves CB_1, CB_2 or GPR55 receptors, remains to be established. Clinical studies in OAB patients have not been reported to our knowledge.

Cystitis

Similar to some of the other bladder pathologies, cyclophosphamide-induced cystitis is accompanied by an up-regulation of CB_1 receptors, without changes of CB_2 receptor expression (Pessinaet al. 2015). In this model, palmitoylethanolamide acting via CB_1 receptors (Pessinaet al. 2015) and the GPR55 agonist O-1602 (Wróbelet al. 2020) improved bladder function. Similarly, in a cyclophosphamide model in mice the CB_2 agonist JWH-133 reduced micturition frequency and inflammation (Liuet al. 2020). The CB_2 agonists beta-caryophyllene and HU 308 also improved bladder function in a lipopolysaccharide-induced cystitis model in mice (Bergeret al. 2019). In contrast, intrathecal arachidonyl-2'-chloroethyl amide was ineffective in acrolein-induced cystitis in rats (Joneset al. 2015), confirming that other cannabinoids had also been inactive upon intrathecal administration in a model of acetic acid-induced bladder irritation (Jianget al. 2017)

In conclusion, cannabinoids improved bladder function in several cystitis models, except when administered intrathecally, indicating that they may mainly act at a peripheral level. To which extent this involves CB_1, CB_2 or GPR55 receptors, remains to be established. Clinical studies in cystitis patients have not been reported to our knowledge.

FAAH

The key enzyme for the degradation of anandamide and other endogenous cannabinoids, is FAAH (**Fig 24**). FAAH is expressed in the mucosa of mouse, rat and human bladder and coexpressed with CB_2 receptors (Strittmatteret al. 2012). Therefore, FAAH inhibitors have been explored as potential treatments in several models of bladder dysfunction. In healthy rats, intravenous or intravesical administration of the FAAH inhibitor oleoyl ethyl amide increased intercontraction intervals, micturition volume, bladder capacity and threshold pressure; while the CB_2 antagonist SR 144,528 abolished all effects of oleoyl ethyl amide, the CB_1 antagonist rimonabant attenuated only those on threshold pressure (Strittmatteret al. 2012).

a peripherally restricted FAAH inhibitor reduced prostaglandin E_2-induced detrusor overactivity and activation of mechanosensitive afferent nerves (Aizawaet al. 2016). In rats with bladder outlet obstruction, oleoyl ethyl amide also reduced detrusor overactivity, and similar findings were obtained the rimonabant or SR 144,528 (Füllhaseet al. 2016).

FAAH knockout mice exhibited greater increases in anandamide upon administration of cyclophosphamide than wild-type animals (Wanget al. 2015). Intravesical NGF caused detrusor overactivity in wild-type mice, which was inhibited by arachidonyl-2'-chloroethyl amide; no effect of NGF was observed in FAAH knock-out mice, but it was restored by the CB_1 antagonist AM 251 (Wanget al. 2015). The FAAH inhibitor URB 937 reduced voiding contractions in lipopolysaccharide-induced cystitis in rats and in the same doses decreased levels of anandamide, but increased those of palmitoylethanolamide (Charrua et al. 2020). Taken together, these animal data suggest that FAAH may be an attractive therapeutic target for bladder dysfunction.

10.3.4. Transient Receptor Potential (TRP) channel family – TRP channel antagonists

TRP channels constitute a large superfamily of cation selective channels. The human TRP family consists of 27 members that are divided in six subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin) and TRPA (ankyrin) (Nilius et al., 2007). A particular characteristic of these ubiquitously expressed channels is that a wide range of physical and chemical stimuli can regulate their activation. Thus, TRP channels can act as polymodal cellular sensors that are involved in numerous sensory and homeostatic processes (Deruyver, et al., 2015). TRP channels, including TRPV1, TRPV2, TRPV4, TRM4, TRPM8 and TRPA1, are highly expressed in, but not restricted to, primary afferent neurons, but can also be found in the urothelium, some interstitial cells and detrusor muscle (Andersson, 2019a; 2019b). In the bladder, urothelial expression is well established for TRPM4, TRPV2, TRPV4 and TRPM7, but controversial for TRPA1, TRPV1 and TRPM8. Expression of TRPA1, TRPV1, TRPM8 and TRPC4 is well established on afferent nerves (**Fig. 25**) (Vanneste et al, 2021). In the LUT, TRP channels are mainly involved in nociception and mechanosensory transduction (**Fig 26**) (Vanneste et al, 2021; Andersson, 2019a; 2019b). TRP channels function as molecular sensors in urothelial cells and afferent nerve fibres and can be considered the origin of bladder sensations. TRP channels in the lower urinary tract contribute to the generation of normal and abnormal bladder sensations through a variety of mechanisms (**Fig 26**) and have demonstrated potential as targets for the treatment of LUTS in functional disorders of the lower urinary tract (Vanneste et al, 2021).

However, how these individual channels influence normal and pathological LUT function remains to be established.

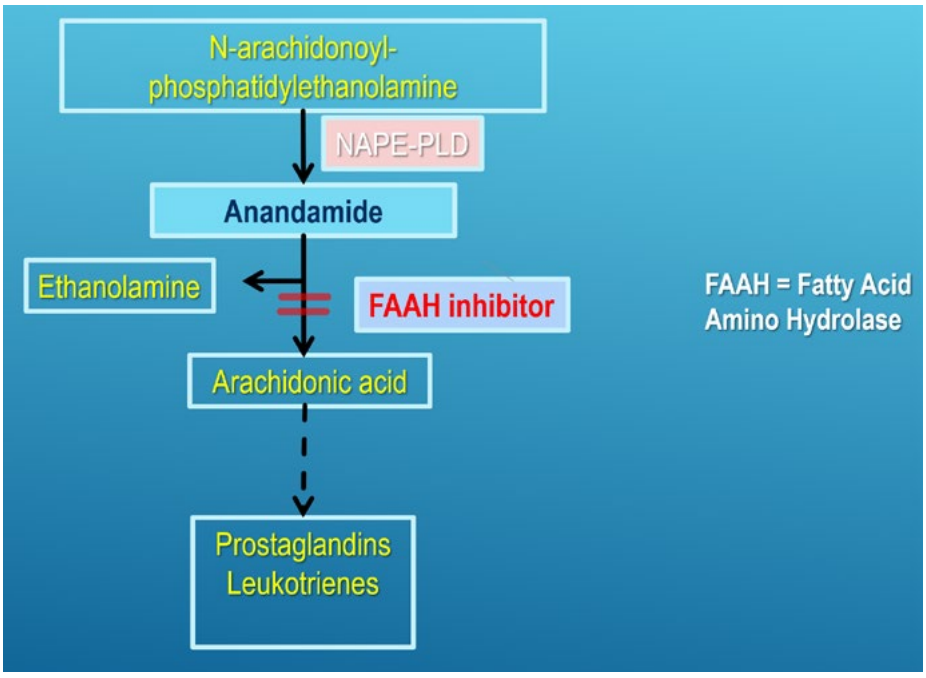

Figure 24: The Fatty Acid Amino Hydrolase (FAAH) system. Site of action of FAAH inhibitors

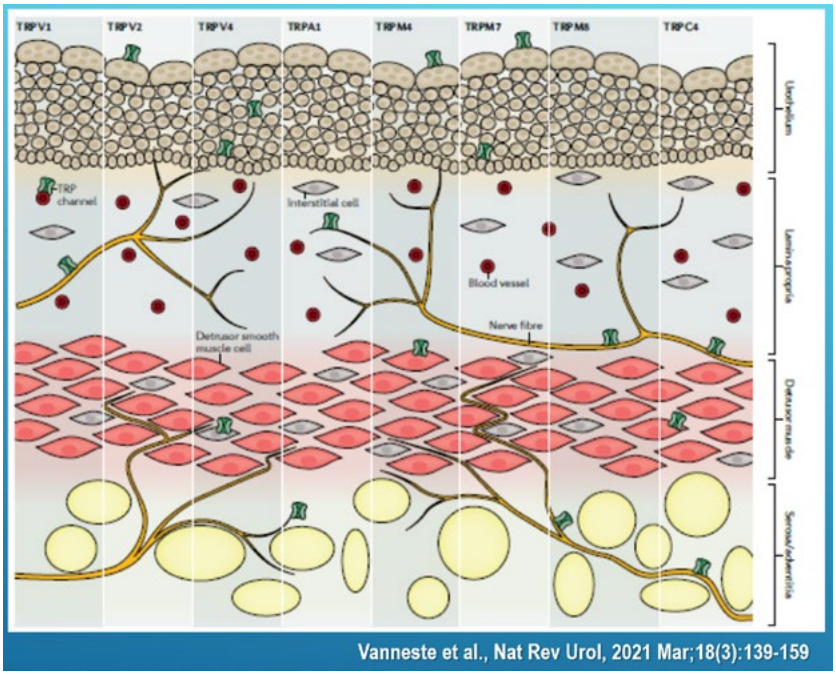

Figure 25: Localization of TRP channels in the bladder wall (Vanneste et al., Nat Rev Urol. 2021; 18(3):139-159

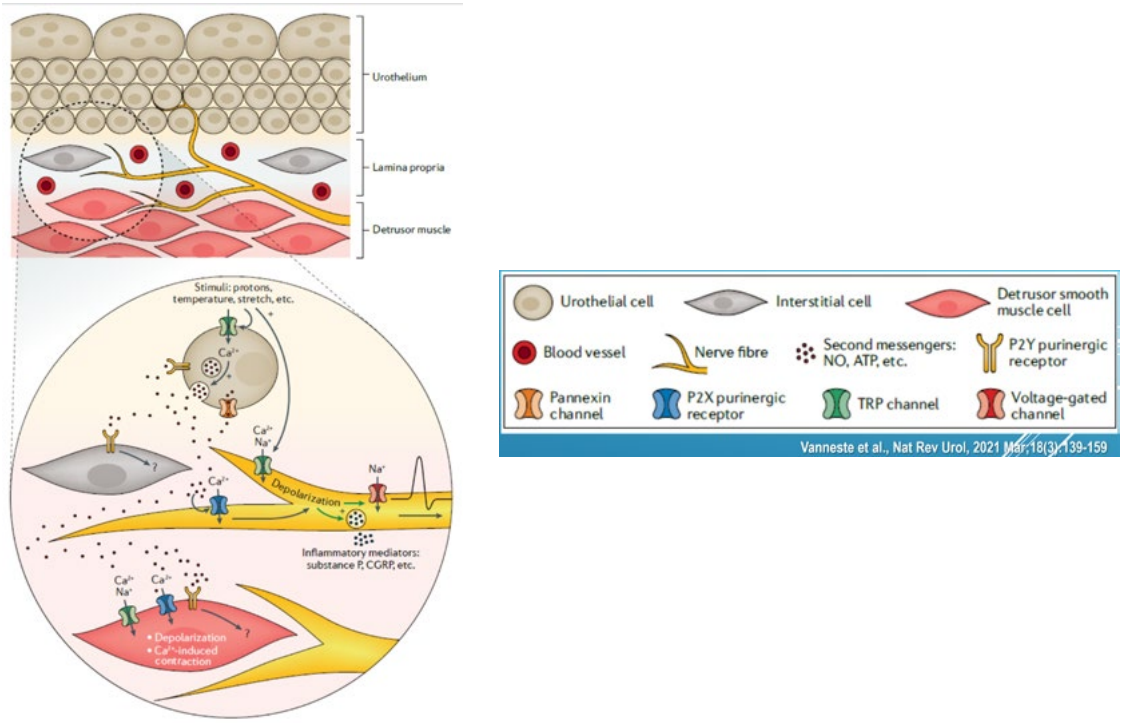

Figure 26: Possible mechanisms of action of TRP channels in the bladder (Vanneste et al., Nat Rev Urol. 2021; 18(3):139-159

10.3.4.1. TRPV1 antagonists

TRPV1 is the best-characterized member of the TRPV subfamily (TRPV1–6) and abundant information on its morphology and function in animal models, and to some extent on the clinical translation of its manipulation, is available (Nilius & Szallasi, 2014). TRPV1 is highly expressed in C-fibres innervating the urinary bladder and urethra in several mammals including rats, mice, and humans (Deruyver, et al., 2015) **(Fig 25; Fig 26).** TRPV1 has been shown to play an integral role in modulating the excitability of bladder afferents and the generation of hypersensitivity, induced by bladder inflammation (Birder et al., 2002).

In several animal models of LUT dysfunction including bladder hyperactivity in mice with lipopolysaccharide (a bacterial toxin)-induced cystitis and in rats with neurogenic bladder overactivity after spinal cord injury, selective TRPV1 antagonists have proven to be promising drug candidates for bladder overactivity and/or inflammation-induced bladder hypersensitivity (Deruyver, et al., 2015). Moreover, it has been reported in six-week-old male mice that social stress can lead to the development of OAB by the induction of TRPV1-dependent an afferent nerve activity, suggesting that TRPV1 channels can be an interesting target also for preventing the development of stress-induced OAB in children (Mingin et al., 2015). In line with these finding in animal models, Zhang et al. (2015) reported increased expression of TRPV1 in the urothelium of 21 female patients with OAB than in nine healthy controls, and the high expression of TRPV1 in the urothelium of the patients was closely correlated to OAB occurrence.

Unfortunately, it became rapidly clear that TRPV1 antagonists cause an increase in body temperature (hyperthermia) and, both in animal models and in humans (Round et al., 2011; Deruyver, et al., 2015), which limits their clinical application. However, Brown et al. (2017) conducted a phase I study I in healthy volunteers on the safety and pharmacokinetics of oral NEO6860, a modality selective TRPV1 antagonist, and found no clinically significant increase in temperature or heat pain threshold/tolerance, but a significant antagonistic effect on intra-dermal capsaicin-induced pain. Whether the new class of TRPV1 antagonists has also a beneficial effect on OAB remains to be clarified.

10.3.4.2. TRPA1 antagonists

As a mediator of inflammation and pain, TRPA1 is considered a potential target in the treatment of visceral hypersensitivity syndromes, e.g. inflammatory bowel disease, OAB, and interstitial cystitis/bladder pain syndrome (IC/BPS). TRPA1 is expressed in the bladder and particularly associated with C-fiber endings in the suburothelium that co-localize CGRP. Agonists acting at the receptor cause bladder overactivity and is suggested to play a role in mechanosensory transduction and in signaling pain (Streng et al., 2008).

A TRPA1 antagonist, HC030031, has been proven effective to ameliorate cystometric parameters in rats with bladder overactivity after spinal cord injury. In these rats, TRPA1 expression in dorsal root ganglia (DRG) was upregulated at the protein and mRNA levels and the effects of the TRPA1 antagonist could be mimicked by TRPA1 RNA knockdown (Andrade et al., 2011). In a visceral pain model, using cyclophosphamide-induced cystitis, HC030031 effectively alleviated cystitis induced bladder hyperalgesia (Deberry et al., 2014). Although these drugs show efficacy in various animal models for bladder pain and hyperalgesia (Ferrer-Montiel, et al., 2012; Kamei et al., 2018), they await clinical validation.

10.3.4.3. TRPV4 antagonists

Functional TRPV4 expression has been shown in bladder urothelial cells in mice, rats, guinea-pigs, and humans [Gevaert, et al., 2007; Deruyver, et al., 2015]. TRPV4 is located predominantly on the surface of the basal urothelial cell layers, in close proximity to the adherence junctions (Janssen, et al., 2011). *In vitro* experiments on cultured urothelial cells showed that cells from TRPV4 KO mice had attenuated Ca2+-influx and ATP release in response to stretch compared with cells from control mice (Mochizuki et al, 2009). Moreover, isolated TRPV4 KO mouse bladders showed reduced stretch-evoked ATP release (Gevaert, et al., 2007). *In vivo,* these KO mice exhibit less frequent voiding [Gevaert, et al., 2007] and larger bladder capacity (Thorneloe, et al., 2008). Moreover, intravesical infusion of GSK1016790A, a potent TRPV4 agonist, can induce bladder hyperactivity in rodents (Thorneloe, et al., 2008; Aizawa et al., 2012) and increase afferent firing of capsaicin-insensitive C-fibres in rats (Aizawa, et al., 2012). Furthermore, systemic administration of the TRPV4 antagonist HC067047 increases bladder capacity and reduces micturition frequency in a mouse model of cyxclophosphamide-induced cystitis (Everaerts, et al., 2010). These findings support the hypothesis that TRPV4 acts as a mechano-sensor in urothelial cells and activates the underlying C-fiber afferent nerves via ATP-release. Further, there is evidence that a co-administration of antagonists to both TRPV4 and TRPV1 can potentiate the effect of each drug and reduce bladder hyperactivity in a rodent model for cystitis (Charrua, et al. 2015).

Interestingly, no significant adverse effects of systemic treatment with the TRPV4 antagonists HC067047 and GSK2193874 have been reported in rodents (Everaerts et al, 2010; Thorneloe, et al., 2012). Recently, two clinical trials of GSK2798745, a highly potent, selective, orally active TRPV4 antagonist, demonstrated its safety and pharmacokinetics in healthy subjects and patients with heart falure and its efficacy for improving pulmonary gas transfer (Goyal et al., 2019; Stewart et al., 202). Although TRPV4 antagonists might eventually precipitate urinary retention (Gevaert et al., 2007), GSK2798745 would be a promssing drug candidate also for OAB.

10.3.4.4. TRPM8 antagonists

TRPM8 is activated by cool temperatures (8–25 °C) and by chemicals that provoke ‘cool’ sensations, such as menthol and icilin. As a cold sensor in the body, TRPM8 is predominantly expressed in a small subpopulation of DRG and trigeminal neurons that do not express TRPV1 (Voets, et al., 2007). TRPM8 expression was shown in a subset of small nerve fibres in the human bladder (Mukerji, et al., 2006) and DRG neurons innervating the rat bladder (Hayashi, et al., 2009).

Lashinger et al. (2008) showed that application of AMTB, a TRPM8 channel antagonist inhibited isovlumetric bladder contractions and bladder nociceptive reflex responses in the rat, suggesting that in addition to cold sensing TRPM8 may also be involved in the afferent control of micturition and nociception. Systemic application of another TRPM8 antagonist, BCTC, reduces cold stress-induced bladder overactivity in rats (Lei, et al, 2013). Ito et al. (2016) showed that TRPM8 have a role in activation of mechanosensitive C-fiber bladder afferent activity recordings in an ex vivo rat model. These experimental findings in animals propose TRPM8 antagonists as a promising therapeutic tool for OAB and hypersensitive bladder disorders.

However, systemic application of TRPM8 antagonists generally decreases deep body temperature (hypothermia) (Almeida, et al, 2012; Ito, et al., 2016), which was believed to limit clinical trials. In contrast to classical TRPM8 antagonists, KRP-2579, a novel TRPM8 antagonist, showed a suppressive effect on acetic-acid- induced bladder overactivity and associated hyperactivity of bladder mechanosensitive C-fibers without affecting deep body temperature in the rat (Aizawa et al., 2018). It has been more recently reported that KRP-5714, another novel TRP M8 antagonist, similarly can improve acetic-acid-induced bladder overactivity and the hyperactivity of mechanosensitive C-fibers of bladder afferents in anesthetized rats (Nakanishi et al., 2020). Moreover, the authors also examined the effects of KPR-5714 on voiding behavior in conscious rats with cerebral infarction and in those exposed to cold in metabolic cage experiments, and found that cerebral infarction and cold exposure induced a significant decrease in the mean voided volume and increase in voiding frequency in rats. Orally administered KPR-5714 dose-dependently increased the mean voided volume and de-

creased voiding frequency without affecting total voided volume in these models (Nakanishi et al., 2020). Furthermore, the combined administration of KPR-5714 and mirabegron or tolterodine tartrate showed the additive effects on bladder overacticity in rats with cerefral infalction or rats exposed to cold temperature, respectively (Aizawa et al., 2021), suggesting that the combination therapy of TRPM8 antagonist and β_3-adrenoceptor agonist or anticholinergic agent can be the potential treatment option for obtaining additive effects in comparison with monotherapy for OAB.

Information on effects of blocking TPM8 channels in humans is scarce. PF-05105679, a selective TRPM8 antagonist, displayed a significant inhibition of pain in the cold pressor test and had no effect on core body temperature in humans. However, an unexpected adverse event (hot feeling) was reported, predominantly perioral which in two volunteers was non-tolerable (Winchester et al., 2014). No clinical trials with TRPM8 antagonists other than PF-05105679 seem not to be available so far.

10.3.4.5. TRPM4 antagonists

The TRPM4 channel is a monovalent cation-selective channel activated by an increase of intracellular Ca2+ (Mathar et al., 2014). It is widely expressed in the body, including rat, guinea pig and human bladder urothelium and detrusor smooth muscle. TRPM4 is implicated in the regulation of many cellular processes e.g., the immune response, insulin secretion, and bladder function (Andersson, 2019a).

In vitro functional studies using guinea-pig detrusor smooth muscle preparations showed that 9-phenanthrol, a selective TRPM4antagonist, reduced spontaneous contractions as well as contractions elicited by carbachol, KCl, and nerve stimulation, indicating that TRPM4 is active at rest, regulates detrusor cell excitability and contributes to contractile activity (Smith et al., 2013a, 2013b; Hristov et al., 2016). Similar investigation using mouse detrusor smooth muscle preparations demonstrated 9-phenanthrol inhibited carbachol-induced contractions but did not inhibit contractions due to intracellular Ca2+ release evoked by the drug, suggesting that TRPM4 channels play a significant role in cholinergic signaling in detrusor smooth muscles at least in mice (Alom et al., 2019). Furthermore, Kullmann et al. (2018) investigating the potential role of TRPM4 in detrusor overactivity following spinal cord transection in mice, found that TRPM4 was upregulated in the urothelium and detrusor smooth muscle after the lesion. The spontaneous contractile activity of detrusor muscle strips in both spinally intact and spinal cord transection mice was significantly reduced.

Even if the preclinical effects of TRPM4 blockade could make the receptor an interesting target for treating detrusor overactivity, no published experiences of TRPM4 antagonists in humans seems to be available.

10.3.4.6. TRPV2 antagonists

TRPV2 is expressed in the umbrella cells of the urothelium, detrusor smooth muscle cells, and nerve fibres within the suburothelium (Yu et al., 2011; Andeersson 2019a). TRPV2 knockout mice exhibit decreased embryonic weight and perinatal viability with surviving adult mice still demonstrating reduced body weight. Behavioural assays and neurophysiological studies failed to demonstrate the necessity for TRPV2 in the detection of noxious heat or mechanical stimulation under normal or pathological conditions. These findings suggest that TRPV2 is important for perinatal viability but is not essential for heat or mechanical nociception or hypersensitivity in the adult mouse (Park, et al., 2011). In primary rat urothelial cells, Ca^{2+} influx was induced by TRPV2 activation, as well as hypotonic stimulation, which can be inhibited by tadarafil, a PDE5 inhibitor. These findings suggest that TRPV2 involves urothelical signal transduction, which can be inhibited by tadarafil (Dong et al., 2018). Increaseed mRNA expression of TRPV2 was reprted in bladder mucosal biopcy sepcimens taken from patients with Hunner type interstitial cystitis as well as patients with bladder pain syndrome, and morever, all symptoms measures correlated with TRPV2 expression (Homma et al, 2013). No study on in vivo LUT function using TRPV2 antagonists seems avaiable so far in either animals or humans. Additional work is needed to determine the role of TRPV2 in bladder function.

10.3.4.7. Summary

Abudant information on preclinical studies from animal experiments and human bladder sepecimens suggests that antagonists for several different types of TRP channels, especially TRPV1, TRPA1, YRPV4, and TRPM8, may be useful for treatment of OAB, DO, and/or bladder pain syndrome. However, so far, the transition from findings from preclinical studies to clinical application has been slow, and presently available information on the use of TRP channel antagonists in humans are restricted to Phase 1 studies on drugs intended to be used in LUT disorders, and thus proof of concept studies in humans are still lacking. (Andersson, 2019b).

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10.4. Critical summary

The preceding sections show that approved treatments for OAB have clear limitations: most patients do not achieve a symptom-free state and few patients stay on treatment for long periods. Thus, there is a clear medical need for improved OAB treatments. Other conditions such as IC/BPS or UAB have no approved treatments. Thus, a clear medical need exists for novel and improved treatments of bladder dysfunction.

A critical look at the above data on emerging treatments yields two striking observations: Firstly, there are several instances where animal models looked promising but clinical proof of concept studies failed either entirely or yielded results that do not suggest an improvement over approved treatment. Examples of this include the K^+ channel opener ZD0947 (Chappleet al. 2006), the EP_1 receptor antagonist ONO-8539 (Chappleet al. 2014) or the NK_1 receptor antagonist netupitant (Haabet al. 2014). This raises questions on the translational value of the animal models we use (Erdogan and Michel 2020). A large number of animal models of OAB exist (Fry 2004, Parsons and Drake 2011). Each of them has specific advantages and disadvantages, but none of them is likely to be representative for the entire spectrum of OAB patients. This raises the question how many animal models should be studied to gain sufficient confidence in the finding that warrants proceeding to a clinical proof-of-concept study. While a specific number most likely cannot be determined, it appears wise to use animal models that represent a spectrum of pathologies and animal species. For instance, the

clinical development program for mirabegron had been based on in vivo studies normal animals with volume-induced bladder contractions, in those with acute bladder irritation caused by intravesical prostaglandin E_2 instillation,

with bladder outlet obstruction, with bladder ischemia, with cerebral infarction and in decerebrate rats and involved rats, dogs and monkeys (Michel and Korstanje 2016). Using a broad panel of models and species led to the successful clinical development of a first-in-class new OAB treatment. Robust studies should also include positive controls, such as treatments that are proven to work. This is a standard approach in clinical phase III studies for the European regulatory authorities. Including such positive controls also in animal models will provide early signals whether novel compounds not only work, but whether they are likely to provide benefit over existing treatments. Finally, it is another aspect of using multiple models that it has been estimated that at least 50% of published studies cannot be reproduced (Freedmanet al. 2015), necessitating intensive efforts to improve the robustness of preclinical data.

The second striking observation is that some compounds showed promising results in phase II data but apparently did not lead to full clinical development programs. Examples of this include the NK_1 receptor antagonist serlopitant (Frenklet al. 2010), the tachykinin release inhibitor cizolirtine (Martínez-Garcíaet al. 2009, Zaturaet al. 2010), the vitamin D_3 analog elocalcitol (Digesuet al. 2012), and cannabinoid receptor ligands (Abo Youssefet al. 2017, Torres-Morenoet al. 2018).

Clinicians and scientists may wonder why promising targets such as rho kinases, purinergic receptors or opioid receptors have not led to clinical proof-of-concept studies despite candidate compounds being available for clinical use and a generally acknowledged medical need for improved treatment options. They may also wonder why compounds with positive proof-of-concept data have not proceeded to full clinical development programs. An obvious answer is lack of commercial promise. Given that most OAB drugs currently are or shortly will become available as cheap generic drugs, the investment in a full clinical development program (easily several hundred million dollars) is only considered promising if the novel treatment has a reasonable chance to be better than existing treatments, preferably regarding efficacy (Michel 2020). Accordingly, it appears that major pharmaceutical companies have discontinued discovery and development programs in the field of OAB.

An additional answer could be due to the original definition of OAB as an “initial diagnosis”, mostly likely representing a range of different pathologies (Abramset al. 2002) that may require different treatment approaches. Therefore, it has been argued that it is a key task of future OAB research to identify subsets of patients with specific underlying pathologies (Michel 2020). These can be used to develop corresponding biomarkers that allow identification of such subgroups for inclusion into clinical trials and, eventually for treatment allocation in a physician office. A drug that is highly effective in a small subset of patients may be valuable for that subset but will not look promising in a general OAB cohort. Thus, identifiable subsets of OAB patients will allow more targeted approaches with a reasonable expectation to yield superior success in those subgroups.

V. DRUGS USED TO TREAT OF STRESS INCONTINENCE IN WOMEN

The pathogenesis of stress urinary incontinence (SUI) in women includes any of the following factors: compromised urethral function, damage to urethrovaginal support, and increased abdominal pressure that puts above normal demands on the continence system [Lemack and Carmel, 2021]. In the Research on Stress Urinary Incontinence (ROSE) study, maxial urethral closure pressure (MUCP) was the factor most strongly associated with SUI [DeLancey et al, 2008]. The loss of sphincteric function and the resultant decreased urethral closure pressure can be increased to achieve continence through a variety of pharmacologic pathways [Hillary et al., 2015].

Factors which contribute to urethral closure include urethral smooth and striated muscle tone and the passive properties of the urethral lamina propria, particularly its vasculature. The relative contribution of these factors is still debatable; however, there is evidence that a substantial part of urethral tone is mediated through stimulation of α-ARs in the urethral smooth muscle by noradrenaline [Andersson and Wein, 2004]. Another contributing factor to SUI in postmenopausal women is decreased mucosal function from low estrogen levels. The pharmacological treatment of SUI increases urethral smooth and striated muscle tone either directly or indirectly. The drugs studied in the treatment of female SUI include α-adrenoceptor agonists, β-adrenoceptor antagonists, β-adrenoceptor agonists, and serotonin-norepinephrine uptake inhibitors; however, the relative lack of efficacy and/or adverse events (AEs) from these drugs have limited their clinical use [Andersson, 2021].

Drugs used in the treatment of stress incontinence in women. Assessments according to the Oxford system (modified)

Drug	Level of evidence	Grade of recommendation
Duloxetine	1	B
Imipramine	3	D
Clenbuterol	3	C
Methoxamine	2	D
Midodrine	2	C
Ephedrine	3	D
Norephedrine (phenylpropanolamine)	3	D
Estrogen	2	D

1. α-ADRENOCEPTOR AGONISTS

Several agonists with effects on peripheral α-ARs have been used in the treatment of SUI. Noradrenaline (NA) is an a_1-AR agonist that acts on the human bladder neck [Michel and Vrydag, 2006]. Also, NA has been shown to act centrally by increasing the excitability of the urethral rhabdosphincter within Onuf's nucleus, an effect due to α_1-AR dependent depolarization [Yashiro et al., 2010]. This central action by NA is the mechanism by which SUI is improved with NA reuptake inhibitors. Norephedrine (phenylpropanolamine or PPA) has been the α-AR agonist used most widely for SUI treatment [Andersson, 2021]. The United States Agency for Healthcare Policy and Research Guidelines in 1992 evaluated 8 randomized controlled trials (RCTs) with PPA at a dose of 50 mg twice daily for female SUI [Agency for Healthcare Policy and Research, 1992]. Dry rates with PPA were listed as 0% to 14%, urinary incontinence reductions were 19% to 60%, AEs were 5% to 33%, and dropouts were 0% to 4%. The most recent Cochrane review on the use of α-AR agonists in the treatment of female SUI identified twenty-two RCTs, 11 of which were crossover trials, and 673 women received an adrenergic drug (PPA in 11 trials, midrodrine in 2 trials, and norepinephrine in 3 trials) [Alhasso et al., 2008]. The authors concluded, "there was weak evidence to suggest that use of an adrenergic agonist was better than placebo in reducing the number of SUI episodes". Furthermore, over 25% of the subjects reported AEs with α-AR agonists; however, when these were due to AR stimulation, they caused discontinuation in only 4% of the subjects.

Both ephedrine and PPA lack selectivity for urethral α-ARs and both can increase blood pressure and cause sleep disturbances, headache, tremor, and palpitations [Andersson, 2021]. Kernan et al. reported the risk of hemorrhagic stroke to be 16 times higher in women less than 50 years of age who had been taking PPA as an appetite suppressant (95% CI, 1.51 to 182.21; p=0.02) and 3 times higher in women who had been taking the drug for less than 24 hours as a cold remedy (95% CI, 0.86 to 11.46; p=0.08) [Kernan et al 2000]. There was no increased risk of stroke in men taking PPA. Although PPA was removed from the market in the United States, it is still used as a SUI treatment in a few countries. Numerous case reports of adverse reactions due to ephedra alkaloids exist, and some had suggested that the sale of these compounds as a dietary supplement be restricted or banned [Bent et al., 2003]. In December 2003, the US FDA decreed such a ban, a move which has survived legal appeal. Recently, Balk et al published a systematic review and network meta-analysis (commissioned by the US AHRQ) of clinical outcomes in women with SUI treated with pharmacotherapy (32 RCTs), and they concluded that there was no difference in cure rates with α-AR agonists compared to no treatment [Balk et al., 2019]. They also found that behavioral therapy was more effective than α-AR agonists (OR, 2.50 [CI, 1.39 to 4.50]). Thus, the effectiveness of α-AR agonists as treatment for SUI in women is moderate at best, and its clinical usefulness remains limited by significant cardiovascular AE.

Many investigators have attempted to develop α-AR agonists with more selectivity for the human urethra. Musselman et al in 2004 reported on a phase 2 study with a peripheral active selective $\alpha_{1A/1L}$-AR partial agonist in 37 women with mild to moderate SUI [Musselman et al, 2004]. Use of the drug after 4 weeks resulted in a lower mean weekly number of SUI episodes compared to placebo (8.4 vs 6.0, p=0.0079); however, despite no difference in blood pressure in the patients given the drug, the drug was not efficacious in subsequent SUI trials. Subsequently, Conlon et al. studied PF-3774076, a partial α_{1A}-AR agonist, in female dogs, and although peak urethral pressure increased dogs and although the drug was selective, subsequent heart rate and blood pressure changes from the drug caused significant concern [Conlon et al., 2009]. Also, Furuta et al. reported that medetomidine, an α_2-AR agonist, inhibited the release of glutamate presynaptically in the spinal cord of female SCI rats [Furuta et al., 2009]. In addition, this α_2-AR agonist potentiated the effects of serotonin/norepinephrine reuptake inhibitors on the EUS, and they proposed that α_2-AR antagonists could be useful as a treatment for SUI; however, this awaits further testing in humans. Finally, Robinson et al. published a phase 2 placebo-controlled trial evaluating PSD503, a topical gel containing phenylephrine 20%, applied vaginally near the urethral sphincter in women with SUI [Robinson et al., 2011]. Only 14 patients were recruited out of a goal sample size of 30. There was a greater median absolute reduction in pad weight gain in patients using topical phenylephrine gel compared to placebo, 22 g vs 10 g. There were no adverse events. Despite the positive effects of PSD503, the poor study accrual suggests that this treatment may not be widely accepted by women.

In summary, it remains to be seen whether increases in urethral tone to a level where patient benefit and long-term compliance is reported can be achieved in the absence of significant cardiovascular events with either full or partial α-AR agonists. Furthermore, none of the α-AR agonist trials reported on whether women who benefitted from treatment continued after the trial period. There is no biological reason to suggest that the desired effect in treating SUI would persist after stopping treatment.

2. β-ADRENOCEPTOR AGONISTS

Although β-AR stimulation results in a decrease urethral pressure [Andersson, 1993], β_2-AR agonists have been reported to increase the contractility of some fast- contracting striated muscle fibers and suppress that of slow contracting muscle fibers [Fellenius et al.,1980]. Some β-AR agonists also cause skeletal muscle hypertrophy, more so in fast twitch than slow twitch fibers [Kim et al., 1992]. Clenbuterol, a selective beta 2-adrenoceptor agonist, was reported to potentiate the field stimulation induced contraction in rabbit isolated periurethral muscle preparations [Kishimoto et al, 1991]. Propranolol suppressed the action of clenbuterol, and the potentiation produced by clenbuterol was greater than that of isoproterenol. These authors were the first to report an increase in urethral pressure with clenbuterol, and they speculated on its potential for the treatment of SUI. Yaminishi et al. studied the contractility of the urethral sphincter of female dogs, and sphincteric fatigue was produced by electrically stimulating the pudendal nerves at 15 V and 20 Hz for 30 to 40 minutes [Yaminishi et al. 1994]. Clenbuterol, given to 17 dogs with sphincteric fatigue, increased the contracting pressure, and propranolol abolished the effect. Clenbuterol had no effect in 9 dogs with non-fatigued urethral sphincters.

These results suggest that clenbuterol act on fast-contracting fibers in the urethral sphincter.

Yasuda et al. described the results of a multicenter, double blind, placebo-controlled trial with clenbuterol in 165 women with SUI [Yasuda et al. 1993]. Women were included if they had 1-2 leaks/day over 3 days and if the urine loss was 2 g or more on a pad test. Patients were randomized to receiving either clenbuterol or placebo daily over 2 weeks. Positive statistical significance was achieved for subjective evaluation of SUI frequency, daily pad usage, and overall global assessment in women receiving clenbuterol compared to placebo. Yet, the difference in baseline pad weights 11.7± 17.9g for clenbuterol and 18.3± 29.0g for placebo) raises questions

about the comparability of the 2 groups. Also, women receiving clenbuterol saw an increase in MUCP of only 3.3 cm H_2O (from 46.0± 18.2 cm H_2O to 49.3± 19.1 cm H_2O). In those receiving clenbuterol, finger tremors were seen in 8/82 (9.8%), and tachycardia was seen in 2/82 (2.4%). The authors concluded that clenbuterol enhanced the striated periurethral sphincter muscle. Ishiko et al. 2000 randomized women with SUI to receive either clenbuterol 20 µg BID, pelvic floor exercises, or both over 12 weeks [Ishiko et al. 2000]. The frequency and volume of SUI and the patient's own impression were used as the basis for the assessment of efficacy. Sixty-one women completed the study, and over half of the patients had mild SUI, defined as < 5 stress leaks/week. No SUI (dry rate) was seen in 76.9% who received clenbuterol (n=13), 52.6% who did exercises (n=19), and 89.5% who did both (n=19), p=0.036. Mild AEs during treatment were reported in 5 patients (numbness and tremor), but none of them were severe enough to discontinue treatment. No subsequent published reports have appeared on the treatment of female SUI with clenbuterol or any β-AR agonist. Larger, well-designed, RCTs investigating the effects of β-AR agonists are needed to adequately assess its potential as a treatment for SUI.

3. β –ADRENOCEPTOR ANTAGONISTS

The theoretical basis for the use of β-AR antagonists in the treatment of SUI is that the blockade of urethral β-ARs may potentiate the effects of noradrenaline on urethral α-ARs. A few studies dating back several decades reported success in treating female SUI with propranolol [Gleason et al. 1974; Kaisary, 1984]. In the Gleason study, the beneficial effects didn't manifest until after 4 to 10 weeks of treatment, a difficult to explain pharmacological phenomenon. Also, Donker and van der Sluis reported that β-AR blockade with iv propranolol and sotalol did not change urethral pressure profile (UPP) in normal women [Donker and van der Sluis 1976]. Although initially suggested as an alternative to α-AR agonists in women with SUI and hypertension, β-AR blockers like propranolol have major potential side effects including heart failure and increased airway resistance. There have been no recently published large RCTs to date supporting the use of β-AR blockers for women with SUI.

4. SEROTONIN-NORADRENALINE UPTAKE INHIBITORS

4.1. Imipramine

Within the urethra, it is thought that imipramine inhibits the re-uptake of noradrenaline and serotonin in adrenergic nerve endings to enhance the contractile effects of noradrenaline on urethral smooth muscle. As such, imipramine has been studied as a treatment for SUI. In an open-label study of 30 women with SUI treated with imipramine 75 mg daily 21women achieved subjective continence, and the mean maximal urethral closure pressure (MUCP) increased from 34 to 48 mm Hg [Gilja et al. 1984]. Furthermore, 35% of the women were reported as cured by pad test. The efficacy of imipramine 25 mg TID was assessed in another open-label study of 40 women with SUI [Lin et al. 1999]. A 20-minute pad test and urodynamics were performed in each woman before and after treatment. After 3 months of treatment, 35% (n=14) were cured and 25% (n=10) improved by ≥50%, resulting in a total of 60% achieving efficacy (95% CI 11.8-75.2). The MUCP was 77 cmH_2O for the treatment success group vs 40 cmH_2O in the treatment failure group (p< 0.0001). The authors concluded that high pre-treatment MUCP served as a predictor of pre-treatment success. More recently, Kornholt et al investigated whether imipramine increased opening urethral pressure [Kornholt et al. 2019]. In a randomized, double-blind, placebo-controlled study of 16 healthy women without SUI where urethral pressure was measured before and 1 hour after receiving either imipramine 50 mg or placebo, imipramine increased urethral pressure by only 6.5 cmH_2O (p=0.07). The authors concluded that the increase in urethral pressure after imipramine was neither statistically significant nor clinically relevant. There have been no recently published RCTs on the use of imipramine in women with SUI.

4.2. Duloxetine.

Duloxetine hydrochloride is another centrally-mediated norepinephrine and serotonin reuptake inhibitor well-studied as a treatment for SUI. Duloxetine was initially studied in a cat model of bladder irritation using acetic acid (Thor and Katofiasc 1995). When these cats were pretreated with duloxetine, urethral sphincteric muscle activity increased 8-fold during bladder storage. This sphincteric effect was reversed by α1-AR and serotonergic antagonists. Serotonin and noradrenaline terminals are particularly dense within the pudendal nerve neurons in Onuf's nucleus in the sacral spinal cord (Fig 17), and activation of these terminals releases glutamate to cause contraction of the urethral rhabdosphincter [Thor and de Groat 2010].

Several RCTs have demonstrated efficacy with duloxetine as a treatment of SUI in women. Dmochowski et al published the first phase 3 RCT of 683 women in North America randomized to either duloxetine 40 mg BID (n=344) or placebo (n=339) for 12 weeks [Dmochowski et al. 2003]. Primary outcome variables included 50-100% decrease in weekly incontinence episode frequency (IEF) and the total score on the incontinence quality of life questionnaire (I-QOL). There was a significant decrease in IEF with duloxetine compared with placebo (50% vs 27%, p < 0.001), and there were significant improvements in quality of life (11.0 vs 6.8, p<0.001). With respect to AE, nausea was seen in 22.7% of women receiving duloxetine versus 2.1% receiving placebo, p<0.001. Nausea was reported in most within 2 days, and the nausea was mild to moderate in severity in 87% of the subjects. Eventually, 6.4% of the women receiving duloxetine discontinued due to nausea. The discontinuation rate for adverse events was 24% for duloxetine compared to 4% receiving placebo, p<0.001. To reduce the risk of nausea, Hashim and Abrams proposed beginning with a dose of 20 mg BID for 2 weeks, then increasing to 40 mg BID [Hashim and Abrams 2006].

A Cochrane review of duloxetine as treatment for women with SUI was performed in 2005, and included 9 primary studies and 6 additional reports related to 1 or 2 of the primary studies [Mariappan et al. 2005]. The definition of treatment response used in most of these studies was a 50-100% decrease in IEF. The authors summarized their results as follows. Subjective "cure" in women receiving duloxetine 40 mg BID was higher than in those receiving placebo (10.8% vs 7.7%, overall RR = 1.42; 95% CI, 1.02-1.98; p = 0.04). Objective cure data, available from only the 1 study by Norton et al which utilized stress pad test, showed no clear drug vs. placebo difference [Norton et al. 2002]. Yet, duloxetine showed greater improvement in I-QOL with the weighted mean difference of .45 for the 80 mg dose (95% CI 2.83-6.18, p<0.00001). With respect to AE, nausea was the most common with an incidence of 23-25%, and nausea was the main reason for discontinuation. Other side effects reported were vomiting, constipation, dry mouth, fatigue, dizziness, and insomnia. In a subsequent systematic review, the same authors stated that further research was needed to determine if duloxetine was clinically effective and cost effective compared to other

surgical SUI treatments and whether there was sustained efficacy with acceptable tolerability [Mariappan et al. 2007].

Mound et al. (2017) considered the benefits and harms of duloxetine for the treatment of SUI in women. They performed a meta-analysis of 4 placebo-controlled studies, the reports obtained from the European Medicines Agency (EMA). Duloxetine was more successful than placebo in terms of percentage change in weekly UI episodes (mean difference 13.5%) and numeric change from baseline (-2.85) and IQOL total score, but the effect sizes were small. A sensitivity analysis (with removal of one trial) showed that the number needed to treat for a Patient Global Impression of Improvement rating of "much better or very much better" was 8. The number needed to harm was 7 discontinuing because of an AE and 7 (95% CI 6 to 9) for experiencing an activation event (agitation, euphoria, anxiety, mania, irritability, akathisia). There was no report of suicidality or violence, but 2 patients (of 958) experienced a total of 5 serious AE potentially predisposing to suicidality ("the harm outweighed the benefits").

Duloxetine has been studied against pelvic floor muscle training (PFMT) alone and in combination. Ghoniem et al randomized 201 women with SUI to 1 of 4 treatments: duloxetine alone at 40 mg BID (n=52), PFMT (n=50), duloxetine and PFMT (n=52), and sham PT with placebo (n=47) [Ghoneim et al. 2007]. The primary outcome measure was IEF, and other efficacy measures included number of pads used/day and I-QOL scores. Overall, duloxetine with or without PFMT was superior to PFMT alone or placebo, and greater improvements in pad numbers and I-QOL were seen in women receiving both duloxetine and PFMT compared to duloxetine alone. The authors concluded that that the complementary modes of action seen with using duloxetine and PFMT together may result in an additive effect in treating SUI. More recently in 2021, Hagovska et al reported their findings from the DULOXING study where 158 women were randomized to either duloxetine 40 mg BID alone (n=79) or to duloxetine 40 mg BID with PFMT [Hagovska et al. 2021]. The study was conducted over 12 weeks, and primary endpoints involved the assessment of IEF/week and results from the International Consultation on Incontinence Questionnaire short form (ICIQ-SF). The I-QOL and PGI-I were used as secondary measurements. PFMT was performed by a physiotherapist over 5 sessions utilizing lumbopelvic stabilization, and the patient performed pelvic floor exercises 5 times/week for 30 minutes. The physiotherapist checked pelvic floor muscle strength and endurance. After 12 weeks, the groups receiving both duloxetine and PFMT saw a 66.7% decrease in IEF/week and the group receiving duloxetine alone saw a 50% decrease in IEF/week, p<0.001. Also, significant differences (p<0.001) favoring the group receiving duloxetine and PFMT were seen with ICIQ-SF, I-QOL, and PGI-1. There were no significant differences in AEs between the 2 groups. Fatigue was the most common side effect seen, and it was seen in 9.2–9.3% in both groups. Nausea was seen in 3.1-4.6% in both groups. The authors concluded that the addition of PFMT to duloxetine greatly improved SUI symptoms in women.

The conitnued use of duloxetine in women as an alternative to SUI surgery has also been studied. Cardozo et al performed an 8-week placebo-controlled RCT of 109 women with SUI given either duloxetine 40 mg BID (n=55) or placebo (n=54) [Cardozo et al 2004]. All subjects had IEF of 14/week or more, SUI was demonstrated on urodynamics, and all had continence surgery already scheduled. At the end of the study, 20% of the women that received duloxetine were no longer interested in surgical treatment for their SUI. All duloxetine responses were observed within 2 weeks; however, 33% discontinued duloxetine because of AEs with nausea seen as the most common. Duckett et al offered duloxetine 40 mg BID to 33 women with SUI and without prolapse awaiting a tension-free vaginal tape (TVT) operation [Duckett et al 2006]. After 4 weeks of duloxetine use, 24% of the women came off the waiting list; however, 48% discontinued duloxetine because of AEs.

The use of duloxetine to treat SUI in elderly women has been investigated. Schagen van Leeuwen et al. studied the efficacy and safety of duloxetine in women 65 years or older with SUI or stress-predominant MUI [Schagen van Leeuwen et al. 2008]. Women in this 12-week, double-blind study were randomized to either duloxetine starting at 20 mg BID for 2 weeks then increasing to 40 mg BID (n=131) or placebo (n=134). Patients receiving duloxetine had a 52.5% decrease in mean IEF/week compared to patients receiving placebo which had a 36.7% decrease in mean IEF, p<0.001. Furthermore, the responder rate (≥50% reduction in IEF/week) was 57.1% in the duloxetine group and 35.2% in the placebo group, p<0.001. Compared to placebo, duloxetine better improved I-QOL total score (p<0.001) and PGI-I (p<0.001). With respect to AEs during active treatment, there was no statistically significant difference in treatment emergent AEs between the 2 groups, p= 0.210. Nausea was seen in only 7.5% in patients receiving duloxetine versus 3.1% of patients receiving placebo, p=0.169, and this was attributed to the lower starting dose. The authors concluded that duloxetine is safe and effective as a treatment of SUI in elderly women.

Several studies have evaluated compliance with long-term duloxetine use. In a study sponsored by Lilly, Bump et al assessed the maintenance of efficacy of duloxetine 40 mg BID beyond 3 months using data from several long-term, open-label studies [Bump et al. 2008]. Data from 1424 patients enrolled in three 12-week, placebo-controlled clinical trials and their uncontrolled, open-label extensions, and in one uncontrolled, openlabel study were used to assess long-term continuation rates and continued efficacy based on responses to the validated PGI-I scale for up to 30 months. The duloxetine continuation rate at 1 year was 42.5%. After 30 months, only 368 patients remained on treatment. Of those that continued treatment beyond 1 year, 83% of patients at 24 months and 88% of patients at 30 months rated their incontinence in one of the three 'better since starting treatment' PGI-I categories. The authors admitted that the results needed to be interpreted cautiously because many patients discontinued duloxetine and those with better responses were more likely to continue taking the drug. Vella et al reported on a cohort of 228 women prescribed duloxetine and followed beyond 1 year of treatment [Vella et al. 2008]. Seventy-one of the women (31%) continued beyond 4 weeks of treatment, of which 103 stopped because of AEs and 54 stopped because of lack of efficacy. Furthermore, only 12% were taking duloxetine at 4 months, 10% remained on duloxetine at 6 months, and 9% were on duloxetine at 1 year. In addition, the authors reported that 1 year later, 187 (82%) women had either undergone a TVT procedure or were awaiting the procedure. Overall, 56% discontinued due to AEs and 33% stopped due to lack of efficacy. The authors concluded that persistence with long-term duloxetine was low due to poor tolerability and due to the option of effective surgical procedures which offers a more definitive form of treatment.

Duloxetine at a dose of 40 mg BID remains approved in the European Union for the treatment of SUI in women with moderate to severe incontinence (defined as 15 or more episodes per week). The use of duloxetine for the treatment of SUI was withdrawn from the US FDA consideration process, but it is approved for the treatment of major depressive disorder, generalized anxiety disorder, fibromyalgia, diabetic peripheral neuropathic pain, and chronic musculoskeletal pain. Also, the product information for duloxetine contains a "black

box" warning of "increased risk of suicidal thinking and behavior in young adults taking antidepressants for major depressive disorder and other psychiatric disorders", and the product information states that "depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide" [Prescribing Information, revised 2019, Eli Lilly and Company, Indianapolis, Indiana 46285]. AEs for the 6801 duloxetine and 4487 placebo treated patients reported in the product information for duloxetine in the FDA approved treatments mentioned are nausea (24% vs 8%), dry mouth (13 vs 5), fatigue (10 vs 5), somnolence (10 vs 3), insomnia (10 vs 6), constipation (10 vs 4), and dizziness (10 vs 5).

In their review of the medical management of urinary incontinence, Shaban et al concurred with the UK NICE guidelines that duloxetine was an optional second-line treatment for women with SUI not willing or unfit for surgery after discussion of the significant side effects [Shaban et al. 2010]. Robinson and Cardozo expressed similar sentiments by stating that whilst duloxetine may be useful in patients who are reluctant to undergo surgery or who have significant co-morbidities and whilst it may lead to a significant reduction in IEF, the actual 'dry' rates remain considerably lower than following continence surgery [Robinson and Cardozo 2010]. In conclusion, further research utilizing both patient-reported outcomes and cost-effective analysis, is needed to decide how to best incorporate duloxetine into the treatment of women with SUI.

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VI. DRUGS USED TO TREAT STRESS INCONTINENCE IN MEN

The pharmacologic treatment of male SUI, most commonly for post-prostatectomy incontinence (PPI), is directed primarily at treating intrinsic sphincteric deficiency as the most important factor maintaining continence in men is sphincteric function [Salvatore et al. 2017]. Unlike in women, loss of urethral support is not a factor in men with SUI. The internal urethral sphincter extends from the

bladder neck through the prostatic urethra. Its function is damaged during prostate surgery, and during radical prostatectomy the internal urethral sphincter is removed. The external urethral sphincter begins distal to the prostate at the membranous urethra and includes the rhabdosphincter (intrinsic skeletal and smooth muscle) and the extrinsic paraurethral skeletal muscle. Damage to the parasympathetic and somatic innervation of the smooth and striated muscle contributes to male SUI after prostatectomy indirectly. Furthermore, compromise of the sphincter support mechanism or post-operative changes such as fibrosis compromises sphincter function.

While the majority of men experience urinary incontinence immediately following prostatectomy, in most this is transient and gradually improves with time. Approximately, 20-27% of men with SUI after prostatectomy achieve immediate continence after urethral catheter removal [Menon et al. 2007]. PFPT recommended as first-line treatment for PPI and performed under the supervision of a physiotherapist with or without biofeedback, is thought to improve urethral stability and increased urethral closure pressure during exertion [Arroyo Fernandez et al. 2015]. Pharmacotherapy for male SUI has been studied as a conservative option before moving onto surgical therapies like artificial urinary sphincter and male sling. Yet, with advancing age there is evidence of rhabdosphincter atrophy and neural degeneration [Burnett and Mostwin 1998]. As such, treatment of male SUI is challenging with drugs that work best with an intact sphincteric apparatus.

Tsakiris et al. published a systematic literature review on pharmacotherapy for male SUI [Tsakiris et al. 2008]. The authors identified nine studies that provided evidence for the use of α-AR agonists, β2-AR agonists, and serotonin-noradrenaline reuptake inhibitors in the treatment of male SUI. Regarding treatment of male SUI with α-AR agonists (ephedrine, phenylpropanolamine, midodrine), all 3 studies were conducted in small populations with a mixture of men and women, and the authors were not able to conclude whether the drugs were effective or not. As for treatment with β2-AR agonists, there was one study of 14 men with SUI after radical prostatectomy treated with clenbuterol 20 mg BID, and 9 men (64%) had improvement in pad scores. [Noguchi et al. 1997]. The drug studied most in the treatment of male SUI is duloxetine.

Kotecha et al searched for articles on the use of duloxetine for the treatment of male SUI published between inception of review to June 2020, and they identified eight studies (n=348 men) for review: 2 RCTs, 1 randomized, non-controlled trial, 4 prospective cohort studies, and 1 retrospective cohort study [Kotecha et al. 2021]. Duloxetine was assessed in two scenarios: (1) early use in two studies (the RCTs) to reduce the time to attain continence following catheter removal after radical prostatectomy and (2) treatment of persistent PPI in six studies after failed PFPT starting at least 6–12 mo after surgery. The primary outcome measures reported in these studies included improvement in urinary incontinence as measured by the number of pads/day, pad weight, dry days, Likert scales, and/or QOL questionnaires. Both RCTs included a comparison arm where patients received either duloxetine and PFPT (n=78) or placebo and PFPT (n=92) [Filocamo et al. 2007] [Alan et al. 2014]. Both RCTs reported an earlier return of continence in those treated with duloxetine and PFPT with dry rates of 78% (compared with 52%) at 4 months and 96.5% (compared with 87%) at 1 year. Only the RCT by Alan et al reported subjective outcomes with the ICIQ-UI SF, and they reported a 48.7% improvement in total score. The other six studies reported that duloxetine was effective in treating PPI, but there was considerable heterogeneity in the outcome measures reported. The mean dry rate of 42% was reported in three studies. In addition, the mean pad number improved by 52%, and the mean 1-h pad weight was significantly improved by 53%. Of the studies with the longest follow-up (9 months), Collado Serra et al noted persistent benefit with duloxetine, with 65% being pad free at 9 months compared with only 37% at 3 months [Collado Serra et al. 2011]. Unfortunately, the lack of a control group meant that the additional benefit of duloxetine above the natural rate of expected continence recovery was unknown. As for AE rates between the eight studies, fatigue, somnolence, and nausea were the most common and reported in 18% of the men. These AEs led to discontinuation of duloxetine in 21%, and the overall discontinuation (due to AEs and lack of efficacy) rate was 38%. The authors highlighted the need for further randomized trials with longer follow-up and consistent outcome reporting measures. Usage of duloxetine for male SUI remains universally off label.

A drug for the treatment of male SUI that demonstrates efficacy and tolerability would be welcome. Yet, larger, placebo-controlled, RCTs with much longer follow-up are necessary to determine the role of pharmacotherapy in men with SUI.

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VII. DRUGS TO TREAT UNDERACTIVE BLADDER/ DETRUSOR UNDERACTIVITY

The symptom diagnosis of underactive bladder (UAB) and the urodynamic diagnosis of detrusor underactivity (DU) describe states with a complex pathophysiology and clinical presentation. UAB and DU had been poorly defined in the past (Chapple et al. 2015), but progress towards a consensus has evolved recently (Smith et al. 2020). The identification of UAB and DU has become even more complex by the recognition that underactive and overactive bladder can coexist, with and without detrusor overactivity and underactivity (Mancini et al. 2020). Moreover, UAB can coexist with SUI (Shapiro et al. 2020). Two recent systematic reviews in the field concluded that clinical studies in the field are largely of poor quality (Colaco et al. 2018, Osman et al. 2018).

UAB is characterized by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms (Drake 2018). The International Continence Society has defined DU as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span (Abrams et al. 2002). While this remains the only generally accepted definition (Osman et al. 2018), it does not provide quantitative guidance. Some authors have proposed more quantitative definitions such as a bladder contractility index of <100 ($P_{det}Q_{max} + 5Q_{max}$), a detrusor pressure at max flow ($P_{det}Q_{max}$) of <30 mm H_2O and a maximum flow rate of <12 ml/sec, and a bladder outlet obstruction index ($Pd_{et}Q_{max} – 2Q_{max}$) of <20 and a Qmax of <12 ml/sec to be indicative of DU (Dan et al. 2020), but there is no generally accepted quantitative definition of DU; rather, it has been proposed to apply context-sensitive definitions (Smith et al. 2020). The International Continence Society defines an acontractile bladder as a detrusor that cannot contract during urodynamic studies resulting in prolonged bladder emptying within a normal time span (Haylen et al. 2010); it has been argued that this unique phenomenon that should be separated from DU (Colaco et al. 2018).

The uncertainty and controversy on the definition of UAB, DU and acontractile bladder has obvious consequences for studies on the prevalence, pathophysiology, and treatment of the condition and also on the validation of animal models thereof. Therefore, it is not surprising that robust knowledge on the of UAB and DU are missing (Osman et al. 2018), but some studies report a prevalence of UAB and/or DU in the range of about 20% (Hartigan et al. 2019, Yamany et al. 2019). However, these data are difficult to interpret because for instance a self-reported difficulty to urinate could result from both UAB or BOO.

1. ETIOLOGY, PATHOPHYSIOLOGY AND ANIMAL MODELS

The main etiological factors of UAB and DU are aging, (long-standing and/or severe) diabetes mellitus, BOO and various neurogenic disorders including injury to the spinal cord, cauda equina and peripheral nerves (Vale et al. 2019, Aizawa and Igawa 2017). Some authors classify UAB occuring in the contrext of physiological aging and that occuring in younger subjects without an identifiable cause as idiopathic (Santos-Pereira and Charrua 2020). Aging is an informative example that a potential cause of UAB may also often have little effect or lead to OAB. Thus, advanced aged is considered as a frequent cause of UAB (Vale et al. 2019, Santos-Pereira and Charrua 2020), but also a risk factor of OAB (Irwin et al. 2006). Moreover, effects of age may manifest differently depending on associated pathologies; for instance, a decreased contractile responsiveness of human detrusor biopsies with age was observed with concomitant BOO or neurogenic voiding dysfunction, but not in biopsies of otherwise healthy individuals (Fry et al. 2011). On the other hand, clinically observed bladder dysfunction in patients with Parkinson's disease was not associated with age upon multivariate analysis (Sammour et al. 2009).

At the cellular and tissue level, contributing factors can be classified into myogenic failure, efferent (motor) nerve dysfunction, afferent nerve dysfunction and brain and spinal cord dysfunction (Aizawa and Igawa 2017); of note, these factors are not mutually exclusive and can coexist (Figures 2, 3, 4 and 5). While most of our knowledge on these factors comes from animal models, factors such as bladder smooth muscle dysfuntion (Fry et al. 2011) or disturbed afferent nerve function (Smith et al. 2015) have also been observed in patients. Similarly, duration of BOO is relevant for the probability to observed OAB or signs of DU in animal models (see below) and, although based on more limited data also in patients (Bosch et al. 2019). Thus, OAB and UAB may not only coexist but may represent different stages of bladder dysfunction with a given underlying pathology (Nomiya et al. 2014). Functional neuroimaging studies in humans studies are beginning to provide insight on central nervous alterations in patients with neurogenic voiding dysfunction (Khavari and Boone 2019). Recent studies also raise the possibility that, similar to other bladder pathologies, the urothelium could also play a relevant role in UAB/DU (Osman et al. 2018).

Animal models of UAB and DU have been selected on the assumed etiologies (Aizawa and Igawa 2017). Aging based models have been reported for rats and mice. A frequent limitation is that rodents should be more than 24 months and at least 18 months old to resemble elderly humans, and generating such animals is resource-intensive. Aged animls have shown features such as impaired contractile responses in isolated detrusor strips and increased collagen disposition (Ito et al. 2015), increased residual urine and decreased voiding efficiency (Ito et al. 2016), shifted pressure-volume relationships and diminished afferent nerve sensitivity (Hotta et al. 1995, Coelho et al. 2019) and a diminished ability to respond to bladder filling with cyclic voiding (Smith et al. 2012).

Various animal models of diabetes exhibit UAB (Daneshgari et al. 2009, Daneshgari et al. 2009). A complication of all models with a more severe diabetic phenotype is that the increased blood glucose levels exceed the renal reabsorption threshold leading to glucose-induced polyuria; they are typically accompanied by an enlargement of the bladder (Arioglu Inan et al. 2018). A second complication is that diabetes models can exhibit both overactive and underactive bladder, with overactivity typically occuring in early and underactivity mostly in later stages of diabetes. Similar to the clinical situation (Mancini et al. 2020), they can also coexist in animal models of diabetes, for instance in the streptozotocin-induced model of type 1 diabetes where an increased residual urine and spontaneous bladder contractions have been observed concomitantly (Christ et al. 2006). Nonetheless, streptozotocin injection remains the most

frequently used animal model of diabetes (Ellenbroek et al. 2018) e>. Goto-Kakizaki rats have been reported to exhibit features of UAB such as reduced voiding pressure, and this was accompanied by a slower conduction velocity of afferent nerves (Aizawa et al. 2013). However, this model also confirms the complexity of studying UAB and DU as in one study residual volume was increased but the contractile responses in isolated detrusor strips were increased (Saito et al. 2008). Zucker diabetic fatty rats exhibited concomitant increases in residual volume and decreases in maximum detrusor contraction velocity (Tatemichi et al. 2015).

Similar to many, but not all animal models of diabetes (Ellenbroek et al. 2018), animal models of BOO typically exhibit a major enlargement of the urinary bladder. A key difference between bladder enlargement in the two pathophysiologies is that BOO is accompanied by bladder fibrosis (Choi et al. 2020), whereas at least in type 1 diabetes model bladder collagen content is reduced (Xiao et al. 2013). The bladder enlargement in BOO is accompanied by a partial denervation of the bladder, which can be observed even within few days of BOO induction (Barendrecht et al. 2007). Rodent models of BOO typically exhibit a decreased voided volume and an increased voiding frequency and residual urine (Hashimoto et al. 2005). Bladders from BOO animals also exhibit an increased collagen disposition, which is accompanied by a greater fraction of smooth muscle cells exhibiting a synthetic phenotype (Matsumoto et al. 2003). However, BOO particularly when examined at early time points after induction of obstruction may exhibit features of OAB such as increased force of contraction (Zeng et al. 2012); contractile responses of isolated detrusor strips have been found to be reduced in some (Schröder et al. 2001), but not other BOO models (Matsumoto et al. 2009).

Based on the multitude of specific causes of neurogenic voiding dysfunction, animal models of UAB based on neurogenic causes are very heterogeneous. As partial denervation of the bladder also is a typical feature of long-standing diabetes (Blaha et al. 2016), animal models of diabetes can also be seen as those of neurogenic voiding dysfunction under some conditions. Examples of other models include spinal cord injury (De Groat and Yoshimura 2010, Salazar et al. 2019), bilateral pelvic nerve injury (Hannan et al. 2017), crush injury to nerve bundles from the major pelvic ganglion (Kim et al. 2013), ventral root avulsion injury (Chang and Havton 2016), and cryoinjury to the serosal side of the organ (Somogyi et al. 2002). Similar to models based on aging, diabetes or BOO, the neurogenic models can exhibit features such as decreased afferent nerve function (De Groat and Yoshimura 2010) and muscle contractility (Kim et al. 2013) or fibrosis (Hannan et al. 2017), but also features incompatible with pure UAB in some cases, for instance increased contractility of isolated detrusor strips (Hannan et al. 2017).

In conclusion, the animal models are as diverse as are the etiologies of UAB/DU. Whether they indeed reflect UAB/DU often depends on specific aspects such as age of the animal or duration of pathology such as diabetes or BOO. In some cases, they concomitantly exhibit features more often associated with OAB. This requires careful consideration of specific aspects of the animal model at hand to determine its translational value for studying phenomena relevant to patients.

2. DIAGNOSIS AND TREATMENT

A recent systematic review concluded that the quality of clinical data on UAB is limited (Osman et al. 2018). No validated symptom scores exist for the diagnosis of UAB (Yamany et al. 2019). While noninvasive measurements such as flow rate, residual urine and emptying efficciency can be useful in the screening for patients with UAB as a cause for their complaints, a clear diagnosis cannot be made without urodynamic assessment to determine factors such as bladder sensation, detrusor pressure or voiding efficiency (Osman et al. 2018). While more studies have become available in recent years, more accurate and practical criteria for the diagnosis of UAB remain to be established.

Particularly in patients with large residual urine, clean intermittent catherization is a therapeutic approach in UAB with the primary aim to prevent damage to the upper urinary tract and the secondary aim to prevent overflow incontinence (Shapiro et al. 2020, Hartigan et al. 2019, Yamany et al. 2019, Cho and Kim 2020, Bayrak and Dmochowski 2019). Behavioral modification may be useful in patients with impaired bladder sensation who do not sense bladder distension (Yamany et al. 2019). Animal studies suggest that caloric restriction may at least partly prevent the development of UAB with age (Ito et al. 2015, Ito et al. 2016).

Another approach to increase detrusor contraction is (intravesical) administration of prostaglandin E_2. However, this has largely been studied in acute post-operative urinary retention, and results have been mixed. While selective EP_2 and EP_3 receptor agonists are under preclinical investigation as potential treatments, prostaglandins are currently not recommended for chronic UAB (Yamany et al. 2019).

While antagonism of muscarinic receptors has been the mainstay of OAB treatment for decades, efforts to treat UAB have focused on the opposite, i.e., providing greater stimulation of such receptors by direct agonists such as bethanechol or indirect parasympathomimectics such as distigmine. While parasympathomimetics typically yielded promising results in animal models (Tatemichi et al. 2015, Hashimoto et al. 2005, Obara and Tanaka 2020), clinical studies have not provided consistent support for their use but have highlighted potential risks associated with such treatments (Cho and Kim 2020, Bayrak and Dmochowski 2019, Barendrecht et al. 2007). Therefore, they are no longer recommended.

An alternative approch to increase detrusor contraction could be the (intravesical) administration of prostaglandin E_2. This has largely been studied in patients with post-operative, acute urinary retention and has yielded mixed results. Data on chronic use in UAB are largely missing (Yamany et al. 2019, Bayrak and Dmochowski 2019) and are insufficient to recommend their use. Specific agonists acting on EP_2 and EP_3 receptors are currently explored in animal models, but have not been tested in clinical studies.

Acotiamide is an approved prokinetic agent in the gastro-intestinal tract and has shown promise in animal models (Singh et al. 2020). Limited, open-label clinical studies in UAB patients showed that it was well tolerated and yielded promising efficacy results. (Bayrak and Dmochowski 2019). Stem cell and gene therapy-based approaches are currently under investigation (Osman et al. 2018, Hartigan et al. 2019, Yamany et al. 2019).

Based on their role in the bladder neck and urethra, α-blockers could potentially be used to reduce bladder outlet resistance and thereby facility voiding particularly if detrusor contractions are weak. While attractive as a concept, only very limited clinical data is available to support this concept and adequately powered, placebo-controlled, randomised, double-blind trials are missing. Therefore, α-blockers are not recommended due to a lack of sufficient supporting evidence (Yamany et al. 2019, Bayrak and Dmochowski

2019). Accordingly, it has generally been concluded that existing pharmacological treatment options are insufficiently effective and/or have too limited data to be recommended (Ladi-Seyedian et al. 2018).

Sacral neuromodulation may have a place in women with non-obstructive urinary retention (Fowlers syndrome), but its value in UAB in general remains unclear (Shapiro et al. 2020, Yamany et al. 2019, Bayrak and Dmochowski 2019). Transcutaneous or intravesical stimulation has been reported to be successful in some patients but the available evidence is too limited for a recommendation. In men with BOO and UAB, surgical removal of the obstruction has largely restored voiding function even if BOO had existed for a long time (Dobberfuhl et al. 2019).

In conclusion, UAB/DU is a condition that appears to be frequent. Treatment modalities proven to be effective and safe in randomized studies are largely missing. Further experimental and clinical research in this area is urgently needed but is hampered by diverse underlying pathologies and unclear definitions.

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VIII. HORMONAL TREATMENT OF URINARY INCONTINENCE

1. OESTROGENS

1.1. Oestrogens and the Continence Mechanism

The oestrogen sensitive tissues of the bladder, urethra and pelvic floor all play an important role in the continence mechanism. For women to remain continent the urethral pressure must exceed the intra-vesical pressure at all times except during micturition. The urethra has four oestrogen sensitive functional layers all of which have a role in the maintenance of a positive urethral pressure 1) urothelium, 2) vasculature, 3) connective tissue, 4) muscle.

Two types of oestrogen receptor, α and β, have been identified in the trigone of the bladder, urethra and vagina as well as in the levator ani muscles and fascia and ligaments within the pelvic floor [Smith et al.,1990; Copas et al., 2001; Gebhardt et al., 2001]. After the menopause oestrogen receptor α has been shown to vary depending upon exogenous oestrogen therapy [Fu et al., 2003]. In addition, exogenous oestrogens affect the remodelling of collagen in the urogenital tissues resulting in a reduction of the total collagen concentration with a decrease in the cross linking of collagen in both continent and incontinent women [Falconer et al., 1998; Keane et al., 1997]. Studies in both animals and humans have shown that oestrogens also increase vascularity in the peri-urethral plexus which can be measured as vascular pulsations on urethral pressure profilometry [Robinson et al., 1996; Endo et al., 2000; Versi and Cardozo, 1986], or by using doppler velocimetry and immunohistochemistry staining[Kobata et al., 2008; Yura et al., 2020].

Big Potassium (BK) channels (novel, non-genomic targets for oestrogens), have been shown to play an important role in urinary bladder smooth muscle (UBSM) excitability and contractility [Petkov, 2014; Hanna-Mitchell et al., 2016]. Animal studies have demonstrated a reduction in UBSM excitability via activation of BK channels, mediated by 17β-estradiol [Provence et al., 2015; Kim et al., 2016]. At present the interspecies variation in experimental animal models means that the precise functional role of BK channels in human UBSM remains uncertain [Malysz, Petkov, 2020]. But it is likely that this represents an exciting target for the development of therapeutic interventions in the future.

1.2. Oestrogens for Stress Urinary Incontinence

The role of oestrogen in the treatment of stress urinary incontinence has been controversial despite a number of reported clinical trials [Hextall, 2000]. Some have given promising results, but this may have been because they were small observational and not randomised, blinded or controlled. The situation is further complicated by the fact that several different

types of oestrogen have been used with varying doses, routes of administration and duration of treatment. Fantl et al. [1996] treated 83 hypo-oestrogenic women with urodynamic stress incontinence and/or detrusor overactivity with conjugated equine oestrogens, 0.625 mg and medroxyprogesterone 10 mg cyclically for three months. Controls received placebo tablets. At the end of the study

period the clinical and quality of life variables had not changed significantly in either group. Jackson et al. [1996] treated 57 postmenopausal women with urodynamic stress or mixed incontinence with oestradiol 2 mg or placebo daily for six months. There was no significant change in objective outcome measures although both the active and placebo groups reported subjective benefit. Weber at al. [2017] conducted a prospective multi-centre trial in Australia, South Africa and the Netherlands, treating 68 postmenopausal women with SUI with vaginal oestriol 1mg/g cream for 6 weeks. At the end of the study period, statistically significant improvements in two out of four subjective domains (Patient's Global Impression of Improvement scale and Urogenital Distress Inventory) were seen. Out of the two objective outcomes measured, only vaginal pH improved significantly following treatment with vaginal oestriol, whereas cough pad tests varied widely.

Two meta-analyses of early data have been performed. In the first, a report by the Hormones and Urogenital Therapy (HUT) committee the use of oestrogens to treat all causes of incontinence in post-menopausal women was examined [Fantl et al., 1994]. Of 166 articles identified, which were published in English between 1969 and 1992, only six were controlled trials and 17 uncontrolled series. The results showed that there was a significant subjective improvement for all patients and those with urodynamic stress incontinence. However, assessment of the objective parameters revealed that there was no change in the volume of urine lost, maximum urethral closure pressure increased significantly but this result was influenced by only one study showing a large effect. In the second meta-analysis Sultana and Walters [1990] reviewed eight controlled and 14 uncontrolled prospective trials and included all types of oestrogen treatment. They also found that oestrogen therapy was not an efficacious treatment for stress urinary incontinence but may be useful for the often associated symptoms of urgency and frequency. Oestrogen when given alone therefore does not appear to be an effective treatment for stress urinary incontinence. Several studies have shown that oestrogen may have a role in combination with other therapies e.g. α-adrenoceptor agonists. In a randomised trial Ishiko et al. [2001] compared the effects of the combination of pelvic floor exercise and oestriol (1 mg per day) in 66 patients with post-menopausal stress urinary incontinence. Efficacy was evaluated every three months based on stress scores obtained from a questionnaire. They found a significant decrease in stress score in mild and moderate stress incontinent patients in both groups three months after the start of therapy and concluded that combination therapy with oestriol plus pelvic floor exercise was effective and could be used as first line treatment for mild stress urinary incontinence. A further study evaluating the effects of intravaginal oestriol and pelvic floor rehabilitation on urogenital aging in post-menopausal women randomised 206 women with symptoms of urogenital aging into two groups of 103 women each. Subjects in the treatment group received intravaginal oestriol ovules 1 mg once daily for 2 weeks and then 2 ovules weekly for a total of six months together with pelvic floor rehabilitation. Subjects in the control group received only intravaginal oestriol. Prior to treatment 83 (80.6%) of the women in the treatment arm complained of stress urinary incontinence compared to 103 (100%) of the control women. At the end of the study only 22 (21.4%) of the treated patients suffered from stress urinary incontinence compared to 93 (90.3%) of the control group representing a significant improvement in stress incontinence as a result of this combination therapy [Capobianco et al., 2012]. In an extrapolation of this work, triple combination therapy (oestrogen ovule in combination with PFR and Lactobacilli Acidophili) resulted in significantly more improvement in symptoms of stress urinary incontinence [Capobianco et al., 2014].

A more recent systematic review and network meta-analysis confirmed these earlier findings. The analysis compared the effectiveness of pharmacological and nonpharmacological interventions to improve or cure all types of incontinence. 84 randomised trials were identified, of which 32 reported stress urinary incontinence outcomes. The results demonstrated that behavioural therapy (pelvic floor muscle training), either alone or in combination with hormones (vaginal oestrogen), were more effective than hormones alone in achieving cure or improvement. Hormones (vaginal oestrogen) also showed no statistically significant difference in cure or improvement rates compared to no treatment [Balk et al., 2019].

Thus even prior to the reported secondary analyses of the heart and oestrogens/progestogen replacement study (HERS) [Grady et al., 2001] and women's health initiative (WHI) [Hendrix et al., 2005] it was already recognised that systemic oestrogen

therapy alone had little effect in the management of urodynamic stress incontinence [Al-Badr et al., 2003; Robinson and Cardozo, 2003].

1.3. Oestrogens for Urgency Urinary Incontinence and Overactive Bladder (OAB)

Oestrogen has been used to treat post-menopausal urgency and urgency incontinence for many years but there have been few controlled trials to confirm that it is of benefit [Hextall, 2000]. A double-blind multi-centre study of 64 post-menopausal women with "urge syndrome" failed to show efficacy [Cardozo et al., 1993]. All women underwent pre-treatment urodynamic investigation to ensure that they had either sensory urgency or detrusor overactivity. They were randomised to treatment with oral oestriol 3 mg daily or placebo for three months. Compliance with therapy was confirmed by a significant improvement in the maturation index of vaginal epithelial cells in the active but not the placebo group. Oestriol produced subjective and objective improvements in urinary symptoms but was not significantly better than placebo. Another randomised controlled trial from the same group using 25 mg oestradiol implants confirmed the previous findings [Rufford et al., 2003], and furthermore found a higher complication rate in the oestradiol treated patients (vaginal bleeding). More recently, a prospective study of 37 women with symptoms of overactive bladder demonstrated an improvement in the subjective assessment of night-time frequency and urgency with vaginal oestriol. In addition, objective urodynamic parameters of storage function, i.e., maximum cystometric capacity ($P<0.001$) and first desire to void ($P<0.001$) improved following vaginal oestriol treatment. It is worth noting however, that the parameters of voiding function and the number of patients with detrusor overactivity did not differ significantly with topical hormonal treatment. [Matarazzo et al., 2018].

Vaginal oestrogen therapy has been shown to reduce the incidence of urgency when used after a tension- free vaginal tape (TVT) compared with those not receiving topical vaginal oestrogen therapy (4% vs. 29%, $P = 0.01$) [Zullo et al., 2005].

Symptoms of OAB increase in prevalence with increasing age and lower urinary tract symptoms and recurrent urinary tract infections are commonly associated with urogenital atrophy. It is quite possible that the reason for this is that the symptoms of urinary urgency, frequency and urgency incontinence may be a manifestation of genitourinary syndrome of menopause atrophy in older postmenopausal women rather than a direct effect on the lower urinary tract [Robinson and Cardozo, 2003]. Whilst the evidence supporting the use of oestrogens in lower urinary tract dysfunction remains controversial there are considerable data to support their use in urogenital

atrophy and the vaginal route of administration correlates with better symptom relief by improving vaginal dryness, pruritis and dyspareunia, greater improvement in cytological findings and higher serum oestradiol levels (Cardozo et al., 1998).

Overall vaginal oestradiol has been found to be the most effective in reducing patient symptoms although conjugated oestrogens produced the most cytological change and the greatest increase in serum oestradiol and oestrone.

The most recent meta-analysis of intravaginal oestrogen treatment in the management of urogenital atrophy was reported by the Cochrane group in 2012 (Cody et al., 2012) Overall 34 trials including 19676 incontinent women of whom 9599 received oestrogen therapy (1464 involved in trials of local vaginal oestrogen administration). The trials used varying combinations of oestrogen, dose, duration of treatment and length of follow up. The combined result of six trials of systemic administration (oral oestrogen) resulted in worse incontinence than placebo. However, there was some evidence that oestrogen used locally as vaginal creams or pessaries improved incontinence. Overall, there was less frequency and urgency in those women treated with local oestrogen. This confirms the results of an earlier meta-analysis which supports the topical route of oestrogen administration in the treatment of UUI and bladder overactivity [Cardozo et al., 2004]. Thus, theoretically there could be a role for combination treatment with an antimuscarinic agent and vaginal oestrogen in post-menopausal women.

However, the clinical trials which have been reported to date differ in their outcome. Tseng et al. [2009] showed superior efficacy in terms of symptom improvement for the overactive bladder when tolterodine was used with vaginal oestrogen cream as opposed to tolterodine alone. However, Serati et al. [2009] found no difference between tolterodine with or without topical oestrogen in women with symptomatic detrusor overactivity. A subsequent study by Ellington et al. [2016] found that combination therapy resulted in greater symptom relief only when tolterodine was added to single therapy intravaginal oestradiol group at 12 weeks but not the converse. This led them to conclude that the addition of an antimuscarinic may only be necessary if intravaginal oestradiol alone has not conferred sufficient benefit.

A study compared the efficacy and safety of solifenacin succinate versus solifenacin succinate with local oestrogen for the treatment of overactive bladder in 104 post-menopausal women randomised to receive either solifenacin 5 mg daily plus Promestriene vaginal capsules or solifenacin alone. The primary outcome measure was change from baseline to end of treatment in the mean number of voids per 24 hours, quality of life was assessed using the international prostate symptom score and overactive bladder symptoms score questionnaires.

The median decreases in number of voids in 24 hours in the two groups were 5.4 and 4.3 respectively which was not statistically different. The median decrease in urgency episodes was 2.0 and 2.5 respectively. In addition, the quality-of-life scores significantly changed in both groups (both the <0.05). The authors concluded that solifenacin with or without local oestrogen was effective and safe for overactive bladder treatment in post-menopausal women. The addition of local oestrogen improved subjective feelings and quality of life [Jiang et al., 2016].

There has been one study comparing the oestradiol vaginal ring with oral oxybutynin for treatment of overactive bladder [Nelken et al., 2011]. Participants were randomised to receive either the ultra-low dose oestradiol vaginal ring or oral oxybutynin for 12 weeks.

The primary outcome was a decrease in the number of voids in 24 hours. Secondary outcomes were quality of life questionnaires, vaginal pH levels and vaginal maturation index. Fifty-nine women were enrolled, 31 were randomised to receive oxybutynin whereas 28 received the oestradiol vaginal ring. Women who received oxybutynin had a mean decrease of 3.0 voids per day and women who received the vaginal ring had a mean decrease of 4.5 voids per day with no significant difference between the groups. There was a significant improvement in urogenital distress inventory and incontinence impact questionnaire scores in both groups with no significant difference in improvement between the two groups, thus ultra-low dose oestradiol releasing vaginal ring and oral oxybutynin seemed to be similarly effective in decreasing the number of daily voids in post-menopausal women with overactive bladder.

Similarly, a small study where 23 women were randomised to either combination therapy with fesoterodine and topical vaginal oestrogen, or fesoterodine alone, showed no statistically significant difference between groups after 12 weeks of treatment. Again however, the improvement in the combination therapy group in all primary outcome measures of this study, was greater than in the single therapy group [Chughtai et al., 2016].

1.4. Evidence Regarding Oestrogens and Incontinence from Large Clinical Trials.

The HERS study included 2763 post-menopausal women under the age of 80 years with coronary heart disease and intact uteri [Grady et al., 2001]. It was designed to evaluate the use of oestrogen in secondary prevention of cardiac events. In a secondary analysis 1525 participants who reported at least one episode of incontinence per week at baseline were close included. Participants were randomly assigned to 0.625 mg of conjugated oestrogens plus 2.5 mg of medroxyprogesterone acetate in one tablet (N=768) or placebo (N=757) and were followed for a mean of 4.1 years. Severity of incontinence was classified as improved, unchanged, or worsened. The results showed that incontinence improved in 26% of the

women assigned to placebo compared to 21% assigned to hormones whilst 27% of the placebo group worsened compared with 39% of the hormone group (P=0.001). This difference was evident by four months of treatment, for both urgency and stress urinary incontinence. The number of incontinence episodes per week increased by an average of 0.7 in the hormone group and decreased by 0.1 in the placebo group (p< 0.001). The authors concluded that daily oral oestrogen plus progestogen therapy was associated with worsening urinary incontinence in older post /menopausal women with weekly incontinence and did not recommend this therapy for treatment of incontinence. However, it is possible that the progestogen component may have had an influence on the results of this study.

The Women's Health Initiative (WHI) was a multi-centre double blind placebo controlled randomised clinical trial of menopausal hormone therapy in 27347 postmenopausal women, age 50-79 years, enrolled between 1992 and 1998 for whom urinary incontinence symptoms were known in 23296 participants at baseline and one year [Hendrix et al., 2005]. The women were randomised based on hysterectomy status to active treatment or placebo. Those with a uterus were given 0.625 mg per day of conjugated equine oestrogen (CEE) plus 2.5 mg per day of Medroxyprogesterone Acetate (CEE+MPA), whereas those who had undergone hysterectomy received oestrogen alone (CEE). At one year hormone therapy was

shown to increase the incidence of all types of urinary incontinence among women who were continent at baseline. The risk was highest for stress urinary incontinence CEE+MPA: RR, 1.7 95% continence interval) CI (1.61-2.18); CEE alone RR 2.15 mg, 95% CI, 1.77-2.62, followed by mixed urinary incontinence CEE+MPA: RR 1.49 95% CI 1.10-2.01. On CEE alone RR was 1.79 95% CI, 1.26-2.53. The combination of CEE and MPA had no significant effect on developing urge urinary incontinence RR, 1.15; 95% CI, 0.99-1.34 but CEE alone increased the risk RR 1.32; 95% CI, 1.10-1.58. For those women experiencing urinary incontinence at baseline frequency worsened in both active groups CEE+MPA; RR, 1.38 95% CI 1.28-1.49; CEE alone: RR, 1.47 95% CI, 1.35-1.61. Quantity of urinary incontinence worsened at one year in both active groups, CEE+MPA: RR, 1.20 95% CI, 1.06-1.76; CEE alone: RR, 1.59 95% CI, 1.39-1.82. Those women receiving hormone therapy were more likely to report that urinary incontinence limited their daily activities CEE+MPA: RR 1.18 95% CI, 1.06-1.32. CEE alone: RR 1.29 95% CI, 1.15-1.45 at one year. Thus, based on this secondary analysis of data from a huge study conjugated equine oestrogen alone or in combination with medroxyprogesterone acetate was shown to increase the risk of urinary incontinence amongst continent women and worsen urinary incontinence amongst asymptomatic women after one year of therapy.

The Nurses Health Study [Grodstein et al., 2004] was a biennial postal questionnaire starting in 1976. In 1996 39436 post-menopausal women aged 50-75 years who reported no urinary leakage at the start of the study were followed up for four years to identify incident cases of urinary incontinence. 5060 cases of occasional and 2495 cases of frequent incontinence were identified. The risk of developing urinary incontinence was increased amongst post-menopausal women taking hormones compared to women who had never taken hormones (oral oestrogen: RR1.54 95% CI 1.44, 1.65; transdermal oestrogen: RR1.68, 95% CI 1.41, 2.00; oral oestrogen with progestin: RR1.34, 95% CI 1.24, 1.44; transdermal oestrogen with progestin: RR1.46, 95% CI 1.16, 1.84). After cessation of hormone therapy there was a decreased risk of incontinence such that 10 years after stopping hormones the risk was identical in women who had and who never had taken hormone therapy.

The most recent meta-analysis of the effect of oestrogen therapy on the lower urinary tract has been performed by the Cochrane Group [Cody et al., 2012] and is notable as the conclusions are starkly different from those drawn from the previous review [Moehrer et al., 2003]. Overall, 34 trials were identified including 19676 incontinent women (1464 involved in trials of local administration) of which 9599 received oestrogen therapy.

Systemic administration (of unopposed oral oestrogens – synthetic and conjugated equine oestrogens) resulted in worse incontinence than placebo (RR1.32; 95% CI: 1.17-1.48). Although this is heavily influenced by the size of the WHI study [Hendrix et al 2005]. When considering combination therapy there was a similar worsening effect on incontinence when compared to placebo (RR1.11; 95% CO: 1.04-1.08). There was some evidence suggesting that the use of local oestrogen therapy may improve incontinence (RR0.74; 95% CI: 0.64-0.86) and overall, there were 1-2 fewer voids in 24 hours and less frequency and urgency. The authors conclude that local oestrogen therapy for incontinence may be beneficial although there was little evidence of long-term effect. The evidence would suggest that systemic hormone replacement using conjugated equine oestrogens may make incontinence worse. In addition, they reported that there are too few data to comment reliably on the dose type of oestrogen and route of administration.

2. GENITOURINARY SYNDROME OF MENOPAUSE

Following a consensus conference held in 2013 the Board of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the Board of Trustees of the North American Menopause Society (NAMS) acknowledged the need to review terminology associated with genitourinary tract symptoms related to menopause [Portman et al., 2014]. They agreed on the term Genitourinary Syndrome of Menopause (GSM) as a more accurate all-encompassing and publically acceptable term than vulvo-vaginal atrophy. As well as genital symptoms this covers the urinary symptoms of urgency, dysuria, and recurrent urinary tract infections. It has long been appreciated that these symptoms respond well to

Table 11

Name of Drug	Type of Oestrogen	Dose (dose in mg for comparison)	Formulation
Vagifem	Oestradiol hemihydrate	10microgram (0.01)	Tablet
Estradiol	Oestradiol hemihydrate	10microgram (0.01)	Pessary
Vagirux	Oestradiol hemihydrate	10microgram (0.01)	Tablet
Estring	Oestradiol hemihydrate	7.5microgram/24hr (0.0075/24hr)	Vaginal ring
Femring	Oestradiol acetate	0.05mg/24hr 0.1mg/24hr	Vaginal ring
Imvexxy	Oestradiol	4microgram (0.004) 10mincrogram (0.01)	Vaginal inserts (ovules)
Premarin Vaginal	Conjugate equine oestrogen	0.625mg/g	Cream
Ovestin	Oestriol	1mg/g	Cream
Imvaggis	Oestriol	0.03mg	Tablet
Gynest 0.01%	Oestriol	100microgram/g (0.1)	Cream
Blissel	Oestriol	50microgram/g (0.05)	Cream

low dose local (intravaginal) oestrogen therapy given long term to post-menopausal women [Baber et al., 2016]. Since the introduction of intravaginal oestrogens, the traditional 25 microgram twice weekly dose of oestradiol vaginal tablets has been replaced by the ultra-low dose 10 microgram twice weekly vaginal tablet, to mitigate the risks of endometrial stimulation associated with the original, higher dose [Simon & Maamari, 2013]. This has unfortunately led to reduced efficacy and does not appear to be adequate for the control of overactive bladder symptoms in post-menopausal women, 50% of whom may suffer from genitourinary syndrome of the menopause if untreated. Fears regarding unopposed oestrogens, have led to the development of ultra-low dose vaginal oestrogen formulations. There are now a variety of preparations and concentrations (see **Table 11**) available. Their efficacy when compared to one another, is , undetermined.

However, the most recent Cochrane review, which included 30 trials with 6235 women, found only low-quality evidence that intra-vaginal oestrogenic preparations improve the symptoms of vaginal atrophy in postmenopausal women when compared to placebo, and confirmed earlier review conclusions that there was no difference between various types of formulation [Lethaby et al., 2016]

3. OTHER HORMONES

3.1. Selective Oestrogen receptor modulators (SERMS)

Selective oestrogen receptor modulators (SERMS) have been reported to have varying effects. Each of the SERMS has receptor ligand conformations that are unique and have both oestrogenic and anti-oestrogenic effects. Initially the best data available related to Raloxifene, as this was the only drug licensed for the treatment of postmenopausal osteoporosis. However, raloxifene has not been shown to have any effect at all on urinary incontinence [Vardy et al., 2003, Waetjen et al., 2004]. Studies evaluating the effect of Tamoxifen on urinary incontinence are limited, and although some have demonstrated an increase in urinary incontinence among breast cancer survivors taking Tamoxifen, none have identified a statistically significant relationship. [Vardy et al., 2003; Morales et al., 2004; Alfano et al., 2006].

More recently, Ospemifene, a third generation SERM, indicated for treatment of moderate-to-severe symptomatic VVA [Nappi et al., 2017] and dyspareunia [Bondi et al., 2016] in postmenopausal women in whom oestrogen therapy is contraindicated, has shown promising results regarding the management of OAB symptoms. A retrospective review of 46 women with VVA found a significant improvement in frequency, nocturia, urgency, and urgency incontinence after 12 weeks of Ospemifene treatment [Schiavi et al., 2017].

A study of 105 patients, aimed at assessing the effectiveness of Ospemifene in the improvement of sexual function in postmenopausal women with VVA and OAB symptoms, found a significant improvement in frequency, nocturia, urgency, and urgency incontinence [Schiavi et al., 2018]. There were also significant improvements in OAB questionnaire scores. These results have subsequently been replicated in a prospective cohort study of 25 women with VVA and OAB symptoms refractory to first-line pharmacologic treatment [Novara et al., 2020]. Additionally, ospemifene has been shown to be effective the treatment of the urgency component of mixed urinary incontinence following insertion of a mid-urethral sling [Schiavi et al.,2019].

3.2. Androgens

Preliminary studies of dihydroepiandrosterone (DHEA) and its sulphate (DHEAS), which are metabolised to oestradiol and testosterone in peripheral target tissues, have demonstrated promising results for the treatment of postmenopausal women with symptoms of vaginal atrophy. However, as there are no reported, clinical trials evaluating the effect of androgens, and, in particular, DHEA, on urinary incontinence in women, it remains to be seen whether this improvement in the VVA aspect of GSM symptoms, will be extrapolated to its lower urinary tract manifestations.

3.3. Progesterone and progestogens

Progesterone and progestogens are thought to increase the risk of urinary incontinence. Lower urinary tract symptoms especially stress urinary incontinence have been reported to increase in the progestogenic phase of the menstrual cycle [Hextall et al., 2001]. In similar studies, progesterone has been shown to increase beta adrenergic activity leading to a decrease in the urethral closure pressure in female dogs [Raz et al., 1973]. However, in the WHI there appeared to be no difference whether or not progestin was given in addition to oestrogen [Hendrix et al., 2005].

Conclusions. Oestrogen has an important physiological effect on the female lower urinary tract and its deficiency is an aetiological factor in the pathogenesis of a number of conditions. However, the use of oestrogen either alone or in combination with progestogen has yielded poor results. The current level 1 evidence against the use of systemic oestrogen for the treatment of urinary incontinence comes from studies powered to assess their benefit in the prevention of cardiovascular events and therefore the secondary analyses have only been based on self-reported symptoms of urinary leakage without any objective data. Despite this, all of these large randomised controlled trials show a worsening of pre-existing urinary incontinence, both stress and urgency and an increased new incidence of urinary incontinence with both oestrogen and oestrogen plus progestogen. However, the majority of subjects in all of these studies were taking combined equine oestrogen and this may not be representative of all oestrogens taken by all routes of administration.

Whilst there is good evidence that the symptoms and cytological changes of urogenital atrophy may be reversed by low dose (local) vaginal oestrogen therapy there is currently no evidence that oestrogens with or without progestogens should be used in the treatment of urinary incontinence.

Although the SERM, Ospemifene, has demonstrated encouraging results regarding the treatment of OAB symptoms, there remains a paucity of high-quality evidence to support its routine use. Most studies concerning Ospemifene do not include improvement in the urogenital symptoms of GSM as their primary outcome. Currently there are no randomised controlled trials comparing either Ospemifene to vaginal oestrogen alone, or in combination with an antimuscarinic for the management of urinary symptoms. More rigorous clinical trials will be needed before SERMs/Ospemifene are included in the stepwise management of overactive bladder symptoms.

The International Menopause Society (IMS) produced recommendations in 2016 on

women's midlife health and menpause hormone therapy (MHT) to help guide healthcare professionals in optimising their management of women in menopause transition and beyond. They have given a Grade A recommendation to the use of local oestrogens

for urogenital symptoms and a Grade B recommendation for the long-term use of such treatment. They have also allocated a Grade B recommendation to the use of low dose local oestrogens in the management of recurrent lower urinary tract infection [Baber et al., 2016].

The British Menopause Society's (BMS) most recent consensus statement [Pitkin et al., 2018] corroborates these recommendations and goes further to support the use of local vaginal oestrogen on a long-term basis, for as long as it is needed. The BMS also quote evidence for the use of local vaginal oestrogens for the management of OAB, especially in cases of concomitant vaginal atrophy.

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4. DESMOPRESSIN

The endogenous hormone vasopressin (also known as anti-diuretic hormone) has two main functions: it causes contraction of vascular smooth muscle and stimulates water reabsorption in the renal

medulla. These functions are mediated by two specific vasopressin receptors of which there are two major subtypes, namely the V_1 and V_2 receptors. The V_2 subtype is particularly important for the anti-diuretic effects of vasopressin. A genetic or acquired defect in making and secreting vasopressin leads to central diabetes insipidus, and genetic defects in the gene encoding the V_2 receptor can cause nephrogenic diabetes insipidus [Insel et al., 2007]. Accordingly, decreased vasopressin levels are believed to be important in the pathophysiology of polyuria, specifically nocturnal polyuria (NP), which can lead to symptoms such as nocturia [Matthiesen et al., 1996; Weiss et al., 2011a, Weiss and Everaerts. 2019]. Nocturia and NP was currently defined by the International Continence Society (ICS), nocturia as "The number of times urine is passed during the main sleep period. Having woken to pass urine for the first time, each urination must be followed by sleep or the intention to sleep. This should be quantified using a bladder diary," and nocturnal polyuria as "Passing large volumes of urine during the main sleep period. This should be quantified using a bladder diary" [Hashim et al., 2018]. Nocturia leads to decreased quality of life [Kupelian et al., 2011, Torimoto et al., 2021], and has been associated with both increased morbidity and mortality [Nakagawa et al., 2010; Kupelian et al., 2012; Pesonen et al., 2020]. While it remains largely unknown in which fraction of patients nocturia can indeed be explained by too little vasopressin, the presence of nocturnal polyuria in the absence of behavioural factors explaining it (such as excessive fluid intake) is usually considered as an indication that a (relative) lack of vasopressin may exist. While it remains largely unknown in what fraction of patients nocturia is explained by too little vasopressin, the presence of NP in the absence of identifiable medical conditions that can explain it (e.g., excessive fluid intake) is usually considered to indicate decreased vasopressin levels [Bosch and Weiss., 2011, Weiss et al., 2011b]. Based upon these considerations, vasopressin receptor agonists have been used to treat nocturia, both in children and in adults [Weiss and Everaerts, 2019].

Desmopressin is the most common vasopressin analogue used to treat nocturia. Desmopressin shows selectivity for anti-diuretic over vasopressor effects. It has a more powerful and longer-lasting antidiuretic action than vasopressin. It is available in formulations for oral, parenteral, and intranasal administration. It has a fast onset of action, with urine production decreasing within 30 minutes of oral administration [Rittig et al., 1998]. An oral lyophilisate (MELT) formulation requiring no concomitant fluid intake is globally the most commonly used for reasons of pharmacokinetics and patient preference, although it has not been approved in many countries, including the United States [Neveus et al., 2020]. The MELT formulation was shown also to have better pharmacodynamic characteristics of than desmopressin tablets [De Guchtenaere et al., 2011]. Another newly approved formulation was AV002 (SER120), a novel, emulsified, microdose desmopressin nasal spray with rapid absorption, high bioavailability, limited duration of action, and low coefficient of variation [Andersson et al., 2019]. AV002 was shown to cause significant improvements over placebo for co-primary and secondary efficacy end points that corresponded with quality of life improvements and had an acceptable safety profile [Kaminetsky et al., 2019].

4.1. Demopressin in children

An excess urine production during sleep is a common finding in children with enuresis and disturbances in the circadian rhythm of arginine-vasopressin (AVP) is found in the majority of children with nocturnal polyuria. Children with enuresis and nocturnal polyuria lack the physiologic increase in AVP levels during sleep and treatment with the AVP analogue desmopressin can restore this rhythm and lead to dry nights [Kemperis, 2021]

The pediatric pharmacology of desmopressin in children with enuresis was recently reviewed by Gasthuys et al. [2020]. Among the various pharmaceutical formulations of desmopressin commercialized for this indication - nasal spray, nasal drops, oral tablet and oral lyophilizate, the lyophilizate is the preferred formulation]. A profound food effect on the oral bioavailability was demonstrated as well as different plasma concentration-time profiles (double absorption peak) of the desmopressin lyophilizate between adults and children. Regarding the safety of the different desmopressin formulations, the use of desmopressin was generally considered safe, but measures should be taken to prevent severe hyponatremia .Because of symptomatic hyponatremia with water intoxication which is the only serious adverse event reported in children, occurred after intranasal or intravenous administration of desmopressin [Thumfart et al., 2005; Robson et al., 2007; Van de Walle et al., 2010], the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) removed the indication for the treatment of primary nocturnal enuresis from all intranasal preparations of desmopressin.

The use of desmopressin in children with nocturnal enuresis was comprehensively reviewed by the Cochrane Collaboration in 2002 [Glazener et al., 2002]. Previous guidelines for the evaluation and treatment of children with enuresis were recently updated by experts affiliated with the International Children's Continence Society (ICCS) [Neveus et al, 2020].

In the Cochrane Collaboration study the authors evaluated 47 randomized controlled trials involving 3448 children, of whom 2210 received desmopressin. According to their analysis, desmopressin was effective relative to placebo in reducing bed-wetting (e.g. a dose of 20 μg resulted in a reduction of 1.34 wets/night (95% CI 1.11; 1.57), and children were more likely to become dry with desmopressin (98%) than with placebo (81%). However, there was no difference between desmopressin and placebo after discontinuation of treatment, indicating that desmopressin suppresses symptom enuresis but does not cure the underlying cause. The Cochrane Group have reviewed a total of 40 randomised or quasi-randomised controlled trials of 1780 children who were in enrolled receiving an active drug other than Desmopressin or a tricyclic. 31 different drugs or classes of drug were tested. For drugs versus placebo, when compared to placebo Indomethacin, Diazepam, Mestorelone and Atomoxetine appeared to reduce the number of children failing to have 14 consecutive dry nights. Althogh Indomethacin and Diclofenac were better than placebo during treatment, they were not as effective as Desmopressin and there was a higher chance of adverse effects [Desphande et a., 2012]. Additionally, not all children responded sufficiently to desmopressin monotherapy. The combination of desmopressin and an enuresis alarm resulted in a greatly improved short-term success rate and decreased relapse rates [Alloussi et al., 2011]. The combination of desmopressin and antimuscarinics resulted in better short- and long-term success rates as well as a lower relapse rate than desmopressin alone [Austin et al., 2008; Alloussi et al., 2009). A Cochrane Review showed that when imipramine combined with desmopressin was compared with imipramine monotherapy there was no different in outcomes. However, when imipramine plus desmopressin was compared with desmopressin monotherapy the combination was more effective with 15% not achieving 14 consecutive dry nights at the end of treatment for imipramine plus demospressin versus 40% for desmopressin monotherapy [Caldwell et al., 2016].

The guidelines of the working group of the ICCS recommended active therapy from the age of 6 years [Neveus et al., 2020]. In nonmonosymptomatic enuresis, basic advice regarding voiding and

drinking habits should be provided. In monosymptomatic enuresis, or if the above strategy did not make the child dry, the first-line treatment modalities are desmopressin or the enuresis alarm. If both these therapies fail alone or in combination, anticholinergic treatment is a possible next step. If the child is unresponsive to initial therapy, antidepressant treatment may be considered by the expert [Neveus et al., 2020].

4.2. Desmopressin in adults

Neurologic disorders. Several studies have explored a possible treatment role for desmopressin in the treatment of nocturia in adults including those with neurological disorders, e.g., multiple sclerosis [Eckford et al., 1994;1995; Haddad et al., 2020]. One study with single dose administration reported a reduction in nocturnal polyuria, but by design did not assess nocturia [Eckford et al., 1995]. Three placebo-controlled double-blind studies with a small patient number (16-33 patients total per study) reported a significant reduction in nocturia [Hilton et al., 1983; Eckford et al., 1994; Valiquette et al., 1996]. Other controlled studies of similar size, most with a crossover design, used micturition frequency within the first 6 h after desmopressin administration rather than nocturia as their primary endpoint. These studies consistently reported that desmopressin treatment for up to 2 weeks was efficacious [Kinn and Larsson, 1990; Fredrikson, 1996; Hoverd and Fowler, 1998]. While desmopressin treatment was generally well tolerated, 4 of 17 patients in one study discontinued treatment due to asymptomatic or minimally symptomatic hyponatremia [Valiquette et al., 1996]. Accordingly, desmopressin is now registered for the treatment of nocturia in multiple sclerosis patients [Cvetkovic and Plosker, 2005]. In a small open-label study, desmopressin was also reported to reduce nocturnal polyuria in spinal cord injury patients [Zahariou et al., 2007].

Haddad et al [2020] systematically reviewed the literature about nocturia in neurological patients by electronic search of Cochrane and Medline databases. The studies were included if their participants had acquired neurological pathology among multiple sclerosis (MS), Parkinson's disease (PD), stroke, spinal cord injury (SCI). Among 132 included studies, nocturia prevalence ranged from 15% to 96% depending on the pathology and definition used. Haddad et al. [2020] concluded that nocturia is highly prevalent in patients with neurological disorders. Causalities and treatments are not different from the general population but are poorly studied in neurological patients.

Absence of neurologic disorders. Further studies have explored the use of desmopressin in adults with nocturia in the apparent absence of neurological damage. The recruited patient populations were based upon different criteria, including having at least two nocturia episodes per night or having nocturnal polyuria. Earlier studies mostly used a desmopressin dose of 20 µg given either orally [Asplund et al., 1999] or intranasally [Hilton and Stanton, 1982; Cannon et al., 1999], and tended to be very small (≤25 patients). Later studies, as part of the NOCTUPUS program, were considerably larger, involving a total of 1003 screened patients, and higher oral doses (0.1-0.4 mg) were administered for a period of 3 weeks of double-blind treatment in adults [Mattiasson et al., 2002; Lose et al., 2003; van Kerrebroeck et al., 2007]. A total of 632 patients entered the dose-titration phase and 422 patients entering the double-blind phase of the three NOCTUPUS trials. To counter the argument that the study was performed in desmopressin responders after the dose titration phase, all patients in the NOCTUPUS trials were washed-out following the dose-titration phase and in order to be randomized, it was a requirement that the patients returned to baseline nocturnal diuresis before inclusion in the double-blind phase. The trials showed that oral desmopressin (0.1, 0.2 or 0.4 mg) is effective in both men and women aged ≥ 18 years with nocturia. The number of nocturnal voids decreased from 3 to 1.7 in the desmopressin group compared to 3.2 to 2.7 in the placebo group. In women, the number of nocturnal voids in the desmopressin group decreased from 2.92 to 1.61, whereas that in the placebo group decreased from 2.91 to 2.36. When clinical response was defined as ≥ 50% reduction in nocturnal voids from baseline, 34% of men experienced clinical response with desmopressin, compared with 3% of men who received placebo. In women, 46% of desmopressin-treated patients experienced a clinical response, compared with 7% of patients on placebo.

Weiss and colleagues reported outcomes on a four week multi/centre randomised double-blind placebo-controlled trial to determine the efficacy of orally disintegrating sub-lingual desmopressin, i.e., "melt" formulation. The authors randomised patients to 10, 25, 50 and 100 micrograms. Approximately 90% of the subjects reported true nocturnal polyuria, 710 patients completed the study. A statistically significant difference in the number of nocturnal voids was seen for all patients with a100 micrograms and 50 micrograms. Women responded to 25 micrograms as well, however for men there was only a statistically significant difference with 100 micrograms. The proportion of patients with at least a 33% reduction in the number of nocturnal voids (primary outcome measure) increased with dosage for all patients but there was a stronger response seen in women at 25 micrograms. A total of 24 patients (3%) experienced hyponatremia which was a more likely occurrence in patients over the age of 65 years [Weiss et al., 2012].

The efficacy of desmopressin for the treatment of nocturia was confirmed in a long-term (10-12 months) open-label study involving 249 patients, which was an extension of the randomized studies in known desmopressin responders. However, a rebound effect was seen when treatment was withdrawn, confirming the association between continued treatment and response [Lose et al., 2004]. An open-label pilot study in a nursing home setting also reported that desmopressin had beneficial effects [Johnson et al., 2006].

Around 75% of community-dwelling men and women with nocturia (≥2 voids/night) have nocturnal polyuria (NP) [Rembratt et al., 2003; Swithinbank et al. 2004]. The key urological factors most relevant to nocturia are NP and OAB in women [Irwin et al., 2008], and NP and benign prostatic hyperplasia (BPH) in men. About 74% of women with OAB have nocturia and 62% of patients with OAB and nocturia have NP. Among men with nocturia, 83% have NP; 20% have NP alone, and 63% have NP in combination with another factor such as a small nocturnal bladder capacity or bladder outlet obstruction [Chang et al., 2006]. Therefore, desmopressin combination therapy with α_1- adrenergic blockers and/or anticholinergics should be considered for patients with treatment–resistant nocturia. Seventy-three percent of α_1- adrenergic blocker-resistant BPH patients experienced a ≥50% reduction in nocturnal voids with oral desmopressin [Rembratt et al., 2003; Yoong et al., 2005]. A randomized, double-blind, placebo-controlled study evaluating the long-term (1, 3, 6, and 12 months) efficacy and safety of low dose (0.1 mg) oral desmopressin in elderly (≥ 65 years) patients reported that low dose oral desmopressin led to a significant reduction in the number of nocturnal voids and nocturnal urine volume in patients with BPH [Wang et al., 2011].

Because nocturia can be caused by different factors, several studies have investigated whether desmopressin may be beneficial in patients with other symptoms in addition to nocturia. In a small, non-randomized pilot study of men believed to have BPH, desmopressin was reported to improve not only nocturia, but also to reduce

the overall international prostate symptom score (IPSS) [Chancellor et al., 1999]. An exploratory, placebo-controlled double-blind study in women with daytime urinary incontinence reported that intranasal administration of 40 μg desmopressin increased the number of leakage-free episodes 4 hours after drug administration (Robinson et al., 2004). One double-blind, placebo-controlled pilot study in patients with OAB treated with 0.2 mg oral desmopressin reported a reduction in voids along with an improvement in quality of life (QoL) [Hashim et al., 2009]. While these data indicate that desmopressin may be effective in treating voiding dysfunction not limited to nocturia, they are too sparse to allow treatment recommendations. Desmopressin was well tolerated in all the studies and resulted in significant improvements compared to placebo in reducing nocturnal voids and increasing the hours of undisturbed sleep. There was also an improvement in QoL.

4.3. Desmopressin and hyponatremia.

One of the main clinically important side-effects of desmopressin is hyponatremia. Hyponatremia can lead to a variety of adverse events ranging from mild headache, anorexia, nausea, and vomiting to loss of consciousness, seizures, and death. Hyponatremia usually occurs soon after treatment is initiated. The risk of hyponatremia appears to increase with age, cardiac disease, and increasing 24-hour urine volume [Rembratt et al., 2003; 2006]. Based on a meta-analysis, the incidence is around 7.6% [Weatherall, 2004]. Increased age and female gender are well-known risk factors for the development of desmopressin-induced hyponatremia [Rembratt et al., 2006]. Bae et al. [2007] assessed the effects of long-term oral desmopressin on serum sodium and baseline antidiuretic hormone secretion in 15 elderly male patients with severe nocturia (greater than 3 voids nightly), who did not show hyponatremia within 7 days of administration of 0.2 mg desmopressin. Desmopressin (0.2 mg) was administered orally nightly for 1 year. Before and 1 month after the 1-year medication 24-hour circadian studies were performed to monitor changes in antidiuretic hormone. Every 3 months during the 1-year medication, serum changes and timed urine chemistry were monitored. The results showed that long-term desmopressin administration gradually decreased serum sodium and induced statistically, but not clinically significant, hyponatremia after 6 months of treatment Administration of desmopressin for 1 year did not affect baseline antidiuretic hormone secretion. The authors recommended that for long-term desmopressin administration serum sodium should be assessed regularly, at least every 6 months.

There has been some research exploring gender differences in the antidiuretic response to desmopressin. Juul et al. [2011] found an increasing incidence of hyponatremia with increasing dose, and at the highest dose level of 100 micrograms decreases in serum sodium were approximately twofold greater in women over 50 yrs of age than in men. A new dose recommendation stratified by gender was suggested in the treatment of nocturia: for men, 50- to 100 micrograms melt was suggested to be an efficacious and safe dose, while for women a dose of 25 micrograms melt was recommended as efficacious with no observed incidences of hyponatremia. Weiss and colleagues investigated the efficacy and safety of 50 and 75 micrograms desmopressin orally disintegrating tablets in 385 men with nocturia. They showed that both doses increased the time to first void from baseline by approximately 40 minutes compared to placebo. The response to desmopressin was seen within a week of treatment and was sustained producing signficant increases in health-related quality of life and sleep quality compared to placebo. Only 2 subjects aged 74 and 79 years respectively developed hyponatremia [Weiss et al., 2013]. A similar study carried out in women explored the efficacy and safety of 25 micrograms of Desmopressin orally disintegrating tablets compared to placebo. 261 women with nocturia were randomised to either 25 micrograms of desmopressin or placebo. Desmopressin significantly reduced the mean number of nocturnal voids compared to placebo and increased the mean time to first nocturnal void by 49 minutes compared to placebo. Once again response was seen within the first week of treatment and sustained throughout the three-month trial. Desmopressin was well tolerated with only three transient decreases in serum sodium level [Sand et al., 2013].

Initiation of desmopressin is currently not indicated for patients aged ≥65 years. The mechanisms behind desmopressin-induced hyponatraemia are well understood, and serum sodium monitoring at baseline and early during treatment of older patients for whom treatment with desmopressin is indicated can greatly reduce their risk of developing the condition. Other advice regarding treatment administration, such as restriction of evening fluid intake and adherence to recommended dosing, should be followed to minimize the risk of hyponatremia [Vande Walle et al., 2007].

Desmopressin is useful for patients with nocturia as well as for children with nocturnal enuresis. It is the only antidiuretic treatment indicated specifically for nocturia due to NP. The drug has been proven to be well-tolerated and effective by several randomized, placebo-controlled trials and is recommended as a first-line treatment (either as monotherapy or in combination with other agents) for patients who have been appropriately evaluated and whose nocturia is related to NP whether or not this isaccompanied by BPH or OAB. For assessment, see Table 2.

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COMMITTEE 10

SURGERY FOR MALE URINARY INCONTINENCE

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COMMITTEE 10

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I. INTRODUCTION AND METHODS

Surgery for male incontinence is currently done primarily for those with leakage resulting from radical prostatectomy. However, some men who have had other treatments for prostate cancer, surgery for benign prostatic disease, who have significant overactive bladder (OAB), some following traumatic injury or those with a history of neurologic disease will have incontinence requiring some sort of surgery. Leakage related to OAB will be primarily covered in the Chapter on Surgery for OAB.

Urinary incontinence (UI) is a common complication after radical prostatectomy (RP) and has a negative effect on quality of life (QoL). Post-prostatectomy urinary incontinence (PPI), like any UI, may be caused by bladder dysfunction, sphincter dysfunction, or a combination of both. Several risk factors have been associated with PPI, including advanced age, obesity, comorbidity index, bladder dysfunction before surgery, prostate volume, pelvic floor dysfunctions and previous transurethral resection of the prostate.

RP for prostate cancer is performed far more frequently now than 25 years ago. Robot-assisted RP (RARP) has become the most frequently used approach for surgical management of localized prostate cancer in the United States, with 85% of all surgical cases performed via the robotic-assisted laparoscopic approach. According to an analysis of the Surveillance, Epidemiology and End RESULTS-Medicare dataset, which identified men who had open RP and minimally invasive RP (MIRP) for prostate cancer from 2003–2009, MIRP was associated with a higher risk of voiding dysfunction (hazard ratio [HR] 1.31, 95% confidence interval [CI] 1.20–1.43) and erectile dysfunction (ED) (HR 1.43, 95% CI 1.31–1.56), but a lower risk of bladder outlet obstruction (HR 0.86, 95% CI 0.75–0.97). However, as experience with the robotic approach has grown, the rate of adverse events has dropped significantly–particularly in high volume centers. In many centers, RARP is utilized for the overwhelming number of cases with excellent outcomes.

Approximately 5–25% of patients will experience incontinence that fails to improve with conservative management, and a substantial minority will ultimately undergo surgical treatment.[1] The incidence of PPI depends on the exact definition of UI, methods of data collection (surgeon vs. patient; complete vs. social continence) and the length of follow-up. The artificial urinary sphincter (AUS) has provided a satisfactory result in most cases, regardless of the degree of UI, with a positive impact on QoL. Sling procedures have emerged as an efficacious treatment in many men with mild to moderate stress UI (SUI). More recently, however, Abrams et al conducted a non-inferiority randomized clinical trial (RCT) to compare the male transobturator sling (N=190) vs. the AUS (N=190) among men with moderate to severe SUI, showing non-inferiority. At 12 months after randomisation, utilizing a very strict definition of continence, incontinence rates were 134/154 (87.0%) for male sling vs. 133/158 (84.2%) for AUS (*P*=0.003). Other minimally invasive options, such as bulking agents have not shown durable long-term results and its use has largely been abandoned. Periurethral balloons are a feasible minimally-invasive option for treatment bothersome PPI in selective reference centers. However, high revision and complication rates have been reported.

Although prostatectomy for benign disease has become less frequent in many countries, the complication of incontinence is a rare but unfortunate occurrence that merits treatment. After a period of conservative therapy has been tried, surgical treatment is indicated following similar strategies applied in post-prostate cancer treatment incontinence, i.e., slings and AUS.

Incontinence following radiation therapy (XRT), cryosurgery, high-intensity focused ultrasound (HIFU), other pelvic operations, and trauma is a particularly challenging problem because of tissue damage inside and outside the lower urinary tract. In such instances, periurethral bulking, sling procedures, and inflatable periurethral balloons have generally proven inefficacious and worsening of incontinence may happen after such surgery. The use of anti-androgen therapy in men with prostate cancer may result in tissue atrophy, which can exacerbate radiation-related SUI. The AUS is the most successful surgical procedure in this setting, but is associated with a higher rate of complications compared to implantation following surgery in the absence of adjuvant cancer therapy. With tissue damage beyond the urinary sphincter, other surgical approaches may be necessary. Patients with unresolved problems from childhood and with associated incontinence from detrusor overactivity may benefit from a variety of complex reconstructive surgical procedures. Patients with primarily OAB symptoms who have failed conservative management may benefit from neurostimulation or botulinum toxin injection. Other complicated problems encountered include urethrocutaneous fistulae, and fistulae between the prostate, bladder neck, or urethra and rectum. Surgical reconstruction, in experienced hands, often in a staged manner, is usually successful. Nonetheless, these cases often have higher complication rates and a multi-disciplinary team approach may be useful (e.g., colorectal, plastic surgeons).

This Chapter is a literature review and summary of the recommendations presented during the 7th International Consultation on Incontinence (ICI) by the Committee on Surgical Treatment of UI in Men.

1. METHODS AND MATERIALS

The Committee was charged with the responsibility of assessing and reviewing the outcomes of surgical therapy that have been published since the Sixth Consultation for non-neurogenic male incontinence.[4] Articles from peer-reviewed journals, abstracts from scientific meetings, and literature searches by hand and electronically formed the basis of this review. The outcomes were analyzed, discussed among the members of the Committee and included in the Chapter.

Incontinence was classified according to its etiology, i.e., either primarily sphincter, bladder related or fistulae (Table 1).

Specific recommendations are made based on published results and determined by the levels of evidence. Consensus of the Committee determined these clinical recommendations, which are found at the end of the Chapter. Recommendations for future research are also included.

TABLE 1. Classification of Surgically Correctable Problems

Sphincter Related	Post-prostatectomy for prostate cancer Post-prostatectomy for benign disease Post-TURP and radiation for prostate cancer Post-cystectomy and neobladder for bladder cancer Post-traumatic After prostato-membanous urethral reconstruction Pelvic floor trauma or dysfunction Unresolved pediatric urologic incontinence Exstrophy and epispadias Neurological (pelvic floor or sphincter) abnormality
Bladder Related	Refractory urgency incontinence Small fibrotic bladder
Fistulae	Prostatorectal (urethrorectal) Urethrocutaneous

II. TIMING OF SURGICAL INTERVENTION AND EVALUATION PRIOR TO SURGICAL THERAPY

1. TIMING OF INTERVENTION

Following RP, there is a consensus that progressive recovery of continence during the postoperative period can be expected.[5,,,,,,,] However, it is not established what duration of recovery time must be allowed to elapse to be confident of the long-term continence outcome. This duration is important, as it gives the patient a timepoint at which they can revise their expectations, and decide when to receive interventional treatment for persisting incontinence. Nonetheless, it is often recommended that patients wait a year after prostate surgery before considering incontinence surgery since improvement in SUI with conservative therapy is often most pronounced in the first year post-prostatectomy.[5,,] While there can be further improvement in incontinence beyond 1 year,[11,,] most patients will plateau by 1 year; although, in some cases, this may occur at 6 months.[20,]

Both the AUS Consensus Conference 2015 and the American Urological Associaion (AUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) 2019 Guidelines for incontinence after prostate treatment recommend surgery for incontinence as early as 6 months post-prostatectomy if the patient's incontinence is not improving.[16,18] These guidelines state that continence stability play an important factor in determining the timing of surgical intervention such that if a patient has severe bothersome symptoms without apparent improvement by 6 months post-prostatectomy, it is unlikely there will be significant improvement over time with conservative management and that it is reasonable to consider incontinence surgery at that stage. However, if minor improvement is seen, even at 12 months, the patient can be advised to consider delaying surgical intervention.

Following surgery for benign prostatic enlargement (BPE), some patients may experience incontinence that is typically transient. As can be seen in Table 2, transient incontinence has been reported after all forms of BPE sugery including TURP, PVP, HoLEP, ThuLEP and open prostatectomy. Up to 50% of PVP patients have been reported to experience transient incontinence postoperatively—typically urge urinary incontinence (UUI). Transient incontinence usually resolves by 6-12 months.[,,] Persistent incontinence post-TURP is often due to underlying sphincteric damage[22] and this will warrant surgical treatment. Given that transient incontinence after BPE surgery is not uncommon and typically resolves by 1 year postoperatively, it is reasonable to counsel men to wait a year before considering surgical therapy for SUI (similar to post-RP incontinence). The degree of urinary incontinence will play an important factor in the decision-making process for surgical intervention. While daily continence-pad requirement provides an objective measurement, various patient factors such as perceived wetness or hygiene practice may affect the number or size of incontinence pads. More recent studies have attempted to improve outcomes assessment with validated questionnaires, such as the domains of Expanded Prostate Cancer Index Composite [EPIC]) or items from the ICI Questionnaire (ICIQ). The person undertaking assessment is a clear-cut bias risk since there is the potential to influence behavior and reporting, or use of less stringent definitions of continence (for example, counting use of a single daily incontinence pad as "continent"). This needs to be discouraged, since patients regard any need for continence pad protection as detrimental to the overall QoL. A significant decrease in QoL is evident when comparing people with no pad requirement, compared with those using a security pad or a single pad. Hence, a strict definition of continence as 0 pads is advocated.

TABLE 2. Studies reporting continence outcomes of various surgeries for benign prostatic enlargement

Paper	Type of Study	N	Mean/ Median Age	Type of Surgery	Follow-up	Continence Status	Continence Assessment
Zhu Z, Shen Z, Tu F, Zhu Y, Sun F, Shao Y, Wang H, Zhong S, Xu C. Thulium laser vaporesection versus transurethral electrovaporization of the prostate in high-risk patients with benign prostatic hyperplasia. Photomed Laser Surg. 2012 Dec;30(12):714-8	Randomized trial	42	70	ThuLVP	12 mo	0 incontinence	Not specified
		56	68	TUVP	12 mo	0 incontinence	
Wei H, Shao Y, Sun F, Sun X, Zhuo J, Zhao F, Han B, Jiang J, Chen H, Xia S. Thulium laser resection versus plasmakinetic resection of prostates larger than 80 ml. World J Urol. 2014 Aug;32(4):1077-85.	Randomized trial	45	70	ThuLRP	18 mo	9% temporary incontinence, 0% long-term incontinence	Not specified
		45	69	PKRP	18 mo	13% temporary incontinence 2% long-term SUI	
Feng L, Zhang D, Tian Y, Song J. Thulium Laser Enucleation Versus Plasmakinetic Enucleation of the Prostate: A Randomized Trial of a Single Center. J Endourol. 2016 Jun;30(6):665-70	Randomized trial	61	68	ThuLEP	12 mo	4.9% transient incontinence	Not specified
		66	70	PKEP	12 mo	4.5% transient incontinence	
Zhihui Zou, Abai Xu, Shaobo Zheng, Binshen Chen, Yawen Xu, Hulin Li, Chongyang Duan, Junhong Zheng, Jiasheng Chen, Chaoming Li, et al. Dual-centre randomized-controlled trial comparing transurethral endoscopic enucleation of the prostate using diode laser vs. bipolar plasmakinetic for the treatment of LUTS secondary of benign prostate obstruction: 1-year follow-up results. World J of Urol (2018) 36:1117–1126	Randomized trial	57	67	DiLEP	12 mo	8.8% transient incontinence	Not specified
		54	69	PKEP	12 mo	8.8% transient incontinence	
Elmansy H, Baazeem A, Kotb A, Badawy H, Riad E, Emran A, Elhilali M. Holmium laser enucleation versus photoselective vaporization for prostatic adenoma greater than 60 ml: preliminary results of a prospective, randomized clinical trial. J Urol. 2012 Jul;188(1):216-21	Randomized trial	43	72	HoLEP	12 mo	25.6% transient SUI 18.6% transient UUI	Not specified
		37	73	PVP	12 mo	13.5% transient SUI 16.2% transient UUI	
Elshal AM, Elkoushy MA, El-Nahas AR, Shoma AM, Nabeeh A, Carrier S, Elhilali MM. GreenLight™ laser (XPS) photoselective vapo-enucleation versus holmium laser enucleation of the prostate for the treatment of symptomatic benign prostatic hyperplasia: a randomized controlled study. J Urol. 2015 Mar;193(3):927-34	Randomized trial	50	71	HoLEP	12 mo	14% transient SUI 10% transient UUI	Not specified
		53	74	PVP	12 mo	5.6% transient SUI 11.3% transient UUI	
Chen YB, Chen Q, Wang Z, Peng YB, Ma LM, Zheng DC, Cai ZK, Li WJ, Ma LH. A prospective, randomized clinical trial comparing plasmakinetic resection of the prostate with holmium laser enucleation of the prostate based on a 2-year followup. J Urol. 2013 Jan;189(1):217-22	Randomized trial	140	74	PKRP	12 mo	2.9% transient incontinence	Not specified
		140	72	HoLEP	12 mo	9.3% transient incontinence	

Paper	Type of Study	N	Mean/ Median Age	Type of Surgery	Follow-up	Continence Status	Continence Assessment
Sun F, Han B, Cui D, Zhao F, Sun X, Zhuo J, Jing Y, Liu H, Xia S, Yang Y, Luo G, Guo F. Long-term results of thulium laser resection of the prostate: a prospective study at multiple centers. World J Urol. 2015 Apr;33(4):503-8	Prospective cohort, multicenter	2216	69	ThuLRP	Up to 8 yrs	8.5% transient incontinence 0.1% persistent SUI	Not specified
Ugwumba FO, Ozoemena OF, Okoh AD, Echetabu KN, Mbadiwe OM. Transvesical prostatectomy in the management of benign prostatic hyperplasia in a developing country. Niger J Clin Pract. 2014 Nov-Dec;17(6):797-801	Retrospective cohort	297	65	Open (suprapubic)	8 mo (mean)	11.1% transient incontinence	Not specified
Karadag MA, Cecen K, Demir A, Kocaaslan R, Altunrende F. Plasmakinetic vaporization versus plasmakinetic resection to treat benign prostatic hyperplasia: A prospective randomized trial with 1 year follow-up. Can Urol Assoc J. 2014 Sep;8(9-10):E595-9.	Randomized trial	96	67	PKRP	12 mo	3.1% transient incontinence	Not specified
		87	68	PKVP	12 mo	1.1% transient incontinence	
Kim JW, Kim YJ, Lee YH, Kwon JB, Cho SR, Kim JS. An Analytical Comparison of Short-term Effectiveness and Safety Between Thulium:YAG Laser Vaporesection of the Prostate and Bipolar Transurethral Resection of the Prostate in Patients With Benign Prostatic Hyperplasia. Korean J Urol. 2014 Jan;55(1):41-6	Retrospective cohorts	43	71	ThuLRP	12 mo	20.9% transient incontinence	Not specified
		43	71	bTURP	12 mo	4.7% transient incontinence	
Ahmed Gadam I, Nuhu A, Aliyu S. Ten-year experience with open prostatectomy in maiduguri. ISRN Urol. 2012;2012:406872	Retrospective cohort	253	69	Open (all kinds)	Up to 10 yrs	6.7% transient incontinence	Not specified
Xing N, Guo Y, Yang F, Tian L, Zhang J, Yan Y, Kang N, Xin Z, Niu Y. Laparoscopic simple prostatectomy with prostatic urethra preservation for benign prostatic hyperplasia. Transl Androl Urol. 2012 Mar;1(1):9-13	Retrospective cohort	51	71	IapSP	NS	0 incontinence	Not specified
Ahmed Gadam I, Nuhu A, Aliyu S. Ten-year experience with open prostatectomy in maiduguri. ISRN Urol. 2012;2012:406872	Retrospective cohort	253	69	Open (all kinds)	Up to 10 yrs	6.7% transient incontinence	Not specified
Xing N, Guo Y, Yang F, Tian L, Zhang J, Yan Y, Kang N, Xin Z, Niu Y. Laparoscopic simple prostatectomy with prostatic urethra preservation for benign prostatic hyperplasia. Transl Androl Urol. 2012 Mar;1(1):9-13	Retrospective cohort	51	71	IapSP	NS	0 incontinence	Not specified
Pereira-Correia JA, de Moraes Sousa KD, Santos JB, de Morais Perpétuo D, Lopes-da-Silva LF, Krambeck RL, Muller VJ, Vaz FP. GreenLight HPS™ 120-W laser vaporization vs transurethral resection of the prostate (<60 mL): a 2-year randomized double-blind prospective urodynamic investigation. BJU Int. 2012 Oct;110(8):1184-9	Randomized, double blind	10	66	PVP	24 mo	50% transient incontinence	ICIQ-SF
		10	64	TURP	24 mo	0 incontinence	

Paper	Type of Study	N	Mean/ Median Age	Type of Surgery	Follow-up	Continence Status	Continence Assessment
Morozov A, Taratkin MS, Kozlov V, Tarasov A, Bezrukov E, Enikeev M, Afyouni AS, Okhunov Z, Glybochko PV, Enikeev D. Retrospective Assessment of Endoscopic Enucleation of Prostate Complications: A Single-Center Experience of More Than 1400 Patients. J Endourol. 2019 Dec 6. doi: 10.1089/end.2019.0630. [Epub ahead of print]	Retrospective cohort	509	67	HoLEP	6 mo	1.7% with SUI	Not specified
		812	67	ThuLEP	6 mo	1.1% with SUI	
		92	68	TUEP (monopolar)	6 mo	3.1% with SUI	
Kim KS, Lee SH, Cho HJ, Suh HJ, Lee DH, Choi YS. Comparison of Bipolar Plasma Vaporization versus Standard Holmium Laser Enucleation of the Prostate: Surgical Procedures and Clinical Outcomes for Small Prostate Volumes. J Clin Med. 2019 Jul 10;8(7).	Retrospective cohorts	32	70	HoLEP	6 mo	17% transient incontinence 1.4% incontinence at 6 mo	Not specified
		31	70	BPVP (button gyrus)	6 mo	1.4% transient incontinence 0 incontinence at 6 mo	
Enikeev D, Okhunov Z, Rapoport L, Taratkin M, Enikeev M, Snurnitsyna O, Capretz T, Inoyatov J, Glybochko P. Novel Thulium Fiber Laser for Enucleation of Prostate: A Retrospective Comparison with Open Simple Prostatectomy. J Endourol. 2019 Jan;33(1):16-21	Retrospective cohorts	40	67	Open (retropubic)	6 mo	5% transient SUI 12.5% transient UUI	Pad test
		60	67	ThuLEP	6 mo	6.7% transient incontinence 4.4% transient UUI	
Peng M, Yi L, Wang Y. Photoselective Vaporization of the Prostate vs Plasmakinetic Resection of the Prostate: A Randomized Prospective Trial With 12-Month Follow-up in Mainland China. Urology. 2016 Jan;87:161-5.	Randomized trial	61	69	PVP	12 mo	0 incontinence	Not specified
		59	69	PKRP	12 mo	0 incontinence	
Chen S, Zhu L, Cai J, Zheng Z, Ge R, Wu M, Deng Z, Zhou H, Yang S, Wu W, Liao L, Tan J. Plasmakinetic enucleation of the prostate compared with open prostatectomy for prostates larger than 100 grams: a randomized noninferiority controlled trial with long-term results at 6 years. Eur Urol. 2014 Aug;66(2):284-91	Randomized trial	80	65	PKEP	Up to 6 yrs	8.8% transient incontinence	Not specified
		80	64	Open (suprapubic)	Up to 6 yrs	13.8% transient incontinence	
Ou R, You M, Tang P, Chen H, Deng X, Xie K. A randomized trial of transvesical prostatectomy versus transurethral resection of the prostate for prostate greater than 80 mL. Urology. 2010 Oct;76(4):958-61	Randomized trial	34	71	Open (suprapubic)	12 mo	2.9% transient SUI	Not specified
		35	71	TURP	12 mo	2.9% transient SUI	
Al-Aown A, Liatsikos E, Panagopoulos V, et al. Laparoscopic simple prostatectomy: A reasonable option for large prostatic adenomas. Urol Ann. 2015;7(3):297–302	Retrospective cohort	11	63	Lap suprapubic	3 mo	0 incontinence	Not specified
Xie JB, Tan YA, Wang FL, Xuan Q, Sun YW, Xiao J, Zhu YP, Zhou LY. Extraperitoneal laparoscopic adenomectomy (Madigan) versus bipolar transurethral resection of the prostate for benign prostatic hyperplasia greater than 80 ml: complications and functional outcomes after 3-year follow-up. J Endourol. 2014 Mar;28(3):353-9	Randomized trial	36	72	Lap retropubic	36 mo	2.8% transient incontinence	Not specified
		54	72	bTURP	36 mo	9.3% transient incontinence	

Paper	Type of Study	N	Mean/ Median Age	Type of Surgery	Follow-up	Continence Status	Continence Assessment
Sorokin I, Sundaram V, Singla N, Walker J, Margulis V, Roehrborn C, Gahan JC. Robot-Assisted Versus Open Simple Prostatectomy for Benign Prostatic Hyperplasia in Large Glands: A Propensity Score-Matched Comparison of Perioperative and Short-Term Outcomes. J Endourol. 2017 Nov;31(11):1164-9	Retrospective, propensity score-matched	59	69	RASP	6 mo	1.7% incontinence	Not specified
		59	68	Open (suprapubic)	13 mo	1.7% incontinence	
Bachmann A, Tubaro A, Barber N et al: A European multicenter randomized noninferiority trial comparing 180 W GreenLight XPS laser vaporization and transurethral resection of the prostate for the treatment of benign prostatic obstruction: 12-month results of the GOLIATH study. J Urol 2015; 193: 570.	Randomized trial	130		PVP	12 mo	2.9% incontinence (any leakage)	ICIQ-SF, OABSS
		126		TURP	12 mo	3% incontinence (any leakage)	
Pereira-Correia JA, de Moraes Sousa KD, Santos JB, de Morais Perpétuo D, Lopes-da-Silva LF, Krambeck RL, Muller VJ, Vaz FP. GreenLight HPS™ 120-W laser vaporization vs transurethral resection of the prostate (<60 mL): a 2-year randomized double-blind prospective urodynamic investigation. BJU Int. 2012 Oct;110(8):1184-9	Randomized, double blind	10	66	PVP	2 yr	50% transient UUI Resolved within 12 mo	ICIQ-SF
		10	64	TURP	2 yr	0 incontinence	
Enikeev D, Rapoport L, Gazimiev M, Allenov S, Inoyatov J, Taratkin M, Laukhtina E, Sung JM, Okhunov Z, Glybochko P. Monopolar enucleation versus transurethral resection of the prostate for small- and medium-sized (< 80 cc) benign prostate hyperplasia: a prospective analysis. World J Urol. 2020 Jan;38(1):167-173	Prospective cohorts	70	67	MEP	12 mo	10% transient SUI Persistent in 1.4%	Not specified
		64	68	TURP	12 mo	7.7% transient SUI Persistent in 3.1%	

2. EVALUATION PRIOR TO SURGICAL THERAPY

2.1. Diagnostic Objectives

- To determine presence, type and severity of incontinence.
- To exclude risk factors for complications.
- To help with treatment selection.
- To establish prognostic factors for outcome.
- Evaluation for presence of symptoms that make it necessary to carry out the diagnostic study early to rule out other complications (urethral stricture, bladder neck contracture, etc.).

2.2. Diagnostic Methods

As with any medical condition, a history is obtained to identify the presence and type of incontinence, the inciting factors, the magnitude and degree of bother. Other lower urinary tract symptoms that may suggest the presence of other issues should also be elicited (see side note). One wants to clarify the underlying causative factor that led to the incontinence (prior surgery and/or XRT, trauma etc.) and also identify any prior treatments for the incontinence (e.g., conservative, medical, surgical therapy) as well as previous lower urinary tract surgery that could impact surgical approach and outcome (e.g., prior urethral surgery such as urethroplasty). Both desire for and acceptance of treatment need to be evaluated, considering patient goals and expectations of treatment and support systems (including caregivers).

The presence of any medical comorbidities should also be determined as these can impact the patient's suitability for additional surgery as well as the outcomes of surgery. Cardiopulmonary risk factors may preclude the patient from receiving anesthesia for surgery while the presence of poorly controlled diabetes may increase the risk for infection with a surgical implant. Along with the general importance of medication review, mechanistically certain drugs may alter sphincter function, notably the antidepressant duloxetine. Hormone therapy of prostate cancer may be relevant, since low serum testosterone level predisposes to artificial urinary sphincter cuff erosion.

2.2.1. Past Medical History

2.2.1.1. Symptoms

The terminology relating to symptoms, signs, urodynamic observations and therapy has been standardized by the International Continence Society.[1]

2.2.1.2. Previous Conservative, Medical and Surgical Treatment

Previous artificial sphincter surgery does not preclude successful outcome for redo surgery. Outcomes for secondary AUS reimplantation are comparable to those of primary AUS implantation and salvage of a good outcome is always probable, even following multiple prior revisions and cuff erosion. The data regarding prior sling surgery generally favors AUS over sling revision, with the exception of late sling failure with a persistently positive repositioning test or in cases where the sling is poorly located postoperatively based on our quantitative analysis of magnetic resonance imaging (MRI) parameters. The impact of prior urethral sling on artificial urinary sphincter outcomes has been reported. AUS placement after failed sling has a high success rate (80–90%) without an increase in the expected complication rate.[39] Patients who require an artificial urinary sphincter after an initial male sling seem to fare as well as those who undergo primary artificial urinary sphincter implantation. However, according Ziegelmann et al,[40] there could be a trend towards worse three-year device outcomes in patients with prior urethral sling, and suggested the need for longer-term studies to determine if slings pose an increased hazard for subsequent sphincter implant surgery.

2.2.1.3. Co-Morbidity

2.2.1.3.1. Cardiovascular Risk Factors

Risk factors such as hypertension, diabetes mellitus, coronary artery disease and smoking need to be evaluated. These represent a concern, given that retropubic radical prostatectomy decreases membranous urethral microcirculation; hence, additional surgical interventions with implants may entail more risk.

2.2.1.3.2. Presence and Severity of Symptoms Suggesting Neurological Disease

This may influence choice of intervention, since male slings may require some residual sphincter functionality.[1] All individuals need to be able to understand proposed management plans and to discuss, where appropriate, alternative treatment options. Use of the artificial sphincter requires adequate cognitive and dexterity function, so formal testing should be considered for individuals where there are concerns regarding memory or attention deficits, and depression screening.

2.2.2. Validated Questionnaires

The use of validated symptom questionnaires allows for a standardized method of grading symptoms to determine severity and degree of bother, as well as track changes/progress over time. This is useful in research studies but also in clinical practice. Questionnaires can be incontinence specific such as the ICIQ-SF that assesses the prevalence, frequency, and perceived triggers of urinary incontinence, and its impact on everyday life, or part of a larger questionnaire assessing symptoms from several systems after prostate cancer treatment such as the EPIC questionnaire. While good correlation between questionnaires and pad usage have be reported, combining symptom scores with pad testing (see below) may be best.

2.2.3. Physical Examination

As with any urologic patient, a focused physical exam is performed. Abdominal exam rarely identifies any significant unexpected findings but the presence of a palpable bladder should alert one to possible outlet obstruction and overflow incontinence. Scarring from previous surgeries should be noted, especially in the inguinal regions where one might place an AUS reservoir. Genital exam should identify any skin pathology that might complicate genital surgery (e.g., lichen sclerosis) as well possible increased risk for infection (e.g., hidradenitis). A hydrocele is typically easily identified and may influence site choice of an AUS pump.

A focused neurological exam is performed to rule out cognitive and/or functional deficits that may impact surgery selection. Dexterity is required to manipulate an AUS pump; a tremor or disfiguring arthritis may preclude this.

2.2.4. Cough Stress Test

A cough stress test (CST), typically done in the standing position is a good way to demonstrate SUI, but in addition, grade its severity.[1] The standing CST was shown to correlate highly with 24-hour pad weights and have predictive value with respect to the outcomes of transobturator slings.[53] A negative CST in the clinic should prompt a repeat CST either at the time of cystoscopy or urodynamic study (UDS).

2.2.5. Bladder Diary

The term frequency-volume chart is used to describe a chart that records the time of each micturition and the volume voided for at least 24 hours. The bladder diary may include fluid intake, incontinence episodes, pad usage, the degree of incontinence as well as a record of episodes of urgency and sensation and activities performed during or immediately preceding the involuntary loss of urine. Therefore, bladder diaries are most suited for the purpose of comprehensive evaluation of urinary incontinence.[35] A frequency-volume chart (FVC) or bladder diary (BD), if properly completed, can confirm all of the following information: daytime urinary frequency, nocturnal frequency/nocturia, urine production, maximum voided volume:, average voided volume, median functional bladder capacity, and the measurement of voided volumes allows for the identification of polyuria contributing to the symptoms.

Recommendations for diary duration vary considerably including 24 hours, 3 days or 7 days; this inconsistency is partially explained by differences among study populations, based on diagnosis, age, sex, and geography, and by differences in methods of analysis and in interpretation of the results. Excessive duration could reduce patient compliance, but too short a duration may produce unreliable measurements.

2.2.6. Pad Testing

An assessment of the magnitude of incontinence is important in determining how aggressive one should be in managing the incontinence and may impact choice of incontinence surgery. While an AUS is suitable for all degrees of incontinence, other therapies such as slings, appear to have greater success when the incontinence is less severe.[,,,]

Incontinence magnitude has been assessed via pad usage and pad weight testing. Pad usage is typically based on the patient's reporting of how many pads they use and will depend on actual incontinence severity as well as type/size of pads and the patient's tolerance for pad wetness (some patients will change a pad upon the slightest amount of urine leakage whereas others may allow their pads to be soaked before changing them).

On the other hand, pad weight testing eliminates these confounding issues and directly measures the amount of urine leakage and is thus considered a more objective measure of incontinence severity and the 24-hour pad weight test is considered the gold standard for measuring incontinence.

Pad usage has been shown to correlate poorly with 24-hour pad weights.[,] However, in the SUFU pad test study, using a more detailed standardized questionnaire, men were able to accurately describe the number, size and degree of wetness of their pads and these parameters correlated well with urine loss as measured by 24-hour pad testing.[62] Furthermore, a single QoL question that asked the extent to which urine loss affects quality of life was able to stratify men into distinct categories based on pad weights. However, there are no publications using the SUFU pad test questionnaire to help guide surgery selection in post-prostatectomy incontinence.

On the other hand, 24-hour pad weight testing may be a predictor of outcomes after male slings. Significantly lower efficacy with transobturator slings has been reported in several studies based on the preoperative 24-hour pad weight testing with the cut off typically around 400 g of leakage,[58,60] and possibly as low as 200 g.

2.2.7. Assessment of Voiding and Emptying

A history of voiding difficulty should alert the surgeon to possible bladder outlet obstruction (possible urethral stricture or bladder neck contracture) and/or a weak detrusor. An assessment of bladder emptying (post void residual) is warranted in most patients in this regard.[16] As well, an unintubated (free) uroflow may confirm if the flow rate is truly abnormal. Cystoscopy would then be warranted to assess for anatomic obstruction. While UDS provides the most definitive testing for outlet obstruction (pressure flow test), some have argued that a normal uroflow and low post-voiding residual (PVR) imply adequate bladder contractility and the absence of outlet obstruction and may suffice for the majority of patients.

In general, abdominal imaging is unnecessary in the evaluation of male incontinence with the exception of the aforementioned PVR that is usually accomplished via an ultrasound bladder scanner. In patients with incontinence following prior incontinence surgery (e.g., AUS, periurethral balloons [ProACT]), imaging may be warranted to assess for the presence of fluid in the system and can be accomplished by plain x-ray (if contrast was used), ultrasound (US) or computerized tomography (CT) scan.[,]

Imaging techniques include plain film of the abdomen (KUB or Kidneys, Ureters, Bladder), in cases of in-continence following artificial sphincter implantation when during the original procedure the hydraulic sys-tem was filled with contrast medium. A KUB immediately following sphincter implantation serves as a reference point for subsequent comparisons.

2.2.8. Urine Testing

As with any patient with lower urinary tract symptoms (LUTS), a urinalysis (with culture as indicated) is mandatory to rule out infection as well as the presence of microscopic hematuria.

2.2.9. Endoscopy

Cystoscopy is indicated in the presence of gross or microscopic hematuria to rule out urethral, bladder, or prostatic pathology as the cause. However, even in the absence of hematuria, both the AUS Consensus Conference of 2015 (Grade of recommendation D) and the recent AUA/SUFU Guidelines on incontinence after prostate treatment (Clinical principle) recommended cystoscopy prior to surgery for incontinence.[16,18]

Cystoscopy allows one to rule out the presence of urethral stricture/anastomotic contracture or other forms of obstruction (e.g., prostatic regrowth after TURP, necrotic tissue/stones after radiation, cryo or HIFU), as well as any bladder pathology (tumor, stones) that may require further treatment prior to incontinence surgery. In addition, one can assess the integrity of the external sphincter as this may have ramifications regarding surgical selection: it has been suggested that a patient who is unable to volitionally contract his external sphincter and/or in whom it is not possible to manually reposition the membranous urethra in a cephalad fashion via perineal pressure may not be a good candidate for a transobturator sling.[,] Furthermore, cystoscopy allows for direct filling of the bladder and performance of a CST to visualize SUI (this is important if a negative CST occurs in the clinic, possibly due to inadequate bladder volume). However, to date, no study has directly addressed the need for cystoscopy prior to incontinence surgery.

2.2.10. Urodynamics

As noted in the AUS Consensus Conference 2015 (Grade of Recommendation C)[16] and more recently the AUA/SUFU Guidelines 2019 (Conditional Recommendation, Evidence Level: Grade C),[18]

UDS may be performed to facilitate the diagnosis of incontinence and/or aid in patient counseling.

UDS may be used for the following reasons:

a) Determine the extent of SUI especially in patients with non-classic SUI or mixed symptoms.

In a study of 60 men with post-radical prostatectomy incontinence, intrinsic sphincter deficiency was demonstrated in 54 patients (90%). However, 27 patients (45%) patients were found to have underlying bladder dysfunction and in 16 cases (27%) incontinence was the result of bladder dysfunction only (rather than ISD).

The determination of Valsalva leak point pressure (VLPP) or cough leak point pressure (CLPP) could improve the assessment of underlying sphincteric function/weakness although there is poor correlation between VLPP and incontinence magnitude based on 24-hour pad test. On the other hand, VLPP was reported to have predictive value for transobturator slings: a VLPP of ≤100 cmH_2O had a HR for failure of 4 compared to a VLPP of >100 cmH_2O (95% CI 0.68–23.7).[61] Caution must be taken regarding the significance of a negative VLPP (no leak at all). When VLPP is measured with a urethral catheter in place, the catheter may create some degree of urethral obstruction resulting in a false reading. In fact, 18-35% of patients with SUI may have negative leak point pressure (LPP) testing with a urethral catheter in situ but demonstrate SUI when the catheter is removed.[,] Thus, it is recommended that the clinician repeat LPP testing without a urethral catheter in-situ.[75] Rectal transducer catheter is then used to determine the LPP during cough/Valsalva (termed abdominal LPP [ALPP]). Another method of assessing external sphincter function is the retrograde LPP [RLPP} which evaluates the ability of the sphincter complex to resist the retrograde leakage of fluid into the bladder. Unlike, the VLPP/ALPP, the RLPP was demonstrated to have good correlation with 24-hour pad testing and was able to differentiate between cases of mild/moderate (<400 g) and severe (≥400 g) incontinence. As such, it has the potential to be a substitute for pad weight testing and help with surgical selection. However, to date, no study has demonstrated the predictive value of RLPP with respect to surgical outcomes.

b) Identify detrusor storage dysfunction (detrusor overactivity [DO], bladder capacity, compliance).

One study found that DO was present in up to 3/4 of patients during UDS and decreased bladder compliance could be observed in up to 2/5 of patients after RP. Preoperative DO has been reported as an adverse predictive factor for successful outcomes for male slings.[79,] However, the data between preoperative DO and AUS outcomes is variable.[66,76,77,78,]

Bladder capacity on UDS (cystometric capacity) has also been reported to be a predictor of successful incontinence surgery. A smaller cystometric capacity (<400 mL and especially <250 mL) has been associated with a greater failure rate with transobturator slings (Advance, Virtue),[79,] adjustable transobturator slings (ATOMS) and adjustable balloons (ProACT). However, as with preop DO, preop cystometric capacity may not have an impact on outcomes of AUS.[82,,] Thus the presence DO and low cystometric capacity on UDS, while not necessarily contraindicating a specific type of surgery, may help in counseling patients regarding postoperative expectations.

Continence surgery performed in a poorly compliant bladder can be an issue if this results in higher bladder pressures and if there are significant urinary postvoid residuals.[82] However, some hypothesize that elevated storage pressures noted on UDS in severely incontinent patients may be the result of a chronically underdistended bladder (because of intrinsic sphincter deficiency [ISD]) being subjected to higher fill volumes than it is accustomed to[86] and many studies on AUS and slings have not identified low bladder compliance to be an adverse prognostic factor.[79,81,,] Nevertheless, the AUS Consensus Conference in 2015 acknowledged this concern noting the role for UDS and the need for close follow-up in patients at risk of low bladder compliance, such as those who have had pelvic radiation or suffer from neurogenic lower urinary tract dysfunction (Grade of recommendation C).[16]

In some patients with severe sphincteric incompetence, it is not possible to fill the bladder to a sufficient volume to fully assess its storage pressures as a steady state of filling and leaking may be reached. A Foley catheter balloon can be utilized to occlude the bladder neck to prevent urine leakage and allow for a better assessment of bladder storage pressures. Alternatively, a penile clamp can also be used to achieve the same result.

c) Assess bladder contractility and emptying (including outflow obstruction)

Anatomic urethral obstruction may be present in a significant number of patients after local treatment for prostate cancer (RP, radiation, cryosurgery, HIFU) as well as BPE surgery, and its presence can complicate management of incontinence. In general, this will take the form of urethral stricture that can be located anywhere from the urethral meatus to the bladder neck, but obstruction may also be due to necrotic tissue (radiation, cryosurgery, HIFU) and prostatic enlargement (in non-RP patients). Pressure-flow testing is the gold standard for diagnosing outlet obstruction in these patients. However, at least in the case of post-RP incontinence, it has been suggested that a normal non-invasive uroflow and complete bladder emptying may be indicative of the absence of significant outlet obstruction and obviate the need for more formal pressure-flow testing.[66] Adequate bladder contractility has been suggested to be needed in patients considering urethral slings because of concern that the sling may cause some degree of urethral obstruction, whereas this would be less of a concern in the setting of an AUS where the urethral compression is reduced during micturition. Impaired contractility was identified in about 47% of patients after RP although most recovered.[80] Despite this concern, it was shown that in patients undergoing a sling (especially a transobturator sling) there was no difference in postop Patient Global Impression of Improvement (PGI-I) scores or PVRs between those with normal preop contractility and those with decreased contractility (using BCI); similar findings were noted when comparing Valsalva voiders to non-Valsalva voiders. However, the use of BCI to assess contractility is questionable since the prostate is absent and BCI was defined in BPE patients. The maximum isometric detrusor pressure, determined via a mechanical stop test, has been recommended as a better surrogate for bladder contractility,[92] although there are no reports of using Piso to guide surgical selection.

III. PATHOPHYSIOLOGY AND RISK FACTORS

Urinary continence in the male is maintained by a complex interaction between the central/peripheral nervous system, bladder (detrusor) muscle, internal and external urinary sphincter musculature, pelvic ligaments/fasciae and pelvic floor musculature.

Incontinence in males, similar to that in females, can occur as a result of:

a) deficiency in the urethral sphincter mechanism (sphincteric incontinence)–typically resulting in SUI.
b) urine storage pressure elevations:

   i) DO/OAB – may result in UUI
   ii) low bladder compliance

c) a combination of a) and b) – mixed urinary incontinence (MUI)
d) urinary retention with overflow (i.e., an emptying dysfunction)
e) fistula

In general, damage to the urethral sphincter mechanism occurs because of some form of direct insult (e.g., surgery, trauma, radiation) to the sphincteric musculature or some neurologic insult affecting sphincteric innervation (neurologic disease, nerve trauma from surgery). Bladder storage pressure dysfunction comes in two forms: an DO and a bladder that stores urine at high pressure (LBC). Incontinence associated with DO occurs when the intravesical pressure overcomes the ability of the urinary sphincters to withstand the intravesical pressure. This may or may not result in the sensation of urgency with UUI. With LBC, there is often an activity related component to the incontinence that is akin to SUI, the difference being that with LBC, the intravesical storage pressure is elevated due to rigidity of the bladder wall whereas with genuine SUI, the intravesical storage pressure is actually low. Both forms of dysfunction may be associated with radical treatment of prostate cancer including surgery and XRT. However, they can also be present prior to therapy, often in relation to pre-existing benign prostatic hyperplasia (BPH), neuropathy or even aging itself. Urinary retention can result in incontinence via an overflow mechanism and as such isn't even a urinary storage issue (the bladder is overdistended with resultant "spillover" or overflow incontinence; alleviating the urinary retention resolves the incontinence). A fistula bypasses the urinary storage mechanisms, which may or may not be concomitantly affected. Bladder storage pressure related incontinence (OAB) will specifically be addressed in a separate chapter while rectourethral fistula is addressed later in this chapter. In this section, the focus will be on incontinence as a consequence of treatment (surgical/nonsurgical) of benign/malignant.

Most studies that report on the incidence of incontinence fail to differentiate the type/etiology of incontinence (e.g., sphincteric vs storage pressure related) and simply refer to the presence of incontinence in general. As such, the risk factors/pathophysiology of incontinence will be presented for the specific insult (e.g., prostatectomy for cancer/BPH, radiotherapy and other prostate cancer treatments, cystectomy with orthotopic neobladder, other pelvic surgery/trauma), and when possible, the different types of incontinence will be addressed.

1. MALE URINARY SPHINCTER

The male urethral sphincter has 2 independent components: an internal sphincter (smooth sphincter) composed of smooth muscle (the bladder neck is part of this) that is under autonomic control and an external (rhabdosphincter) sphincter composed of striated muscle that is under voluntary control. The smooth muscle of the internal sphincter, being able to maintain tone for long periods with minimal exertion, maintains continence during normal activity when there is little stress on the bladder outlet (passive continence).[1] As delineated by Strasser et al, the external (rhabdosphincter) sphincter (EUS) is a vertically oriented muscle extending from the bulb of the penis to the bladder neck (BN), separate from the levator ani. It is omega shaped spanning the anterior (between symphysis and urethra) and lateral aspects of the membranous urethra. Both ends of the omega shaped sphincter insert at the perineal body, and posterior to the membranous urethra (between urethra and perineal body), smooth muscle and connective tissue appear to predominate. Contraction of the rhabdosphincter pulls the urethra towards the perineal body thus compressing the membranous urethra against Denonvillier's fascia and rectourethralis muscle to achieve active continence.[95]

The rhabdosphincter is anatomically related to and physiologically assisted by the pelvic floor muscles (levator ani, bulbocavernosus) in the voluntary constriction of the urethra. As will be discussed, they may play an even more important role after prostatectomy.

There are multiple support structures of the membranous urethra and bladder neck (BN) that act to stabilize the position of the BN and EUS complex and anchor the membranous urethra to the pubic symphysis. Anteriorly: the pubourethral ligaments (pubovesical and puboprostatic); posteriorly: perineal body/central tendon, Denonvillier's fascia, rectourethralis muscle, levator ani muscle; and laterally: arcus tendinous/endopelvic fascia. Damage to these structures during radical prostatectomy is thought to be a contributor to post-prostatectomy incontinence and efforts to preserve/reconstruct these structures have resulted in improved continence rates, as will be discussed.[1]

The innervation of the EUS is very complex and still yet to be completely elucidated. There appears to be somatic and autonomic co-innervation: somatic via 1) pudendal nerve which has extrapelvic branch (via Alcock's canal) and in some patients, intrapelvic branches that travel through the levator ani muscle and enter EUS at 5 or 7 o'clock near the apex of the prostate; and 2) somatic branches of S2, 3, 4 that travel with the autonomic fibers of the pelvic plexus to innervate the EUS. Autonomic innervation has been identified via intrapelvic branches of the hypogastric and pelvic plexuses that have been observed at the posterolateral aspect of the prostate apex.[98] In fact, stimulation of the neurovascular bundles during radical prostatectomy has been shown to elicit significant increases in intra-urethral pressure. Communication between somatic and autonomic pathways exist, especially as one follows the fibers more proximally.[98]

2. INCONTINENCE RELATED TO PROSTATE CANCER TREATMENT

2.1. Post-Prostatectomy (Radical) Incontinence (PPI)

RP for prostate cancer involves surgical removal of the prostate and frequently seminal vesicles with anastomosis of the bladder to the membranous urethra. The bladder neck is transected proximally (the majority of the internal sphincter is lost) and the membranous urethra distally. Thus, both the internal and external urinary sphincters are at risk. The neurovascular supply and rhabdosphincter itself are intimately associated with the prostate and thus at risk for damage. The surgical steps associated with greatest risk for incontinence after radical prostatectomy include wide excision at the level of the seminal vesicles, the periprostatic dissection and dissection at the prostate apex where convergence of nerve fibers occurs and nerves are within millimeters of the dissection plane and suture bites.[98] In fact, Egawa et al demonstrated that the urethral sphincter innervation lies 0.3–1.3 cm away from the prostate apex.

These issues will predispose the patient to sphincteric/SUI. Since the majority of patients recover continence within 6–12 months, true direct sphincter damage is unlikely in these patients and it is more likely that trauma to nerves and support structures results in the temporary incontinence. The nerves innervating the sphincters are at risk for injury either directly (transection, cautery) or indirectly (retractor stretching). As reviewed, by Porena et al,[80] ISD represents the primary diagnosis in 55–100% of PPI patients.

Autonomic denervation of the membranous urethra after RP was demonstrated by Catarin et al who prospectively identified alterations in the pelvic and membranous urethral afferent and efferent innervation after nerve sparing RP by using several neurophysiological tests as well as a validated questionnaire. Sensory and motor pudendal innervation was unaffected after surgery, whereas autonomic afferent denervation of the membranous urethral mucosa was found in 77% of patients, including 92% of patients with urinary leakage (especially occasional leakage).

Surgery can also result in a bladder dysfunction that may be related to nerve injury as well (the pelvic plexus sits on the surface of the rectum). Bladder dysfunction as it relates to incontinence may take the form of OAB/DO and/or LBC. In their review of 10 prospective and 9 retrospective studies that included UDS after RP, Porena et al noted the following reported incidences: *de novo* DO in 2%-77% of patients, impaired bladder compliance in 8–39% of patients (*de novo* in about 47%, persistent in 26% after 8 months), and impaired detrusor contractility in 29–61% of patients (*de novo* in 47%, recovered in about 50% of patients). Most patients with DO had other associated UDS dysfunctions such as ISD and impaired contractility. Isolated DO was noted in up to 10% of patients.[1] Postoperative decentralization of the bladder, inflammation and/or infection, and geometric bladder wall alteration associated with preexisting hypoxemia with/without neuroplasticity have been posited as causes of detrusor dysfunction particularly when an isolated finding.[1]

An association between DO and SUI/ISD in PPI patients has been noted by many[75,,,] and might be related to activation of the urethrovesical reflex via C-fiber afferent effect: urine leaking across an incompetent sphincter into the proximal urethra triggers DO.[1,]

However, in many cases, the urodynamic demonstration of DO and low bladder compliance (LBC) when associated with ISD/SUI on post-RP cystometry may be an “artifact” of UDS. Some have suggested that because of ISD/SUI, there’s an inability to adequately store urine on a day to day basis resulting in the bladder dysfunction noted on UDS (DO or LBC): on UDS the bladder is getting filled at supraphysiologic rates to higher than normal volumes, which then triggers the apparent bladder dysfunction.[72,86,] Furthermore, it’s been reported that DO and bladder compliance are not adverse prognosticators and may improve after SUI surgery.[89,107] Whether this improvement is a direct effect of the SUI surgery preventing activation of the urethrovesical reflex or via the SUI surgery allowing for more urine storage/better bladder filling on a day to day basis is unclear.

Studies Reporting Continence Outcomes of Various Surgeries for Prostate Cancer are shown in table 3.

TABLE 3. Studies Reporting Continence Outcomes of Various Surgeries for Prostate Cancer

Paper	Type of Study	N	Mean/ Median Age	Type of Surgery	Continence Definition	Continence Assessment	≥ 12 mo Continence Rate (%)
Haglind E, Carlsson S, Stranne J, Wallerstedt A, Wilderäng U, Thorsteinsdottir T, Lagerkvist M, Damber JE, Bjartell A, Hugosson J, Wiklund P, Steineck G; LAPPRO steering committee. Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. Eur Urol. 2015 Aug;68(2):216-25	Prospective, cohort	1847	63	RARP	Change of <1 pad in 24 hr	Questionnaire	79
		778	63	ORP			80
Gershman B., Psutka S.P., McGovern F.J., Dahl D.M., Tabatabaei S., Gettman M.T., Frank I., (...), Karnes R.J. Patient-reported Functional Outcomes Following Open, Laparoscopic, and Robotic Assisted Radical Prostatectomy Performed by High-volume Surgeons at High-volume Hospitals. European Urology Focus, (2016) 2:172-179	Retrospective, cohort	441	62	ORP	0-1 pads	Questionnaire (EPIC)	95.4
		156	62	LRP			96.8
		1089	62	RARP			95.1
Kim M, Park M, Pak S, Choi SK, Shim M, Song C, Ahn H. Integrity of the Urethral Sphincter Complex, Nerve-sparing, and Long-term Continence Status after Robotic-assisted Radical Prostatectomy. Eur Urol Focus. 2019 Sep;5(5):823-830	Prospective, cohort	529	66	RARP	0 pads + no unwanted leakage	Pad test, Questionnaire (EPIC)	87

Paper	Type of Study	N	Mean/ Median Age	Type of Surgery	Continence Definition	Continence Assessment	≥ 12 mo Continence Rate (%)
Coughlin GD, Yaxley JW, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, Teloken P, Dunglison N, Williams S, Lavin MF, Gardiner RA. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. Lancet Oncol. 2018 Aug;19(8):1051-1060	Randomized clinical trial	135		ORP	0 pads	Questionnaire (EPIC)	91
		146		RARP			90
Haese A, Knipper S, Isbarn H, Heinzer H, Tilki D, Salomon G, Michl U, Steuber T, Budäus L, Maurer T, Tennstedt P, Huland H, Graefen M. A comparative study of robot-assisted and open radical prostatectomy in 10 790 men treated by highly trained surgeons for both procedures. BJU Int. 2019 Jun;123(6):1031-1040. doi: 10.1111/bju.14760. Epub 2019 Apr 12. PMID: 30927303	Prospective, cohort	7007	64	ORP	0-1 pads	Questionnaire	88.8
		3783	63	RARP			90.3
Schmeller N, Keller H, Janetschek G. Head-to-head comparison of retropubic, perineal and laparoscopic radical prostatectomy. Int J Urol. 2007;14(5):402–405	Prospective, cohort	50	63	ORP	0 pads	Questionnaire	89
		50	66	RRP			89.6
		50		LRP			50
Menon M, Dalela D, Jamil M, Diaz M, Tallman C, Abdollah F, Sood A, Lehtola L, Miller D, Jeong W (2018) Functional recovery, oncologic outcomes and postoperative complications after robot-assisted radical prostatectomy: an evidence-based analysis comparing the Retzius sparing and standard approaches. J Urol 199:1210–1217	Randomized clinical trial	60	62	RARP	0 pads or no urinary leakage in 24 hr	Questionnaire	88.1
		60	61	RS-RARP			95.8
"Sayyid RK, Simpson WG, Lu C, Terris MK, Klaassen Z, Madi R (2017) Retzius-sparing robotic-assisted laparoscopic radical prostatectomy: a safe surgical technique with superior continence outcomes. J Endourol 31:1244–1250"	Prospective, cohort	100	62	RARP	0-1 pads	Questionnaire	68.5
		100	61	RS-RARP			97.5
Ota Y, Hamamoto S, Matsuyama N, Hamakawa T, Iwatsuki S, Etani T, Taguchi K, Naiki T, Ando R, Nakane A, Okada A, Kawai N, Kubota Y, Yasui T. Pelvic Anatomical Features After Retzius-Sparing Robot-Assisted Radical Prostatectomy Intended for Early Recovery of Urinary Symptoms. J Endourol. 2020 Nov 5. Epub ahead of print. PMID: 32935558.	Retrospective, cohort	25	69	RARP	0-1 pads	Patient reported pad usage	84
		25	67	RS-RARP			96
Kohjimoto Y, Yamashita S, Kikkawa K, Iba A, Matsumura N, Hara I. The Association of Length of the Resected Membranous Urethra With Urinary Incontinence After Radical Prostatectomy. Urol J. 2020 Mar 16;17(2):146-151. PMID: 30882170.	Retrospective, cohort	98	68	LRP	0-1 pads	Questionnaire (EPIC)	81.6
		81	67	RARP			87.8
Student V Jr, Vidlar A, Grepl M, Hartmann I, Buresova E, Student V. Advanced Reconstruction of Vesicourethral Support (ARVUS) during Robot-assisted Radical Prostatectomy: One-year Functional Outcomes in a Two-group Randomised Controlled Trial. Eur Urol. 2017 May;71(5):822-830	Randomized, clinical trial	31	63	PR-RARP	0 pads	Questionnaire (ICIQ-SF)	61.3
		30	65	AR-VUS-RARP			86.7

Paper	Type of Study	N	Mean/ Median Age	Type of Surgery	Continence Definition	Continence Assessment	≥ 12 mo Continence Rate (%)
Ludovico GM, Dachille G, Pagliarulo G, D'Elia C, Mondaini N, Gacci M, et al. Bilateral nerve sparing robotic-assisted radical prostatectomy is associated with faster continence recovery but not with erectile function recovery compared with retropubic open prostatectomy: the need for accurate selection of patients. Oncol Rep 2013;29:2445-50.	Prospective, cohort	48	67	ORP	0-1 pads	Questionnaire	98
		82	68	RARP			95
Geraerts I, Van Poppel H, Devoogdt N, Van Cleynenbreugel B, Joniau S, Van Kampen M. Prospective evaluation of urinary incontinence, voiding symptoms and quality of life after open and robot-assisted radical prostatectomy. BJU Int. 2013 Nov;112(7):936-43. doi: 10.1111/bju.12258. Epub 2013 Aug 13. PMID: 23937206.	Prospective, cohort	109	62	ORP	0 g leakage for 3 consecutive days	24 hr pad test	96
		61	61	RARP			97
Cho DS, Choo SH, Kim SJ, Shim KH, Park SG, Kim SI. Postoperative membranous urethral length is the single most important surgical factor predicting recovery of postoperative urinary continence. Urol Oncol. 2020 Dec;38(12):930.e7-930.e12.	Retrospective, cohort	121	68	ORP	0 pads	Patient reported pad usage	87
		75	63	RARP			95
Martis G, Diana M, Ombres M, Cardi A, Mastrangeli R, Mastrangeli B. Retropubic versus perineal radical prostatectomy in early prostate cancer: eight-year experience. J Surg Oncol. 2007 May 1;95(6):513-	Randomized clinical trial	100	65	ORP	0 pad use + absence of leakage	Patient report pad use + 1 hour pad test	95 at 24 mo
		100	64	PP			96 at 24 mo

2.1.1. UDS Findings After RP

Urodynamic evaluation of patients, pre and post-RP, has yielded varying results regarding the types of storage dysfunctions that are present in the PPI patient. Giannantoni et al performed UDS before RRP and longitudinally postoperatively in 54 patients in whom 37 had 3-year follow-up and reported bladder and sphincter function changes in a significant number of patients after RRP including: ISD/SUI in 74% at 8 months with persistence at 36 months in 59%, DO in 70% at 8 months (although preoperatively present in 61%) and 56% at 36 months, and *de novo* decreased compliance in 32% of patients at 8 months with persistence at 36 months in 28%. Song et al, in a prospective study, similarly did UDS before RRP and serially postop up to 36 months and found reductions in maximum cystometric capacity (MCC), maximum detrusor pressure ($Pdet_{max}$) and maximum urethral closure pressure (MUCP) at 3 months, all of which remained relatively unchanged over time. At 3 years, the mean MCC changed from 393.0mL before RP to 322mL (P<0.001), the MUCP from 64 to 53cmH_2O (P=0.001), and $Pdet_{max}$ from 54 to 45cmH_2O (P=0.001). DO was present in 38% of patients before RP and it persisted in 74% of them at 3 years. However, only 24% of patients with DO at 3 years felt the symptoms were severe enough to warrant medication. Incontinence was noted in 46% and 18% of patients at 3 and 6 months after RP respectively, but all were continent by 3 years. Kadono et al did UDS before RARP (with or without nerve sparing [NS]), 3-4 days after catheter removal, and approximately 1 year postop in 84 patients. MUCP was noted to decrease immediately after catheter removal but at approximately 1 year postop, recovered to approximately 70–90% of preop values depending on nerve sparing: there was less of an early decline and a greater degree of improvement by 1 year with greater degree of NS. ALPP, cystometric capacity and bladder compliance also had a trend of early deterioration and late improvement to almost preop levels but there were no significant differences between degrees of nerve sparing. Ventimiglia et al used UDS and neurophysiologic testing (pudendal nerve somatosensory evoked potentials [SEP], perineal EMG) in 51 patients with incontinence at 8–24 months after RP. They found DO in 63% (isolated DO in 35%, DO + SUI in 28%), and SUI in 65% (isolated in 37%). Patients with isolated DO had intact perineal muscle and pudendal nerve function. The remaining patients had varying degrees of injury/dysfunction of the perineal musculature/pudendal nerve with associated SUI. The most severe group had sphincteric incontinence with very poor perineal muscle function and SEPs suggestive of more severe nerve injury (neurotmesis) and these patients were also noted to have decreased bladder compliance. They believe that the high rate of DO in PPI patients is due either to a high rate of pre-existing DO that was missed or due to a neuropathic mechanism related to trauma to the pelvic plexus during the surgery (i.e., bladder denervation). A more recent report by the same group had similar findings. Recently, MacKenzie et al evaluated 64 men with post-robotic assisted laparoscopic prostatectomy lower urinary tract symptoms

(RALP LUTS)/incontinence using the ICIQ on Male Lower Urinary Tract Symptoms Long Form (ICIQ-MLUTS) and UDS. There was a significant increase in total ICIQ-MLUTS and bother scores at 6, 12 and 18 months postop and postop UDS showed 81% had urodynamic stress incontinence (isolated SUI in 64%), 17% had SUI and DO, and 3% had isolated DO. Low bladder compliance (≤12.5 mL/cmH_2O) was present in 5%, outlet obstruction in 11%, detrusor underactivity (using the bladder contractility index) in 46%, while 16% had no urodynamic abnormalities identified.

Thus, while sphincter incontinence is the main storage dysfunction after RP (and the main indication for surgical management of incontinence in men), bladder dysfunction also occurs in a significant number of patients. Regardless of urodynamic findings after radical prostatectomy, i.e., phasic DO, incontinence following this surgery is overwhelmingly due to sphincteric insufficiency.

2.2. Risk Factors for PPI

Studies have shown that the incidence of incontinence after prostatectomy for cancer varies considerably depending on clinical and surgical factors as well as methods of assessment (including who is reporting, surgeon or patient) and the definition of urinary incontinence. Surgical approach/technique, surgeon experience as well as patient factors including age, obesity, anatomic issues (membranous urethral length, prior benign prostate surgery, prior XRT) have all been implicated as risk factors for PPI (see below). Incontinence has been defined via questionnaire responses regarding the presence or absence of incontinence and/or use of pads we well as formal pad testing. While it has been noted that a 0 pad per day definition of continence is more reliably associated with patient perception of continence, many studies reporting on incontinence after prostatectomy consider up to 1 pad per day, typically referred to as a safety pad to deal with minimal dribbling incontinence, as “social continence” and use this as their outcome measure. The use of patient reported outcomes via questionnaire is widely considered superior and more reliable compared to surgeon reported outcomes, and often yields significantly higher rates of reported PPI.

Various factors have been associated with the recovery/lack of recovery of urinary continence after RP. Broadly divided, there are surgical and patient factors:

2.2.1. Surgical Factors

2.2.1.1. Surgical Approach/Surgeon Experience

The literature regarding which approach to RP has the best continence outcomes is inconclusive. While several meta-analyses over the past 10 years have concluded that RARP is associated with better continence rates than open RP (RRP, radical perineal prostatectomy [RPP]) and standard laparoscopic approaches,[20,,] others have not shown a significant difference.[,,] In their often cited systematic review and meta-analysis, Ficarra et al analyzed 5 studies comparing RRP to RARP and noted better 12-month urinary continence recovery after RARP in comparison with RRP: the absolute risk of incontinence was 11.3% post RRP and 7.5% post RALP (a 3.8% absolute risk reduction) (OR: 1.53; *P*=0.03). Similarly, in 5 studies comparing RARP to LRP: the absolute risk of incontinence at 12 months after LRP was 9.6% vs 5% after RARP (a 4.6% absolute risk reduction) (OR: 2.39; *P*=0.006).[117]

A Cochrane Review was only able to analyze 2 randomized trials comparing RARP/LRP to open RRP using EPIC questionnaires, and assessed the quality of the evidence according to GRADE.[119] They concluded that urinary and sexual QoL-related outcomes appear similar between the various surgical approaches and the quality of the evidence was moderate.

In the LAPPRO trial, a multicenter, prospective trial (not randomized) comparing open RRP to RARP, Haglind et al,[114] using questionnaires to assess continence (<1 pad change/24 hour) reported no significant difference in 12 month postop incontinence (21.3% after RARP vs 20.2% after RRP). This lack of a statistically significant difference was maintained at 24 month follow-up (19% after RARP vs 16% after RRP; AOR 1.29, 95% CI 1.00–1.67; *P*=0.053). Coughlin et al[27] conducted a randomized study of open RRP vs RARP and found that urinary function scores (EPIC) did not differ significantly between the groups at 6 months, 12 months or 24 months postop.

Haese et al prospectively compared 10790 consecutive treated patients undergoing either RARP or RRP and found slightly better continence rates (0–1 pads) at 12 months after RARP compared to RRP (90.3% vs. 88.8%; *P*=0.01), but when stratified by age there were no significant differences.

Other recent studies have similarly found no significant difference between open RRP, laparoscopic radical prostatectomy (LRP) or RARP with respect to urinary function/bother (using EPIC questionnaires).[17,] As well, when RPP was compared to RRP by Martis et al, no differences in continence (1 hour pad test) were noted at 6 (74% vs 76%) or 24 months (96% vs 95%) postop between groups, while Jafri et al reported that RARP had greater overall urinary recovery (using EPIC questionnaire) compared to RPP at 6 months but there was no difference at or beyond 12 months.

Thus, whether or not the surgical approach matters with respect to postoperative continence is still unresolved. However, there is little question that the skills of the surgeon performing the surgery will impact the functional outcomes of RP. While not specific to the issue of postoperative incontinence, Vickers et al determined that for open RRP the learning curve for prostate cancer recurrence is steep and does not start to plateau until approximately 250 cases, presumably related to improved technique with more experience. For LRP, the learning curve is longer: the 5-year risk of cancer recurrence decreased from 17% to 16% to 9% for a patient treated by a surgeon with 10, 250, and 750 prior LRPs, respectively (risk difference between 10 and 750 procedures 8.0%, 95% CI 4.4-12.0). A study on RARP noted that postop urinary continence rates improved amongst several surgeons from ~60% early in the RARP learning curve to almost 90% after more than 400 procedures. In a single institution review, Hashimoto et al reported a learning curve of 100 cases with respect to 12 month post-RARP continence. On the other hand, others have found that with intensive structured modular training, fewer than 100 live cases are needed to optimize urinary continence after RARP. Recently, Nyberg et al confirmed the issue of surgeon experience in their analysis of the data from the LAPPRO trial. They found significant heterogeneity in incontinence (as well as ED and oncologic) outcomes among surgeons with differences in surgeon volume explaining 42% of the observed heterogeneity for incontinence (*P*=0.003).

2.2.1.2. Preservation/Reconstruction of Functional and Anatomical Support Structures

2.2.1.2.1. Nerve sparing

Many studies reporting on the incidence of PPI have found an association between nerve sparing and postop urinary continence.[110,,,]

This association between NS and postop continence may be relevant only with respect to early (first 6 months postop) continence. In a systematic review and meta-analysis of data from 13,749 participants in 27 studies, Reeves at al noted that NS (especially bilateral) appears to improve early postop continence rates up to 6 months but beyond that there is no difference compared to nonNS. The authors hypothesized that preservation of intrapelvic somatic nerves to the sphincter may help hasten recovery of continence. They also suggest that compensation by other continence mechanisms (e.g., pelvic floor muscles) may explain the lack of longer-term difference in incontinence between NS and nonNS. However, more recent studies have shown that NS may in fact be beneficial at 12 months postop. Kadono et al[110] evaluated predictive factors for postop continence in 111 patients who underwent RARP using UDS, MRI and 24-hour pad testing. On univariate and multivariate analyses, NS was the only variable that was predictive of postop continence (24-hour pad test <2 g). In 84 patients who underwent serial UDS postop, similar fluctuations in postop MUCP were noted between NS and non-NS patients (early decrease in MUCP with later partial recovery) but a higher degree of NS was associated with a lesser decrease in MUCP postop (3-4 days after catheter removal) and a higher MUCP at approximately 1 year. Kim et al, in a prospective study on 529 RARP patients, noted significantly greater return of continence at 12 months (pad free and no unwanted leakage) with bilateral NS (93%) compared to unilateral NS (78%) or non-NS (77%). Bilateral NS was independently associated with continence return 12 months postop (OR=3.671).[136] And in the CEASAR study, a prospective, population based, observational study of men diagnosed with localized prostate cancer in 2011 to 2012 comparing surgery to radiation, on multivariable analysis younger age, nonblack racial group and BilatNS (BNS) were associated with better urinary incontinence scores (EPIC) 3 years after surgery. However, this benefit of BNS on the urinary incontinence score was only significant in men with high baseline sexual function. On the other hand, Park et al,[134] in a retrospective review of 360 patients with preop erectile dysfunction undergoing NS or non-NS LRP or RARP, still found significantly higher urinary continence (0 pad usage) recovery rates at 3, 6, and 12 months in NS patients with the 12 month continence rates being 78% in the nnsRP group and 85% in the nsRP group, respectively (*P*=0.02). On multivariate analysis, age (HR 1.254; 95% CI, 1.002–1.478; *P*=0.026) and nerve-sparing status (HR 0.713; 95% CI, 0.548-0.929; *P*=0.012) were independently associated with recovery of urinary continence.

Considering that NS in patients with preop ED can still be associated with continence improvement after RP suggests the nerve function itself may not be the key but rather the careful apical dissection that accompanies NS RP. Hefermehl et al in a prospective study of patients having open RRP evaluated the effect of NS (using both surgeon defined NS based on operative report and postop international index of erectile dysfunction (IIEF)-defined NS [i.e., successful NS = postop IIEF >11]) on urinary continence using EPIC questionnaire. With a median follow-up of 48 months multivariate analysis for regaining continence demonstrated no significant difference between NS and NNS regardless of how NS was assessed (surgeon defined, IIEF) with 65% being continent at 3 years.[139] Furthermore Michl et al retrospectively analyzed 18427 men who underwent RP from 2002 to 2014 comparing patients having bilateral NS RP vs primary NNS RP, and those who ultimately had secondary resection of the neurovascular bundles(NVBs) for positive frozen-section results after an initial bilateral NS RP (secNNS – i.e., they had initial nerve sparing dissection). Continence rates (0–1 safety pad/day) at 12 months after surgery did not differ significantly between patients who had bilateral NS and those who had secNNS (i.e., resection of both NVBs after an initial NS technique). In contrast, secNNS had significantly higher continence rates after 12 months compared to primary NNS suggesting the careful dissection rather than actual preservation of NVB is the key to postop continence.

The benefit of NS and/or careful apical dissection may not just extend to ISD/SUI: there could also be a benefit with respect to OAB. Matsukawa et al,[106] in a prospective study on 230 RARP patients, using IPSS and OABSS to diagnose OAB and a 0 pad definition of continence, identified *de novo* OAB in 38% of patients at 3 months postop and a significantly greater rate of incontinence at 3 months in patients with *de novo* OAB (92% vs 20%). There was a significant difference in the nerve-sparing rate between the two groups (40% of OAB free patients vs 23% *de novo* OAB patients, *P*=0.01). Furthermore, postop MUCP and functional profile length were significantly lower in the *de novo* OAB group; postop MUCP was found to be the most significant risk factor for *de novo* OAB. A postop MUCP of 50 cmH2O was determined to be the optimal cut-off value for *de novo* OAB with a sensitivity of 81% and a specificity of 72%. On the other hand, Kadono et al[110] did not find an effect of nerve sparing on longer term bladder storage function based on UDS at 1 year.

It remains unclear whether actual nerve preservation and/or careful apical dissection preserves functional urethral length and a more competent distal sphincter mechanism results in the improvement in OAB. Regardless, nerve sparing with careful apical dissection appears to reduce both postoperative SUI and OAB.

2.2.1.2.2. Anterior/Posterior/Total Reconstruction

Reconstruction of the anterior and posterior support of the membranous urethra and urethrovesical anastomosis appears to hasten the recovery of continence after RALP.[99] Anterior suspension mimics the puboprostatic and pubovescial ligament function and alleviates downward prolapse of the bladder on anastomosis. In posterior reconstruction, the aim is to maximize urethral length (by preventing caudal retraction), maintain a more anatomic position that avoids anastomotic tension, and provide a posterior platform that buttresses the sphincter complex to facilitate contraction.[9] In meta-analysis of studies on RARP using posterior ± anterior reconstr, Ficarra et al[117] noted posterior musculofascial reconstruction with or without anterior reconstruction was associated with a small advantage in urinary continence recovery 1 month after RARP but not at 3 or 6 months.

In an updated review in 2016 (21 studies including 3 RCTs), Grasso et al[143] noted that posterior reconstruction improved early continence recovery rates up to 90 days after catheter removal and had significantly lower anastomotic leakage rates with no difference in positive surgical margins or complications (urinary retention, anastomotic stricture).

The combination of anterior and posterior reconstruction (total reconstruction) may provide the best continence outcomes.[99] In their meta-analysis of RARP studies, Ficcarra et al[117] noted that only total reconstruction (anterior + posterior) provided a significant advantage in urinary continence 3 months after RARP (odds ratio [OR]: 0.76; *P*=0.04), but not after 6 months.

On the other hand, Wu et al,[146] in a recent meta-analysis of 10 studies, found that total reconstruction was associated with significantly better urinary continence outcomes at all time points assessed from 1 week postop to 52 weeks postop (at 52 weeks, OR 4.10, 95% CI 1.80–9.38, *P*< 0.001) without increasing the complication rate over the standard approach.

In a randomized trial comparing the standard posterior reconstruction in RARP to a more total reconstruction that includes anterior, posterior and lateral (bladder to arcus tendinous) fixation (ARVUS), using a 0 pad/day definition of continence, Student et al[148] reported statistically significantly more patients being continent at 6 (75% vs. 44%, [*P*=0.013]) and 12 months (87% vs. 61%, *P*=0.04) with the total reconstruction and with a quicker return of continence. On the other hand, Kováčik et al, in a partially randomized controlled study did not find any benefit to total reconstruction with respect to postop urinary continence (0–1 pads) using the ARVUS technique whereas nerve sparing had a significant positive association.

There may be a benefit of total reconstruction in open RRP. Ficarra et al[147] reported significantly fewer incontinent patients at all time intervals up to 3 months after catheter removal in a cohort of patients who had urethral fixation during RRP (basically a form of total reconstruction) compared to standard anastomosis–90% vs 63% continent at 12 weeks, *P*=0.001). Reconstruction was an independent predictor of continence recovery at all assessed times with odds ratios of 4–7.7.

2.2.1.2.3. Retzius Sparing/Fascial Preservation (Lateral)

Retzius sparing RARP (RS-RARP) is a newer posterior approach to RARP (via the pouch of Douglas) that preserves the endopelvic fascia, arcus tendineus, neurovascular bundle, deep dorsal vein plexus, and puboprostatic ligaments thought to be involved in the maintenance of urinary continence.[,] Several recent systematic reviews and meta-analyses (generally of the same studies), including a Cochrane review, have found that RS-RARP is associated with a faster and greater rate of continence recovery (0–1 safety pad) over conventional RARP.[,,,] However, they have yielded somewhat conflicting results with respect to longer term continence rates (12 months) with some finding better 12-month continence rates with the RS approach,[152,154] while others found no difference.[153,155] As well, there is some concern regarding a higher risk for positive surgical margins with the RS approach although there does not appear to be any difference in complications.[152,153,155]

2.2.1.2.4. BN Sparing/Reconstruction

As noted earlier, the bladder neck is a part of the internal sphincter (smooth muscle) mechanism thought to be involved in passive continence (maintenance of continence during normal activity). Prostatectomy separates the prostate from the bladder neck and often results in significant damage to the bladder neck rendering it nonfunctional. Sparing the bladder neck is thought to help preserve some of the internal sphincter complex and this appears to hasten the return of continence and lower the rate of PPI. Ma et al in a systematic review and meta-analysis (13 studies) noted that BN preservation improved early and late urinary continence rates (6 mo, OR = 1.66; 95% CI, 1.21–2.27; *P*=0.001; >12 mo, OR = 3.99; 95% CI, 1.94–8.21; *P*=0.0002). In a long term (mean followup ~4 years) update from a randomized trial on BN preservation, Nyarangi-Dix et al reported significantly higher continence rates (*P*=0.004), less pad-use (*P*<0.001), reduced frequency (*P*=0.023) and amount (*P*=0.009) of urine loss, and higher QoL outcomes (*P*=0.012) after BN preservation. BN preservation was the only independent predictor of urinary continence (OR=8.1, *P*=0.008). The type of RP (RARP vs RRP) did not affect the results and BN sparing did not appear to compromise oncologic outcomes.

2.2.1.2.5. Fibrosis

It has been suggested that fibrosis of the urethra in the region of the urethrovesical anastomsosis/external sphincter may be associated with worse continence. Anastomotic stricture (AS) occurs in approximately one-quarter of patients after RRP.[103,] Eastham et al noted that postop AS was a significant negative predictor of postop continence after RRP. Park et al reported that fewer patients with anastomotic stricture became totally continent (62% vs. 92%) and fewer were able to be pad free (54% vs. 88%) at 1 year after RRP. Sacco et al[5] evaluated 985 men who had RRP and found that anastomotic stricture was a significant prognosticator of postoperative incontinence (RR 2.42 (1.66–3.53, *P*<0.001). Desautel et al noted 67% of patients with sphincteric PPI had evidence of urethral fibrosis on cysto. Tuygun et al, using pelvic MRI to identify periurethral/urethral fibrosis after TURP, open simple prostatectomy and RRP and found that 100% of patients with postop incontinence had fibrosis whereas only 29% of patients who were continent had fibrosis (*P*<0.001). Furthermore, the most severe fibrosis was seen in the RRP patients (*P*<0.001). However, there was no relation between the severity of the fibrosis and the magnitude of incontinence or cystoscopic findings. Similarly, Paparel et al, comparing, preop to postop MRIs looking at urethral length and fibrosis, observed that patients with a high grade of periurethral fibrosis postop tended to have worse postoperative continence although this wasn't statistically significant. However, the decrease in membranous urethral length postop was significantly associated with postop continence. They postulated that periurethral fibrosis may impede continence recovery by altering the elasticity of the external sphincter.

2.2.1.2.6. Postoperative Membranous Urethral Length

The length of the membranous urethra (MUL) postop has been reported to be an important variable with respect to postoperative continence. Cameron et al, reported that on postop MRI the MUL was 31-35% shorter in incontinent men compared to continent men after RP (open, RARP -no difference). Kadono et al reported that the residual length of the urethral stump was a significant predictor of urinary incontinence after RARP (24-hour pad test) and leaving the urethral stump as long as possible at the transection between the urethra and the prostate may have a positive impact on urinary incontinence. Haga et al, using VCUG to assess MUL in 60 consecutive patients after RARP, reported that postoperative MUL was significantly associated with urinary continence in the early postoperative period (OR 1.94; 95% CI, 1.22-3.12; *P*<0.005) and using ROC analysis determined an optimal cutoff value of 17mm which had an AUC of 0.76, sensitivity of 0.76 and specificity of 0.4. A postoperative MUL > 17mm was significantly associated with early acquisition of urinary continence (*P*=0.006, log-rank test). Neurovascular bundle preservation was associated with a longer MUL. Similarly, Cho et al, using pericatheter urethrography to measure MUL, found that a shorter MUL was an independent predictor of delayed continence (0 or 0–1 pads) recovery after RP (open or RARP).

Consistent with these findings regarding postop MUL, Kahokehr et al, using MRI before and after transobturator (TO) sling for postprostatectomy incontinence, noted that compared to continent RP patients (controls), preop sling patients had a significantly shorter urethral length (from the urethrovesical anastomosis to penile bulb, i.e., MUL) at rest (1.92cm controls vs. 1.27cm pre-TO Sling, *P*=0.0018) and at Valsalva (2.13cm controls vs. 1.72cm pre-TOS, *P*=0.0371) but after sling placement these differences were no longer significant (i.e., the urethral length increased after the retrourethral sling). This is consistent with the importance of MUL for postop continence and might explain part of the mechanism of action of the retrourethral sling.

2.2.2. Patient Factors

2.2.2.1. Age

Older age appears to be associated with worse continence outcomes after RP. Mohamad et al, in a population-based analysis of

over 16,000 patients undergoing radical prostatectomy in Austria between 1992–2003 (95% of all RPs in the country), found that increasing age was associated with an increased risk of future AUS implant. Only 0.5% of patients in the 45–49-year-old group had subsequent AUS whereas 2.5% in the 70-74 year old group did (i.e., a 5-fold increase). Shikanov et al reviewed their results in over 1,400 robotic RPs and using UCLA-PCI questionnaire (continence defined 0 pads), reported the predicted probabilities (95% CI) of continence at age 65, 70 and 75 years were 0.66 (0.63, 0.69), 0.63 (0.57, 0.68) and 0.59 (0.52, 0.66), respectively. Older age was an independent predictor of postop incontinence on multivariate analysis, granted only 5% of their patients were 70 or older. Nilsson et al, in a series of 1,411 patients who underwent open or robotic RP between 2002–2006 found that age at surgery predicts in an exponential manner long-term urinary incontinence (defined as ≥ 2ppd based on questionnaire). They noted an estimated relative increase of 6% per year. Incontinence was prevalent in 19% of the oldest patients compared to 6% in the youngest (prevalence ratio of 2.4 [95% CI, 1.5-8.1]).

More recent studies have similarly reported the negative influence of older age.[133,135,] Mandel et al,[133] in a retrospective review of 5,902 patients undergoing open or robotic RP, found the 12-month continence rate (≤1 safety pad/day) was 91% overall with 1-year continence rates for age groups < 65, ≥ 65 and < 70, ≥ 70 and < 75, and ≥ 75 years of 93.2%, 90.8%, 86.0%, and 86.5%, respectively. Older age was a significant adverse factor for postop continence on univariate and multivariate analyses. Nerve sparing, BMI and pT category were also significant predictors on multivariate analyses. Lee et al,[135] in a retrospective review, compared patients older than 70 years to patients younger than 70 years undergoing RP (open or RARP). Using a ≤ 1 security pad/day definition of continence and with a median follow-up of 58 months, 60.9% and 88.6% of patients aged ≤ 70 years and 52.6% and 81.5% of those aged > 70 years recovered urinary continence within 3 and 12 months after surgery, respectively (*P*<0.001; between both groups). Nerve sparing and membranous urethral length were found to be predictors of continence recovery.

Older age could contribute to PPI via pre-existing LUTS (e.g., BPH) and/or age-related changes in bladder, urethra, and pelvic floor anatomy/function. Strasser et al[96] identified an age-related reduction in striated muscle cells of the male rhabdosphincter, with an increase in smooth muscle fibers and connective tissue, that was postulated to contribute to the apparent increase in PPI in men over 70. Tai et al, using MRI with 3 D reconstruction to compare post prostatectomy patients with ED and urinary incontinence to healthy young males and older controls, found there was age related atrophy in the puborectalis and ischiocavernosus muscles and postulated that this may predispose older patients to UI and ED following RP.

Older age is also associated with a greater incidence of bladder dysfunction such as DO which itself can be a cause of incontinence. This may be secondary to benign prostatic obstruction and subsequently resolve after prostatectomy (for BPH or prostate cancer) but it may also be independent of any obstruction (or there may not be obstruction present) and persist after prostatectomy.[176] The presence of pre-RP DO was shown in a recent meta-analysis to be negative predictor of postop continence.

On the other hand, some studies have not shown age to be an issue. Labanaris et al reviewed 2000 patients undergoing RARP and compared patients 75 years or older to the overall cohort and failed to show a significant difference in 12-month continence rates (no pads and/or no leakage): 87% in ≥75 yearr vs. 93% in the whole cohort (*P*<0.05). However, the clinical significance of the study is limited by the small number (45) of elderly patients.[133] Kumar et al retrospectively analyzed 3362 patients undergoing RARP stratifying them into groups based on various possible adverse features one of which was age ≥ 70 years and compared them to patients without risk factors (age < 70 years). Using a 0 pad and no leakage (based on EPIC questionnaire) definition of continence, they found no significant difference in 12-month continence rates between groups. However, patients without risk factors achieved continence faster. Recently, Nyarangi-Dix et al, in a retrospective analysis of 350 high risk prostate cancer patients undergoing RARP, found no significant difference on multivariable analyses in urinary continence (0 pads) recovery rates at 12, 24, and 36 months after surgery between men aged <70 years and ≥ 70 years.

2.2.2.2. Obesity, diabetes and metabolic syndrome

Many studies have found that obesity (typically defined as BMI >30), adversely affects continence outcomes after RP. In a meta-analysis of four studies comprising six trials with 2,890 participants, Wei et al found that obesity increased UI risk at 12 months in patients who underwent RARP (OR 2.43, 95% CI 1.21, 4.88, *P*=0.01). Similarly, Xu et al, in a meta-analysis of 4 studies (1 overlap with Wei et al[181]) that compared 735 obese patients with 2,662 nonobese patients, reported that obese patients had significantly higher probabilities of incontinence at 1 year (OR: 1.41; 95% CI, 1.13-1.77, *P*=0.003).

In a retrospective review of RP patients (open and lap), Wolin et al noted that obese patients, especially when physically inactive, were significantly more likely to have incontinence than non-obese patients. At 58 weeks postop, 31% of obese versus 18% of non-obese patients were incontinent (*P*=0.05). When considering obesity and physical activity together, at 58 weeks postop, non-obese men who were active were 26% less likely to be incontinent than men who were obese and inactive (RR 0.74, 95% CI 0.52-1.06). Furthermore, being active appeared to offset the negative consequences of obesity: obese and active men had the same prevalence of incontinence (25%) as nonobese inactive men (24%). In a multicenter review of open RRP, LRP and RARP patients (N=470) from Italy, using waist circumference (WC) to assess obesity (WC ≥ 102cm), Gacci et al noted a significant positive correlation between WC and postprostatectomy incontinence severity: the risk of needing at least two pads per day was 2.5 times greater in obese men than non-obese men (adjusted OR = 2.435, 95% CI 0.321-7.668, *P*=0.007).

On the other hand, some have not found a negative effect of obesity on PPI. Hsu et al noted no significant association between body weight and postop continence in 1024 men who had open RRP, Kumar et al[179] found no statistically significant difference in 1-year postop (RARP) incontinence rates between patients with obesity (BMI ≥ 35) and those without (although it took longer to achieve continence in obese patients), and Kadono et al[110] reported that BMI was not an independent predictor of 1 year post-RARP incontinence.

Diabetes and metabolic syndrome may be associated with OAB/DO in its early stages and thus may also be a contributors to urinary incontinence in both prostate cancer and BPH surgery (please refer to sections 3.3.2.2.2. and 3.3.2.2.3.).

2.2.2.3. Prostate Size

There have been conflicting reports as to whether or not prostate size impacts post-RP continence. Boczko et al noted that 6-month post-extraperitoneal RARP continence rate (no leakage and 0 pads)

was significantly lower in men with prostate size < 75g compared to >75g (97% vs 84%, *P*<0.05). They noted that larger prostate size resulted in less maneuverable space and a higher rate of urinary complications (postop retention, UTI); although, there was no difference in positive surgical margins. Konety et al, using the patients with preop prostate volume measurements in the CaPSURE database, noted lower 6- and 12-month continence rates (based on the UCLA-PCI) after RP if prostate size was greater than 50cc. However, the rates equalized at 24 months. They postulated that men with larger prostates may have subclinical bladder dysfunction related to the prostatic enlargement that then becomes more manifest after RP.

On the other hand, Foley et al did not find a difference in post-RRP incontinence in patients with prostate volume greater than 75g or less than 75g using self reported questionnaires (ICSmale). Similarly, both Pettus et al and Kadono et al[110] did not find prostate volume to influence post-RP continence outcomes.

2.2.2.4. Preop LUTS/OAB/DO/LUTD

As noted elsewhere, men undergoing prostate cancer treatment not uncommonly have LUTS. The ProtecT Study, a randomized trial of active surveillance vs RP vs radiotherapy published their baseline patient characteristics and noted that while LUTS were fairly common (e.g., nocturia in 22%), overall urinary function was good (EPIC score 95.1) and bother due to LUTS was low. Interestingly, 30% of men had some degree of incontinence; although, fewer than 1% were using pads or reported incontinence as a big problem. Followup data has not been published yet.

Preoperative urinary continence status was noted to be a significant predictor of postop urinary continence on multivariate analysis by Wei et al in a prospective study of RP patients. They noted that 12% of their patients had incontinence preoperatively; although, they did not specify what type of incontinence was present. More recently, Kurimura et al, using the 1-hour pad test, similarly found that the presence of preoperative incontinence resulted in postop incontinence being present for a longer duration after RARP compared to patients who were continent preop (*P*=0.042). They found a significant correlation between the result of the preoperative 1-hour pad test and the OABSS (R=0.32, *P*<0.01) suggesting that it may have been UUI in these patients preoperatively and this potentially was provoked by the activities of the one-hour pad test.

Preop LUTS may also impact post-RP functional outcomes. Choi et al reported that patients with severe preop LUTS (using AUASS) had higher post RARP urinary bother scores (EPIC) compared to those with milder preop LUTS. Similarly, Yamada et al reported that preop OAB was a negative predictor of return of continence at 12 months after RARP. More recently, Collette et al, using patient reported outcome measures with a median follow-up of 36 months after RARP, found the severity of preop LUTS (based on IPSS) was an independent predictor of PPI (≥ 1 ppd) (OR 0.56, *P*=0.004).

The presence of DO on preop UDS may increase the risk for incontinence post-RP. Comparing preop UDS to that at 2 years postop, Dubbelman et al noted preop DO was present in significantly more patients who had persistent incontinence at 6 months postop compared to those who regained continence (34% vs 5%, *P*=0.015). A systematic review and meta-analysis by Kim et al,[177] incorporating 9 studies with 419 participants, determined that PPI was more likely to occur in patients with preoperative DO [pooled OR 2.30; 95 % CI 1.39-3.82], as compared to patients who were DO negative. However, they were unable to correlate preoperative DO with subtypes of PPI (SUI vs UUI) due to study limitations.

On the other hand, RP can improve preop LUTS and DO.[111] Gordon et al compared men with severe preop LUTS (using AUASS) to those with mild to moderate LUTS undergoing RARP and noted that in men with severe preop LUTS, long term AUASS improved by 70% with 59% improving to the mild category. However, significantly fewer preop severe LUTS patients were continent (0 pads) postop (71% vs 89% (*P*=0.002).

2.2.2.4.1. Neurogenic Lower Urinary Tract Dysfunction

There is very little data on patients with significant neurologic disease undergoing RP. Given that NGB can be associated with significant bladder and sphincter dysfunction (see elsewhere) the expectation is that patients might be more prone to PPI. In a review of 20 Parkinson's disease (PD) patients who underwent RP, Routh et al reported that *de novo* incontinence occurred in 20% at 1 year, was mild (none needing >2 pads/day) and all had another known risk factor for PPI including (prior XRT, TURP, non-nerve sparing technique). None of the 15% with preop incontinence regained continence after RP but there was no worsening of the UI. They felt that even in PD patients, it is reasonable to consider RP for CAP.

2.2.2.5. Preoperative Membranous Urethral Length

As noted earlier, the postoperative MUL has been associated with post-RP continence. Not surprisingly, the preoperative MUL has also been positively associated with post-RP continence. In a recent systematic review and meta-analysis, Mungovan et al determined that based on 4 studies (1,738 patients) reporting hazard ratios, every extra mm of preop MUL was associated with a faster return to continence (hazard ratio: 1.05; 95% CI: 1.02-1.08, *P*<0.001). Similarly, in 11 studies (6,993 patients) that reported odds ratios for the return to continence at one or more postoperative time points, MUL had a significant positive effect on continence recovery at 3 (OR: 1.08, 95% CI: 1.03-1.14, *P*=0.004), 6 (OR: 1.12, 95% CI: 1.09-1.15, *P*<0.0001), and 12 months (OR: 1.12, 95% CI: 1.03-1.22, *P*=0.006) following surgery. Every extra millimeter of MUL was associated with significantly greater odds for return to continence (OR: 1.09, 95% CI: 1.05-1.15, *P*<0.001) such that for every extra 10mm of MUL, the odds of continence recovery is increased by between 63% and 205% (OR: 2.37, 95% CI: 1.63–4.05).[202]

More recently Kim et al, in a prospective study on 529 patients undergoing RARP, reported significantly higher continence rates at 12 months in patients with a preoperative MUL ≥ 11.7mm (92% vs 80%).[136] This is consistent with the findings of Coakley et al in RRP patients: 89% of patients with a preop MUL >12mm had an 89% rate of continence at 12 months postop compared to 77% of patients with an MUL of ≤ 12mm.

2.2.2.6. Pelvic Floor Muscle Function

The status of a patient's pelvic floor muscle (PFM)/sphincter prior to RP may predict UI/incontinence after RP. Majoros et al compared preop and postop (2 months) UDS in 63 RRP patients and reported that patients who were continent postop had significantly higher preoperative maximal voluntary sphincter contraction pressure (125 vs. 96.5 cmH_2O, *P*<0.0001) and those who were immediately continent following catheter removal had higher preop and postop MUCP and no preop LUTS compared to those who had delayed return of continence. Dubbelman et al similarly found higher median preop and postop MUCP in RP patients who regained continence after 6 months compared to men with persistent incontinence with a preop MUCP cut off of 53 cmH_2O.

Preoperative PFM status has been evaluated with MRI. Song et al correlated levator ani muscle thickness on preop MRI (as a gauge of their integrity) with early (3 months) post RP continence but not

longer term (6 months). Interestingly, they noted that preop incontinence was present in 16% and UUI in 13%. They concluded that patients with better developed pelvic floor muscles, especially in relation to the size of the prostate, can be expected to achieve earlier recovery of continence after radical prostatectomy. Similarly, in a recent study it was observed that significantly more continent (based on ICIQ < 6) than incontinent post RARP patients had, on preop MRI assessing perfusion quality of pelvic muscle structures, a higher perfusion ratio (comparing perfusion of levator ani complex to surrounding pelvic muscle structures). Furthermore, there was a negative correlation between perfusion ratio and ICIQ score (higher perfusion ratio negatively correlated with ICIQ score) which is consistent with patients who have better preoperative pelvic muscle function tending to have better postop continence. As well, a systematic review and meta-analysis on the effect of preop pelvic floor therapy on postop urinary continence after RP reported that preop pelvic floor exercises improved early postop (3 months) continence rates.

The importance of good pelvic floor muscle function was recently demonstrated by Stafford et al who, using transperineal ultrasound, compared various measures of pelvic floor muscle function (e.g., contraction of the striated urethral sphincter, puborectalis, bulbocavernosus muscles, displacement of urethrovesical junction/bladder neck) during voluntary muscle contractions and coughs between post-prostatectomy patients with and without incontinence (based on ICS-male SF) and a continent control group. They found that post-prostatectomy continent patients can voluntarily activate their pelvic floor muscles at least as well if not better than continent controls, especially during a cough, whereas PPI patients were not. The recently published AUA SUFU guidelines on incontinence after prostate treatment recommends pelvic floor physiotherapy postoperatively, and also that it should be considered preoperatively with the goal of improving pelvic floor strength.[18]

2.2.2.7. Stage of Disease

As noted in ICI 6, stage of disease has not been correlated with postop urinary incontinence. Stage of disease might affect surgical technique (e.g., less likely to do nerve sparing in higher clinical stage patients) and that could impact postop incontinence rates but this is more a reflection on technique rather than stage of disease. Loeb et al reported in their series of high risk or locally advanced prostate cancer patients undergoing RRP that 92% of patients were continent (dry and 0 pads) postop. They were able to perform at least some degree of nerve sparing in about 85% of patients despite the adverse cancer factors and this might have contributed to their results. More recently, Kumar et al[179] reported on RARP patients with various adverse risk factors including a cohort with prostate size greater than 80g and compared these groups to a group without risk factors and did not find any significant difference in the 1-year postop continence outcomes although those without adverse risk factors achieved continence sooner.

2.2.2.8. Prior BPH Surgery (e.g., TURP, HoLEP)

There is conflicting data regarding prior BPH surgery as a risk factor for PPI.

2.2.2.8.1. BPH Surgery Is a Risk Factor

In a recent systematic review and pooled analysis (12 studies) of patients undergoing RARP or LRP, Veccia et al compared patients with a history of bladder outlet surgery to those without. They found that a history of bladder outlet surgery was associated with lower continence recovery at 12 months (OR 1.61, 95% CI 1.14-2.27, *P*=0.007). But patients with a history of bladder outlet surgery tended to be older, have more complications and were less likely to have nerve sparing performed. In a retrospective review of over 18,000 patients undergoing RP, including 470 with prior TURP, using propensity score matching, Pompe et al reported that TURP patients had a higher risk for urinary incontinence (> 0-1 safety pad/24 hour) at 3 months (OR: 1.47; 95% CI 1.01-2.12, *P*=0.04) and 12 months postop (OR: 2.06; 95% CI 1.23-3.42, *P*=0.006).

2.2.2.8.2. BPH surgery is not a risk factor

Palisaar et al compared open RRP patients with a history of TURP to those without and found similar 1 year continence (0 pads) rates (81% vs 82%). Su et al, in a retrospective review of 2693 patients who had RARP, compared those with prior TURP to those without and found no significant difference in urinary continence (0 ppd), social continence (1 ppd) and overall AUASS between the groups at 12 months postop.

Suardi et al compared various types of pre-RRP bladder outlet surgeries (HoLEP, TURP, open prostatectomy) using the ICIQ-SF to assess post-NSRRP incontinence and found no significant difference between groups: 6-month postop continence rates were 93%, 93% and 80% for HoLEP, TURP and open prostatectomy, respectively (*P*>0.05). There was no difference in ICIQ-SF scores between groups at most recent followup (mean follow-up 24 months). More recently, Kretschmer et al noted that on multivariable analysis, prior HoLEP did not have an adverse impact on urinary continence (0 pad use) at 1 year post RARP or open RP (OR 0.87, 95% CI 0.74–1.01, *P*=0.07), whereas Abedali et al, comparing prior HoLEP to no prior HoLEP, found no statistically significant difference in social continence (0–1 pads/day) at a median of ≤ 6 months post-RARP (59% vs. 81% *P*=0.156) although the HoLEP group had fewer patients who had complete continence (pad free + leak free): 22% vs 74% *P*<0.001, and the time to achieve continence took longer (24 months vs. 13 months, *P*=0.007).

While not commonly performed, RPP may be preferred over open RP in patients with a history of BPH surgery. Imperatore et al retrospectively compared patients with a history of BPH surgery who underwent RPP vs RRP and noted that significantly more RPP patients achieved complete continence at 3, 6, and 12 months compared to RRP. However, the timing of RPP relative to TURP may be important. Elder et al reported that if RPP was performed between 4 weeks and 4 months after TURP, there was a 50% incidence of incontinence whereas when performed less than 4 weeks or more than 4 months after TURP, no patient experienced post RPP incontinence. They recommended waiting at least 4 months after TURP before performing RPP.

2.2.2.9. Prior XRT – Salvage RP

Patients with a history of XRT for prostate cancer already experience some risk for urinary incontinence (see section **3.2.2.2.10**). When they then undergo RP for persistent/recurrent disease, there are the added risks for incontinence that are associated with RP. Rosoff et al in their review of the literature on salvage RP (SRP) between 1980 and 2012 reported postop urinary incontinence rates ranged from 36 to 81%. In a systematic review of publications between 1980 and 2011, Chade et al noted continence (0 pads) rates of 21–90% for open RP, 67–78% for lap RP, and 33–80% for RARP, and that overall complications appeared less frequent in the more recent publications. More contemporary series also show that while there is still a significant incidence of incontinence after SRP, it does seem less than previously reported. Mohler et al, in a multicenter prospective study, reported on patients undergoing open SRP at a median of 64 months after XRT: 45% of evaluable patients had urinary incontinence (≥3 pads/day) prior to SRP with 88% reporting urinary incontinence at 6 months, 85% at 12

months and 63% at 24 months after SRP. Given their definition of incontinence, their results may actually underestimate the true incidence of incontinence. Gontero et al retrospectively reviewed results from 18 institutions comparing 186 open to 209 robotic SRPs. They noted fewer anastomotic strictures with robotic SRP (8% vs 17%, *P*<0.01) and better continence preservation (0 pads): at 6 and 12 months more patients in the robotic SRP group were continent (26% vs 22%, *P*=0.0234 and 32% vs 23%, *P*=0.0432, respectively). On multivariable analysis, robotic SRP was an independent predictor of continence preservation (OR 0.411, 95% CI 0.232-0.727, *P*=0.022). Salvage RP has also been performed after focal therapy (FT) for prostate cancer including HIFU. In a retrospective review, Herrera-Caceres et al found that after a mean follow-up of about 4 years, 91% of patients were continent after salvage RP for FT. However, the remainder had moderate (>1 pad/day) to severe incontinence (needed AUS). De Groote et al retrospectively reported that 83% of patients were either completely or socially continent (0-2 pads) more than 2 years after salvage RARP (post HIFU, EBXRT, brachytherapy, cryo). They noted better continence rates after prior FT versus whole gland treatments (88% vs. 72%); although, not statistically significant.

2.2.2.10. Radiation Therapy (Without Surgery) and Incontinence

XRT can affect the lower urinary tract via changes in the structure and function of the detrusor and the urinary sphincter. It can be administered via external beam or directly into the prostate tissue via seed implant (brachytherapy). It can be used as primary or adjuvant/salvage therapy after RP. When used after RP (adjuvant/salvage XRT), one is already dealing with the potential lower urinary tract effects (especially sphincter deficiency) of the surgery which may then be compounded by the effects of the XRT.

Radiation causes edema initially followed by gradual degeneration and fibrosis (related to ischemia from radiation-induced vascular damage) in the primary target tissue (i.e., prostate cancer) and surrounding tissues (bladder/urethra/ureter). As such, similar to after prostatectomy, both sphincteric and detrusor related (DO/OAB, low compliance) incontinence may occur. UPP showing inflexible parts of the external sphincter has been identified in some patients over time after XRT and it has been suggested this is related to fibrosis. Shortening of the membranous urethral length (a risk factor for post-RP incontinence) as well as alterations in urethral and pelvic muscle signal intensity on MRI have been reported after various froms of XRT. OAB after XRT may be due to BOO (bladder neck stenosis, urethral stricture), bladder stones (dystrophic calcification of prostate) or mucosal inflammation.

Older series of external beam radiotherapy (EBXRT) have shown a generally low rate of post-treatment incontinence. Lawton et al reported an ~8% risk of long-term urinary complications after EBXRT, proportional to dose. Perez et al noted incontinence in <1% of patients after XRT. Shipley et al in their review of multi-institutional and single institutional studies similarly noted that UI as a direct result of EBXRT is rare (<1%). Budäus et al in their review of the literature between 1999–2010 reported that long-term total UI and other severe urinary symptoms (RTOG grade > 2) are rare; although, early storage symptoms are common. Recently, Hoffman et al examined functional outcomes (using EPIC) of patients undergoing active surveillance, nerve sparing RP, EBXRT or low dose rate brachytherapy and found that at all time points up to 5 years, EBXT patients had incontinence domain scores that were not significantly different than active surveillance patients. RP patients had the worst incontinence scores (compared to other modalities) throughout the 5 years, whereas LDR brachytherapy patients had worse incontinence scores compared to active surveillance patients at 6 months but not beyond.

Radiotherapy for prostate cancer has evolved to become more focused to deliver more accurate dosing to the prostate and minimize effects on surrounding tissues. EBXRT has progressed to more intensive/higher dose treatments that are able to be more focused to the target organ. A systematic review and meta-analysis by Ávila et al[121] noted that for various types of EBXRT there is a small worsening of UI after treatment without statistically significant differences among the five modalities (proton therapy, stereotactic body radiotherapy, intensity modulated radiotherapy, EBXRT, and 3-Dimensional [3D] conformal radiotherapy). Evans et al similarly showed no significant difference in incontinence after IMRT, SBRT or brachytherapy in a multi-institutional pooled cohort analysis of patient-reported QoL [EPIC-26] pre and post XRT.

Recently Pan et al, using outcomes of patients undergoing SBRT who completed EPIC 26, were able to create models via machine learning that could predict urinary toxicity (irritation/obstruction, incontinence). At 12 months, 41.2%, 27.3%, and 56.5% of patients experienced a clinically significant decline in urinary irritation, UI, and bowel function, respectively. Bladder dose-volume metrics (e.g., the bladder volume and radiation dose received by the bladder) strongly predicted patient-reported urinary irritative and incontinence symptoms (area under the curves [AUCs] of 0.79 and 0.87, respectively) at 12 months.

The importance of adequate follow-up with respect to outcomes after XRT was highlighted by Pinkawa et al. They surveyed patients using EPIC questionnaire up to 12 years after 3D conformal EBXRT. The rate of UI (need for pads) increased over time (8% of patients pre-XRT vs. 15% of patients 10 years post-XRT, *P*=0.01). As well, there was worsening of urinary bother scores compared to baseline over time and a higher radiation dose was associated with increased urinary problems.

2.2.2.10.1. Urodynamic Studies

There is limited literature on the issue of post-XRT UDS and much of it relates to salvage XRT after RP. In a prospective study, Choo et al evaluated 15 patients, pre- and 18 months post-EBXRT, for prostate cancer using symptom questionnaires (IPSS, QoL) and UDS. They found no statistically significant change in self-assessed urological symptoms at 18 months post-RT compared to pre-RT baseline. On UDS, only the volume at first sensation and cystometric capacity were significantly different (lower) at 18 months. There were no significant differences between pre-XRT and 18-month post-XRT with respect to: DO, low bladder compliance, outlet obstruction, urinary urgency or urgency urinary incontinence. However, the small sample size and follow-up limited to 18 months makes significant conclusions, particularly regarding long term issues, impossible. To this point, Ervandian et al[229] assessed urodynamic parameters and Danish Prostatic Symptom Scores (DAN-PSS) in 16 patients (none with SUI on UDS) who had salvage XRT after RP (median time from SRT to UDS was 7.7 years – range 5.8-10 years). They found that cystometic capacity, bladder compliance (low compliance was <30-40mL/cmH_2O), and bladder function were affected: 11/16 had decreased MCC (<350mL), 10/16 had low compliance, 7/16 had DO. Based on questionnaire, over a 6-year period after XRT there was an increase in the prevalence of incontinence. The authors noted that longer term follow-up (of which there currently is very limited UDS data) is needed to fully comprehend the effects of XRT with respect to fibrosis and its effect on bladder function.

In a recent publication, Hoffman et al[236] compared men with a history of XRT to those without who were undergoing AUS or sling surgery for SUI (due to prostatectomy, XRT or both). They noted that more men with a history of XRT had DO on UDS (70% vs. 38%, *P*<0.0001) and had a lower maximum cystometric capacity (255 vs. 307mL, *P*=0.01). They were also more likely to use OAB meds preop. After AUS, radiated patients were mo re likely to use OAB meds (44% vs. 25%, *P*=0.01) and more likely to require third line OAB therapy (9% vs. 1%, *P*=0.01).

2.2.2.11. Adjuvant/Salvage XRT

There is conflicting data as to whether adjuvant/salvage XRT after RP increases the risk for incontinence. A Cochrane Review in 2011 found 3 randomized controlled trials comparing RP + XRT to RP alone, involving 1815 men; although, the information about continence was reported only in a subset of 100 men treated at a single institution, representing 5.5% of the men studied. UI was not increased at 5 years (RD 0.06; 95% CI -0.02 to 0.15; *P*=0.15) or 10 years (RD 0.04; 95% CI -0.00 to 0.08; *P*=0.07) for men who received adjuvant radiation. On the other hand, Suardi et al analyzed RP patients with adverse pathologic features at (positive margins, pT3) and compared patients who did (153 patients) and did not (208 patients) have adjuvant XRT to look at the impact of XRT on continence (defined as 0 pads). They found that adjuvant XRT patients were less likely to recover continence at 1 and 3 years than non-XRT patients (51% and 59% vs. 81% and 87%, *P*<0.001). Even when controlling for age, non-organ confined disease and nerve sparing, adjuvant XRT was an independent predictor of worse continence recovery (HR: 0.57; *P*=0.001) resulting in a 1.6-fold higher risk of incontinence. Van Dessel et al retrospectively reported on 244 patients who had salvage XRT (3D-CRT or IMRT) for biochemically recurrent prostate cancer after RP to assess the effect on urinary continence (score of 0 on Common Terminology Criteria for Adverse Events [CTCAE]). 70% of their patients were continent prior to SRT. *De novo* incontinence (grade ≥ 1) was reported in the acute (within 90 days of XRT) and late (>90 days after XRT) phases in 6.1% and 17.6% of patients, respectively. Worsening of preop incontinence or persistence of acute *de novo* incontinence beyond 90 days occurred in 9.8% of patients.

The timing of post-RP XRT, adjuvant (soon after RP) or salvage (delayed after RP) has inconsistently been reported to influence functional outcomes. Adam et al, in a questionnaire based observational study reported that while patients after RP + XRT had a 4% higher overall incontinence rate (87%) and a higher rate (4%) of severe incontinence (>3 pads) compared to matched RP-only patients (91% continent, 2% severe), the timing of RT after RP had no influence on continence at 3 year followup. Nyarangi-Dix et al, using the ICIQ-SF questionnaire in a survey, similarly found worse continence over time after post-RP XRT (only 22% of the men who were continent at the time of XRT remained continent afterwards) and the timing of XRT (adjuvant vs. early salvage vs salvage) did not make a difference with respect to incontinence or its effect on quality of life. Baumgarten et al, in a post hoc analysis of RTOG 9601 trial cohort, similarly found that the timing of XRT after RP (≤ 2.1 yrs vs. > 2.1 years) did not seem to predict urinary adverse events. Huelster et al, in the CESAR trial, evaluated functional outcomes up to 60 months after RP alone, RP + adjuvant XRT (median 7 months after RP) and RP + salvage XRT (median 29 months after RP) and found that both adjuvant and salvage XRT patients had worse urinary (incontinence, storage symptoms) domain scores (EPIC) than patients who had RP alone and the timing (adjuvant vs. salvage) did not appear to make a difference (although delayed XRT occurring 24 months after RP had better sexual function than earlier XRT).

On the other hand, Jenkins et al reported that at 2 years post sEBXRT, there was a significant worsening of EPIC scores in the urinary function, bother and incontinence subscales with the most severe being incontinence (worsened by more than 10 points from 66.49–56.14, *P*=0.0003). When they compared early sEBXRT (1 year or less after RP) to late (>1 year after RP), the urinary domain summary score was worse in the late group (i.e., sEBXRT more than 1 year after RP fared worse than those treated sooner).

Interestingly, Parker et al, in the RADICALS-RT trial, a randomized trial comparing adjuvant XRT (>90% within 6 months post-RP) to early salvage XRT (at prostate-specific antigen biochemical progression; 1/3 of patients received sXRT (within 8 years of randomization) at time of analysis), reported that adjuvant XRT did not have any oncologic benefit compared to early salvage XRT, but did increase the risk of urinary and bowel morbidity at 1 year; although, not beyond (granted the data is immature).

While adjuvant/salvage XRT appears to be a risk factor for incontinence, the dose of XRT may or may not affect continence. In a multicenter randomized trial of patients with biochemical recurrence having SRT grouped by radiation dose (64Gy vs. 70Gy) Ghadjar et al found no difference between groups in the incidence of de novo incontinence or in the improvement in post-RP incontinence at 3 months (32% of population had post-RP incontinence prior to SRT and continence recovery was achieved 3 months after SRT by 44% vs. 41% with 64 vs. 70 Gy, respectively [*P*=0.8]).

On the other hand, Bresolin et al, in a prospective study using ICIQ-SF, recently noted a possible independent detrimental effect of both fractionation and higher XRT doses on the risk of severe urinary incontinence following both aXRT and sXRT. Importantly, baseline PPI prior to XRT was the strongest predictor of mid term (2 years) post-RP patient-reported continence recovery, regardless of subsequent aXRT or sXRT.

2.2.2.12. BPH Surgery Prior to XRT

Pre XRT BPH surgery appears to be a risk factor for incontinence after XRT. In a systematic review of the literature up until 2011, Ishiyama et al reported higher incontinence rates in XRT patients with a history of TURP. Odrazka et al found on multivariate analysis, prostatectomy for BPH (TURP, open) carried out before EBXRT (including IMRT), significantly increased the risk of Grade 2 or higher GU toxicity (risk ratio 1.88). The 5-year actuarial likelihood of Grade 2-3 urinary incontinence was 23%, compared to 9% for those without prostate surgery (*P*=0.01).

2.2.2.12.1. Brachytherapy

Brachytherapy (BT) is another form of guided XRT in which radioactive seeds are implanted into the prostate and has generally been tolerated by patients with mild GU toxicity. In their literature review from 1999–2010, Budäus et al[235] noted that after BT the predominant acute toxicity is radiation urethritis that tends to improve in the majority over the course of a year. Morgan et al compared low dose rate (LDR) BT to high dose rate (HDR) BT using AUASS and noted that while there was a deterioration in the short term (≤2 months), by >30 months, for each group there was no significant difference compared to baseline AUA score. On the other hand, Hathout et al found that HDR BT patients had better EPIC urinary irritative scores on repeated measures at 1, 3, 6 and 12 months compared to LDR BT patients although there was no significant difference in the urinary incontinence scores between groups at any time point. However, over time the effects may worsen. Stone et al followed patients after BT using AUASS and noted that for patients with minimal baseline symptoms the 10- and 15-year estimates for

freedom from worse symptoms were 72.9% and 39.1%, respectively. They identified risk factors for worsening LUTS over time: EBRT boost (HR 1.45, *P*=0.004), biologic equivalent RT dose >200 Gy2 (HR 1.25, *P*=0.024), hypertension (HR 1.37, *P*=0.006), and alcohol use (HR 1.46, *P*=0.001). Boettcher et al compared changes in LUTS (questionnaire based including ICSmale) up to 36 months after radical prostatectomy and BT. They reported that after adjusting for age and pretreatment symptoms, more BT patients complain of OAB symptoms (urgency) at 36 months (30% vs. 11%, *P*<0.025). Repeated measurements showed that the OAB symptoms were highly fluctuating and that in patients treated with BT compared to RP, the severity of symptoms as well as variability of symptoms was significantly higher. They also noted that the presence of LUTS before BT was significantly associated with higher rates of OAB after BT.

Incontinence can occur after BT and ICI 6 noted an overall rate of post-BT incontinence of 0-45%. Both sphincteric incontinence (SUI) and OAB issues may develop after BT. Blaivas et al studied men with persisting LUTS for at least 6 months after BT for CAP using IPSS, 24-hour voiding diary, VUDS and cystoscopy and they compared them to a previous study on men with LUTS without CAP. They reported that UDS showed: DO in 47% vs. 85%, decreased compliance in 9% vs. 25% and urethral obstruction in 69% vs. 73% of nonCAP patients with LUTS vs. BT patients, respectively. While not significantly different with respect to urethral obstruction incidence, after BT more patients had urethral strictures and adherent stones. Leapman et al reviewed a prospective database of 2461 men who underwent BT with or without EBXRT (2 months after the implant, 3D conformal therapy or IMRT) who had > 2 year follow-up (median 6 years). They reported an overall rate of UI (need for a pad for involuntary leakage) of 4.4% at a median of 1.8 years (IR 5 months-4.4 years), but there was a gradual deterioration in urinary continence beyond 5 years. Of patients reporting UI, 28% had SUI whereas 72% had UUI. Two-thirds (2/3) of incontinent patients used 1 pad per day whereas 11% were using at least 3 pads per day. The 2-, 5- and 10-year freedom from incontinence rates were 99%, 97% and 93%, respectively. Schlussel et al in a retrospective analysis of 902 patients reported UUI in 9% of patients after BT and SUI in 8%; the numbers were even higher in patients who had BT + EBXRT (UUI in 22%, SUI in 11%).

Probably the most important risk factor with respect to incontinence after BT is surgery for prostatic obstruction/BOO. This is typically done for urinary retention issues that can occur in 1-14% after BT. Ragde et al noted that incontinence after BT and TURP was nearly always preceded by various degrees of superficial urethral necrosis, visualized as areas of shaggy, mucoid concretions mixed with calcifications adherent to the distal walls of the resected prostate cavity. Because the distance between the sphincter muscle and urethral wall after TURP could be significantly decreased, necrosis and accompanied inflammation of the urethral wall could thus affect the function of sphincter muscle. Leapman et al,[259] when comparing patients who had TURP to those who did not, found that post-BT men without TURP had a 3% rate of UI whereas men who had TURP after BT monotherapy had 26% rate of UI and those with TURP after BT + EBXRT had 38% rate of UI (*P*<0.001). On multivariate analysis, UI was associated with combination EBRT (HR = 3.87), higher baseline IPSS scores (HR = 1.62), and posttreatment TURP (HR = 2.72). Post-implantation TURP was the single factor that was significantly associated with the development of SUI (HR 4.01, 95% CI 1.98-8.15), whereas combination EBRT, baseline IPSS ≥7, and post-implantation TURP were significantly associated with UUI.[259] The timing of TURP after BT may have an impact on UI. Kollmeier et al reported that the rate of post-TURP UI was 8% in patients who had TURP 2 years or less after BT compared to 36% in patients undergoing TURP more than 2 years after BT (*P*=0.04). They found no significant correlations between radiation dose, preimplant prostate volume or hormonal therapy with regard to this UI risk.

BPH surgery prior to BT may or may not increase the risk for UI. Leapman et al[259] reported that TURP prior to BT monotherapy had a 3% rate of UI while TURP prior to BT + EBXRT had a 21% rate of UI (*P*<0.01). After excluding patients having post-implantation TURP, they noted that TURP prior to BT was significantly associated with the development of UI. Peigne et al reported 16% of patients had *de novo* UI at 1 year, but only 4% persistent mild symptoms at 3 years in patients having channel greenlight PVP at least 6 weeks prior to BT, while Salembier et al reported UI (≥ 1 pad) in 2% of patients who had TURP at least 3 months prior to BT (median follow-up 49 months).

The need for more than one TURP may further increase the risk for incontinence. Mock et al reported a 25% incidence of UI in BT patients who had subsequent TURP whereas 3% had UI with BT only (OR 10.4, 95% CI 6-18, *P*<0.001). They noted that if >1 TURP was needed, 53% of patients experienced UI compared to 19% who only had 1 TURP (OR 4.9, 95% CI 1.5-16, *P*=0.006).

2.2.2.13. Cryosurgical Ablation of the Prostate

Cryosurgical ablation of the prostate (CSAP) uses multiple freeze-thaw cycles via transrectal ultrasound guided, perineally implanted probes to treat prostate cancer. Thermocouples are placed to maintain warmer temperatures in at risk structures (e.g., external sphincter, neurovascular bundles, Denonvillier's fascia/rectal wall) to minimize UI, ED and rectal injury/fistula. A urethral warming catheter is also used to protect the urethra from cold induced sloughing.

CSAP can be used for both whole gland treatment as well as more FT for CAP (primary or salvage therapy after XRT). A Cochrane review by Shelley et al in 2007 noted a relatively high incidence of side effects after whole grand CSAP: Impotence (47–100%), incontinence (1.3–19%), urethral sloughing (3.9–85%), fistula (0–2%), bladder-neck obstruction (2–55%), stricture (2.2–17%) and pain (0.4–3.1%). This was based on older CSAP techniques that have been modified/improved over the years (thermocouplers, urethral warming catheters). A review of the cryo-online data (COLD) registry noted a 4.8% rate of post-CSAP UI with a pad use rate of 2.9% at 12 months. A prospective case series noted incontinence (≥ 1 pad) in 5.6%, urinary tract obstruction in 1.9%, urethral sloughing in 5.6%, hematuria in 1.9%, perineal pain in 11.1%, rectourethral fistula in 0.9%, and erectile dysfunction in 98.1%. More recently, in a prospective study comparing whole gland CSAP to HIFU + TURP, Liu et al reported a 24 month UI rate (≥ 1 pad) of 1.6% (vs 2.5% for HIFU+ TURP, *P*=0.5).

When used as primary therapy for higher stage CAP, a 2.6% rate of *de novo* UI, 6% rate of urinary retention and 1.1% rate of rectourethral fistulization after CSAP was reported using the COLD registry.

However, the type of incontinence present after CSAP is not specified in these reports. On the other hand, Kimura et al reported that 9.5% of their patients had temporary incontinence after CSAP and 2.7% had prolonged mild stress incontinence. The presumed mechanism would be cold induced damage/necrosis of the tissues of the internal and external urinary sphincters resulting in SUI. They also noted that after CSAP there was an initial deterioration in IPSS and bother scores but these recovered at 12 and 18 months, respectively.

CSAP more recently been used in a focal fashion to treat unilateral CAP and seems to have fewer complications. A systematic review of focal CSAP reported low rates of incontinence between 0-3.6%. A recent publication from a multicenter registry reported UI (any pad use) occurred in 6% at 3 months and 0% by 6 months after focal CSAP.

CSAP has also been used as salvage therapy after XRT failure and appears to be associated with an increased risk for incontinence. In an older publication, Cespedes et al reviewed 143 patients who had salvage CSAP after prior XRT with a median follow-up of 27 months. They noted that UI occurred in 42% of patients, but resolved in 47% such that the long-term incontinence rate was 28%. In Pisters et al's review of the COLD registry they identified 137 patients who were continent prior to salvage CSAP and noted that at 12 months, 5.8% experienced incontinence without needing pads and 4.4% were using absorbent pads. A recent systematic review/meta-analysis of salvage CSAP case series reported an incontinence rate of 12-15%.

Generally, patients who undergo CSAP for prostate cancer are older and have more comorbidities than those undergoing RP.[270,] Given the previously discussed age related changes in the lower urinary tract that may predispose the elderly to incontinence following ablative/destructive procedures, the relatively low rates of incontinence that have been reported more recently after CSAP attests to the technical improvements over time.[278] Another possible risk factor for post-CSAP incontinence is TURP (either pre or post CSAP). TURP prior to CSAP has been considered a relative contraindication because of a significant risk for urethral slough due to poor coaptation around the urethral warming device.[270] This increases the risk for incontinence after CSAP, (7.6% of patients reported by Benoit et al). Some patients can also experience bladder outlet obstruction after CSAP. This can be due to the presence of necrotic tissue slough or urethral stricture. Roberts et al,[279] using SEER/Medicare data, reported that by 12 months post CSAP, 29% of patients underwent various procedures to deal with lower urinary tract obstruction. Ingrosso et al,[278] in their recent meta-analysis of salvage CSAP series, reported a urinary obstruction/retention rate of 5% (95% CI 2–9%; I2 = 86%). While TURP will alleviate the obstruction/retention issues, it carries a risk for incontinence. This is particularly problematic in the context of salvage CSAP after XRT. In Cespedes et al[276] series (using older cryo techniques), 60% of patients needing TURP after salvage CSAP developed UI.

2.2.2.14. HIFU

HIFU is a minimally invasive modality to treat CAP that uses high intensity ultrasound to selectively destroy prostate tissue (cancer) via coagulative necrosis. Despite its focused nature, it can also be associated with functional lower urinary tract complications. Three systematic reviews/meta-analyses reported similar findings with respect to adverse effects of HIFU. Warmuth et al reported bladder neck/urethral stenosis/stricture in 2–17%, prolonged urinary retention in 3–14%, urinary tract infection in 2–58%, UI in 2–34% and rectourethral fistula in 0–3%. Cordeiro et al reported urinary retention in <1-20%, urinary tract infections in 1.8-47.9%, UI in <1-34.3%, and rectourethral fistula in <2% of patients. Recently, He et al reported in their meta-analysis a UI rate of 10% (95% CI 0.06–0.14, *P*<0.00001), urinary obstruction rate of 15% (95% CI 0.10–0.20, *P*<0.00001), urinary retention rate of 11% (95% CI 0.07–0.16, *P*<0.00001) and urinary infection rate of 7% (95% CI 0.03–0.12, *P*<0.00001).

Mearini et al did UDS pre and 3-6 months post HIFU in 30 consecutive patients. Incontinence was defined as >1 pad/day and type of incontinence (UUI vs SUI) was assessed via voiding diary. At baseline, one-fifth of patients had urgency and UUI on voiding diary while on UDS DO was detected in 53% of all patients; impaired or poor bladder compliance in 30% and BOO in 23%; 1 patient had SUI. At 3–6-month follow-up, there was no difference in LUTS (IPSS) and no patient reported *de novo* SUI. However, 27% and 17% of patients had UUI at 3 and 6 months, respectively (*P*=0.341), with a significant increase in *de novo* UUI at 3 months compared with baseline (*P*=0.04). On follow-up UDS at 3 months, *de novo* DO was detected in 10% and 40% of patients had impaired bladder compliance (<20 mL/cmH_2O) compared to 30% pre-HIFU. Postoperative urethral sloughing may be etiologic in the early postoperative urinary storage symptoms after HIFU and with time this seems to improve.[285,] By 6 months, only 26% of patients showed impaired bladder contractility (BC) and 53% had DO (similar to pre-HIFU). SUI was detected urodynamically in 7% at 3 months and 3% at 6 months. Bladder capacity was unchanged. BOO was found in 10% of patients at 3 months and 3% of patients at 6 months.[285]

More recently, partial gland/hemiablation HIFU has been performed and may have less adverse effects than whole gland HIFU because of the sparing of more tissue. In their recent meta-analysis, He et al[284] reported a post-hemiablation HIFU UI rate of 2% (95% CI 0.01–0.03, *P*=0.004), urinary obstruction rate of 2% (95% CI 0.00–0.034, *P*=0.01), urinary retention rate of 9% (95% CI 0.00–0.12, *P*<0.00001), and urinary infection rate of 11% (95% CI 0.05–0.17, *P*=0.00007). HIFU hemiablation was compared to RALP by Albisinni et al in a matched pair analysis and was noted to be associated with better and faster recovery of continence (0 pads), with 82% not needing pads at 1 month postop whereas only 40% of RALP patients had 0 pad usage at 1 month (*P*<0.001). However, 13% of HIFU patients ultimately needed treatment of the contralateral side.

HIFU has also been used as salvage therapy after XRT and not surprisingly appears to have a higher rate of UI than primary HIFU. In their meta-analysis of sHIFU studies, Ingrosso et al[278] reported a UI rate of 28% (95% CI 19–38%). This rate was greater than that for sEBXRT, sBT or sCSAP. Furthermore, sHIFU had the worst rate of urinary obstruction (26%, 95% CI 15–39%). In a retrospective comparison of salvage HIFU to SRP (most were open RP), Devos et al noted that while there were no significant differences in estimated 5-year survival, sHIFU had a lower rate of complications and incontinence – at 12 months after treatment, 22.2% of sHIFU vs. 56.0% of sRP patients were using pads (*P*=0.0104).

3. INCONTINENCE AFTER SURGERY FOR BPH

Surgery for benign prostatic obstruction (BPO) may take the form of resection, vaporization or enucleation procedures. All of these can be done endoscopically with monopolar/bipolar electrocautery/plasma energy or laser energy (KTP/Greenlight, Diode, Holmium, Thulium) whereas enucleation procedures may also be performed via an open/laparoscopic approach (simple prostatectomy). Endoscopic approaches are the more commonly performed procedures and at least in the US, there has been a decrease in the use of simple prostatectomy over time.

Incontinence following BPH surgery may occur secondary to bladder and/or sphincter dysfunction (similar to post-RP) and may be transient or persistent. Sphincteric incontinence after BPH surgery is due to damage to/weakness of the external urethral sphincter coupled with the deliberate destruction of the internal sphincter/

bladder neck. The nature of benign prostatectomy is such that the bladder neck is deliberately destroyed and thus postop continence relies on the function of the more distal sphincter mechanism (at and below the level of the verumonatum). This region may be at risk with endoscopic procedures, particularly at the 12:00 position. Bladder dysfunction associated with post-BPH surgery incontinence has been postulated to have several causes: Irritation from healing of the prostatic fossa, thermal injury to the prostate capsule (especially with HoLEP), associated UTI and pre-existing DO/OAB have all been implicated in bladder dysfunction associated with BPH surgery.

Pre-existing DO/OAB may be secondary to BPO that causes elevated bladder pressure resulting in partial denervation of the detrusor leading to postjunctional denervation supersensitivity and DO. As well, it might be mediated via aberrant C fiber activity, abnormal sensory stimuli/altered prostatic urethral anatomy related to BPH, altered adrenoceptor function, neurotransmitter imbalance, neuroplasticity, or an actual myogenic deficit.[176] For further information on OAB, including neuromodulation techniques and botulinum toxin, please refer to chapter 11 (Surgery for Urinary Incontinence in Women) and 12 (Neurogenic Patients), respectively.Some patients may experience temporary incontinence after BPH surgery that improves with time postop, typically by 3-6 months (transient urinary incontinence [TUI]) and this may be sphincteric and/or bladder related (i.e., SUI, UUI, MUI). In their literature review of complications of TURP, Rassweiler et al[22] noted that early post-op incontinence is typically urge related and occurs in up to 30-40% of patients. Early postop UUI is often associated with irritative symptoms secondary to fossa healing, associated UTI or pre-existing DO caused by long-standing BPH. This will often improve. Persistent late incontinence may be iatrogenic stress incontinence and is rare (<0.5%).[22] Transient SUI and UUI are more common after HoLEP than TURP, but by 12 months they are comparable. In their review of the HoLEP literature, Shah et al[291] noted a rate of TUI between 1–44% with persistent UI in 0–2.4%. Enucleation procedures may be associated with a greater incidence of transient post-op incontinence than resection/vaporization procedures, possibly related to the more aggressive apical dissection. There is more complete removal of the adenoma and when this is done close to the external sphincter temporary damage to the continence mechanisms may occur. The retrograde dissection at the prostatic apex, particularly with transurethral enucleation procedures may stretch the inner longitudinal layer of the internal sphincter (lissosphincter) at the level of the prostate apex resulting in damage to the urethral sphincter and resultant transient incontinence. Hirasawa reported a 14% rate of incontinence at 3 months after transurethral bipolar enucleation of the prostate and they contrasted that to the rate of TUI after open simple prostatectomy of 5.6–9.4% reported by others.[,] They noted that open prostatectomy is done in an antegrade fashion (from bladder neck to prostate apex) and therefore does not stretch the inner layer of the sphincter at the prostatic apex.[297] Consistent with this is the report by Endo et al who modified the traditional retrograde approach to enucleation of HoLEP (apex to BN) to an antegrade approach (BN to apex) and saw a reduction in postop TUI from 25% to 3%. They believe the antegrade technique allows the apical gland to be removed from the sphincter without causing damage.

TUI associated with HoLEP resolves in 95–98% of patients by 6-12 months post-HoLEP (similar to TURP and PVP) and persistent incontinence after HoLEP generally occurs in about 5% or less beyond 1 year out to 10 years of follow-up.[22,,,,,]

3.1. UDS Findings

The limited number of studies that have used UDS to evaluate patients with post-BPH surgery incontinence, present mixed findings. Goluboff et al evaluated incontinence after TURP (N=31) and RRP (N=25) with UDS at a mean of 37 months post-op. They identified the cause of incontinence in TURP patients to be DO alone in 77%, SUI alone in 3% and mixed DO + SUI in 19% whereas for RRP patients 40% had DO alone, 8% had SUI alone and 52% had mixed. Thus, DO was the most common UDS findings after TURP occurring in 97% of incontinent patients in this study. Older age (>75 years) and the presence of neurological disease were more prevalent in the post-TURP patients with DO. On the other hand, Winters et al in a similar study of incontinent patients at least 1 year (mean 6.4 years) post-TURP (N=27) or post RP (N=65) found that sphincteric incontinence was the most common finding occurring in 93% of post TURP patients (44% had isolated SUI, 48% had SUI + DO) and 99% of post RP patients. More TURP patients than RP patients had DO (57% vs 29%, *P*=0.019) but isolated DO was present in only 7% of post-TURP patients. Not surprisingly, the TURP patients were significantly older (74 years vs 68 years, *P*=0.03). Theodorou et al also identified mixed findings after BPH surgery in their review of 56 patients with incontinence noting that while 41% had isolated DO or SUI, 43% had mixed incontinence and/or associated pathology (e.g., BOO) making them more “complex” cases. More recently, Bruschini et al[290] compared symptoms and UDS findings in incontinent patients after TURP (N=81), open simple prostatectomy (N=44) and RRP (N=21) at a mean of 21 months post-op. The symptom of SUI was noted in 43%, 73% and 52% of TURP, open prostatectomy (OP) and RRP patients respectively, whereas UUI was noted in 16%, 2% and 2% and total incontinence in 40%, 25% and 47%, respectively. On UDS, SUI was detected in 67%, 80% and 86% of TURP, OP and RRP patients, bladder dysfunction (DO and/or decreased compliance) in 59%, 57% and 57% patients (isolated DO in 16%, 14% and 10% of patients [*P*=0.848]), mixed incontinence (SUI + DO) in 10%, 21% and 14% and isolated decreased compliance (<12.5 mL/cmH_2O) resulting in incontinence in 14%, 5% and 0% patients, respectively. On logistic regression, there were no significant differences in the UDS findings between the different surgical approaches. However, age was a significant predictor of bladder dysfunction (DO and/or decreased compliance).

Studies reporting postop UDS that document DO and SUI are less common after laser BPH surgery and tend to include patients who aren’t incontinent. UDS was performed pre and postop after Greenlight PVP in 45 men with UD proven BOO by Hamann et al. They reported the incidence of DO dropped from 22% preoperatively to 11% after 3 months and to 9% after 12 months. *De novo* DO was found in 4% at 3 months and this reduced to 2% by 12 months. SUI did not occur in any patient. Nomura et al compared PVP to TURP in a prospective study using UDS and found similar improvements in outcome variables between the procedures within 12 months. Pre and post OP DO was present in 49% and 27% (*de novo* in 8%) of PVP patients and 53% and 29% (*de novo* in 8%) TURP patients, respectively. Transient SUI was noted in 1.3% after PVP and 2% after TURP (1 patient each group) and resolved by 6 months.

Naspro et al, in their review of the literature from 2006–2008, reported on the types of postop incontinence (not based on UDS) and noted rates after Greenlight PVP (with 6-60 month follow-up) of: UUI in 0-26% and SUI in 0-3%. For HoLEP they noted (with followup > 2 years): SUI in 0.6-3.2% and UUI in 0-28%.

3.2. Risk Factors for Incontinence After BPH Surgery

Similar to RP, both surgical and patient factors have been reported to be possible risk factors for incontinence after BPH surgery.

3.2.1. Surgical Factors

3.2.1.1. Surgical Approach

Broadly, surgical management of BPH can be classified into 3 categories based on their mechanism prostate tissue removal: resection procedures (e.g., M-TURP, B-TURP, ThuRP), vaporization procedures (PVP) and enucleation procedures (HoLEP, ThuLEP, DiLEP, TUEB, simple prostatectomy). All are reasonable options for small to large prostates (<90cc) but for very large prostates enucleation procedures are generally favored.[,] A meta-analysis of 31 publications involving 26 RCTs with a total of 3283 patients compared enucleation procedures (HoLEP, ThuLEP, PKEP, DiLEP [diode laser]) to resection procedures (m-TURP, b-TURP).[292] Efficacy was not different between groups with respect to IPSS and Qmax at 24 months postop (although, at 12 months better results were noted in the enucleation group). While resection procedures took less operative time, enucleation procedures had a shorter hospital stay. There were no significant differences in postop UUI or SUI between enucleation and resection groups although UUI did occur more frequently in PKEP compared to B-TURP groups.

In addition to the different mechanisms of prostate tissue removal, there are different energy sources that can be used: monopolar/bioplary electrocautery (TURP), plasma, laser (KTP, Holmium, Thulium). A recent systematic review/meta-analysis of 27 studies (4382 patients) compared lasers (HoLEP, thuLRP/ThuLEP, DiLEP) to bipolar technology (resection or enucleation) and determined that there were no significant differences between lasers and bipolar technology in the maximum flow rate (Qmax) and international prostate symptom score (IPSS) at a minimum of 3 months after treatment or in complications, including urethral stricture, urinary incontinence, urinary tract infection, re-catheterization and blood transfusion. In a systematic review and meta analysis of 69 randomized trials of different transurethral procedures for BPO, Cornu et al did not find a difference in efficacy or postop incontinence rates between monopolar and bipolar TURP, although B-TURP had fewer perioperative complications. A recent Cochrane review of 59 randomized trials (8924 participants) similarly found no difference in the risk of postop incontinence between M-TURP and B-TURP, although B-TURP slightly reduced TUR syndrome and blood transfusions.

Other meta-analyses have similarly shown no difference in incontinence between PVP vs TURP [Zhou et al did a meta-analysis of 4 randomized trials involving 559 patients comparing PVP to TURP and found no difference in the postop incontinence rates] and ThuLRP vs TURP [Jiang et al did a meta-analysis of 6 studies comparing ThuLRP to TURP and found that while ThuLRP was associated with less transfusion and shorter catheterization time, it had a longer surgical time. However there was no difference in postop UI (UUI, SUI)].

Open simple prostatectomy was historically the gold standard for large BPH but its use has been supplanted by the various endoscopic/energy modalities. The 2010 AUA guidelines for the management of benign prostatic hyperplasia in their review of publications on open prostatectomy from the early 2000s, noted that incontinence was reported at rates between 0.5% and 8% (confirmed).

More recently, Ugwumba et al reported on their results using open prostatectomy (transvesical) in the developing world and noted transient UI in 11%. In a randomized trial comparing TURP, TUVP, BPEP (bipolar enucleation) and OP, Geavlete et al found no difference in incontinence at 1-12 months between groups.

Simple prostatectomy can also be performed laparoscopically and by 2012, about 5% of simple prostatectomies were done in a minimally invasive fashion.[289] Using an extraperitoneal laparoscopic approach in 51 patients in which the prostatic urethra is preserved, Xing et al had a 0% rate of postop incontinence following simple prostatectomy as well as preservation of erectile function and antegrade ejaculation. When they compared LSP to bipolar TURP in a randomized trial, they noted transient incontinence (resolved in 1 month) in 2.8% of LSP vs 9.3% of b-TURP patients.

Table 2 shows results of various publications on BPH surgery with respect to postop incontinence.

3.2.1.2. Surgeon Experience

Surgeon experience influences operative time and complications including capsular perforation, urethral stricture and potentially incontinence ratres (especially for enucleation procedures).

Yang et al reported the learning curve of DiLEP was 20 cases. Shah et al noted that the HoLEP learning curve takes about 50 cases. Shigemura et al found that increasing surgical experience significantly contributed to surgical time, enucleation time and postop incontinence after holmium laser enucleation. They identified a learning curve of at least 20 cases. This is consistent with Kobayashi et al who noted enucleation time >100 min to be associated with postop UI).

3.2.2. Patient Factors

3.2.2.1. Age

Multiple studies over the years have identified increasing age to be an independent risk factor for incontinence following BPH surgery. Bae et al[302] noted that age was an independent predictor of postop UUI in patients undergoing PVP, while Hirasawa et al[297] and Xu et al noted age to be an independent predictor of transient urinary incontinence after endoscopic enucleation (bipolar, PK). Several studies have shown increasing patient age to be a significant predictive factor for TUI after HoLEP.[,]

Aging might be a factor because of an increased incidence of bladder dysfunction (e.g., DO) that is associated with increasing age.[290] Bruschini et al[290] calculated that each additional year of age increases the likelihood of bladder dysfunction by 5% and bladder dysfunction was 2.3 times more likely in patients older than 70 years (P=0.017).

Aging is also associated with decreasing external sphincter muscle function as demonstrated by Strasser et al[96] and thus might even be a contributor to post-BPH surgery SUI. Nam et al showed that advanced age and longer operative time were significant risk factors for TUI after HoLEP.[330] They suggest that compression, stretching, and tearing by the resectoscope during the operation coupled with the reduced sphincter muscle (atrophy) that occurs with aging may be the reason why age appears to be a risk factor for incontinence.[330]

3.2.2.2. Obesity/Metabolic Syndrome

Obesity and MetS appears to be associated with benign prostatic enlargement. Gacci et al in a systematic review and meta-analysis found that patients with MetS had significantly higher total prostate volume when compared with those without MetS (+1.8 mL,

95% CI 0.74-2.87; *P*<0.001) although no differences in IPSS. On meta-regression analysis differences in total prostate volume were significantly higher in older (adjusted R=0.09; *P*=0.02) and obese patients (adjusted R=0.26; *P*<0.005). Obesity was also noted to be associated with increasing LUTS (using IPSS) over time in a prospective study by Mondul et al. They found that the risk of LUTS and LUTS progression increased with increasing body mass index (≥35kg/m^2), waist circumference (>42 inches) and weight gain since age 21 years (≥50 lbs).

In addition to obesity/MetS having an impact on LUTS, it also appears to affect LUTS outcomes (storage symptoms) after BPH surgery. Sener et al prospectively compared men with and without MetS undergoing TURP using IPSS and uroflowmetry and found that patients with MetS had significantly higher postop IPSS and lower Qmax than non-MetS patients. Furthermore, while both groups of patients had significant improvement in QoL after TURP, the effect was greater in the non-MetS group. Obesity had a significant negative correlation with postop QoL (OR 7.286, *P*=0.043). Likewise, Gacci et al assessed LUTS using IPSS in a multicenter prospective study on men undergoing TURP or simple open prostatectomy (OP). They found that a waist circumference (WC) >102 cm was associated with a higher risk of an incomplete recovery of both total IPSS and storage IPSS. Furthermore, despite a similar resolution of obstruction, obese patients achieved only a 50% improvement in storage LUTS whereas nonobese patients had complete resolution. Elevated BMI was significantly associated with UI at 3 months (OR per SD = 1.23 [1.09-1.38], *P*>0.001) and at 6 months (OR per SD = 1.25 [1.03-1.5], *P*=0.02) after HoLEP in a retrospective study of 2346 patients.[331]

3.2.2.3. Comorbidities: DM, Neuropathy

Patients with neurologic issues are more prone to bladder and sphincter dysfunction and thus may be at greater risk for urinary storage problems after BPH surgery. Parkinson's disease has historically been a concern with respect to post-TURP incontinence. Staskin et al noted an increased rate of post-TURP incontinence (17% preop, 28% postop) and identified an association between normal voluntary sphincter control and postop urinary continence. Patients with preoperatively poor voluntary sphincter control were more likely to experience postop incontinence than patients with normal preop sphincter control (83% vs 4%). *De novo* incontinence developed in 20% and it was UUI. However, more recently Roth et al called into question this finding because of the possibility that many of those patients may have had multisystem atrophy which is more severe than Parkinson's. They reviewed 23 patients with Parkinson's disease who had TURP for BPO and of 10 with preop UUI, 8 had improvement or resolution post TURP. Furthermore, no patient developed *de novo* UI after TURP at a median followup of 3 years. They argued that Parkinson's is not a contraindication to TURP provided that BPO is proven. However, their patients were predominantly stage 2 Parkinson's (none >3) and thus were on the milder spectrum of disease.

Diabetes may be associated with OAB/DO in its early stages and thus may be a contributor to these issues after BPH surgery. However, Elmansy et al reported that the presence of diabetes mellitus was also a statistically significant predictor of post-HoLEP SUI and posited that the pathophysiology might related to the effect of DM on the nerve supply to the external sphincter. Diabetes was the main predictor of UI at 6 months post-HoLEP in a retrospective review of 2346 patients.[331]

3.2.2.4. Preop LUTS/Bladder Dysfunction

Abrams et al identified DO in 60% of patients prior to prostatectomy that decreased to 25% postoperatively. Machino et al noted in 62 patients undergoing TURP for symptomatic BPH that preoperative DO associated with BOO is more likely to resolve after TURP (73%) than preoperative DO without BOO (40%) and patients with preoperative DO without BOO have significantly worse symptomatic and overall outcomes after TURP. De Nunzio et al[294] followed 101 patients with urodynamic BOO who underwent watchful waiting, medical management (alfuzosin/finasteride) or surgery (TUIP, TURP) with repeat UDS at a mean of 2 years. They found DO at baseline in 52% overall and 40% at followup. The watchful waiting and medical management groups as well as the TUIP group showed no significant change in prevalence of DO on followup UDS whereas in the TURP group prevalence of DO decreased from 68% at baseline preop, to 31% at follow postop (*P*=0.02). This would be consistent with DO resolving after improvement in BOO caused by the BPH.

However, DO is not always associated with BOO and may be a consequence of aging itself. In a study on UDS in healthy elderly males, Andersen et al identified DO in 53% on UDS and a lack of correlation between BOO and DO. Gormley et al evaluated elderly males (mean age 80 years) with pre- and post-TURP UDS. All had DO preoperatively and it persisted postop in in 92%. They suggested that in the elderly, DO is age related and not necessarily due to BOO. Antunes et al noted that in 46 BPO patients undergoing TURP, older age was more common in patients with preop DO (65 vs 61 yr, *P*=0.041) as well as those with persistent DO postop (69 vs 63 yrs, *P*=0.043). Consistent with all of this is the fact that DO may recur after several years after prostatectomy despite sustained reduction in BOO (noted in 40-64%).[94]

It is possible that there is a sensory neural issue at play. Chalfin and Bradley were able to abolish urodynamic DO in patients with BOO by administering a prostate nerve block (that does not alter BOO). This suggests a possible abnormal afferent effect from the prostate (possibly secondary to the BOO), may be responsible for DO. Rather than via reduction of BOO with surgery, it is possible surgery causes a "deafferentation" of the afferent neurones responsible for initiating the involuntary detrusor contractions characteristic of detrusor overactivity and causing symptoms of overactive bladder.[176] This theory is consistent with why TURP can be effective in improving LUTS in patients without actual urodynamic obstruction. De Nunzio et al[294] noted that TUIP and TURP significantly reduced BOO, but detrusor overactivity was permanently reversed, with fewer *de novo* cases in the TURP group. The finding could be explained by TURP resulting in greater destruction of the prostatic urothelium and submucosa compared to TUIP.[176] Consistent with this is the finding in the CLAasP trial, that compared conservative therapy to standard TURP and a side-fire laser (vaporization) treatment of BOO, that laser was as effective as TURP in reducing preoperative overactive bladder symptoms and urodynamic detrusor overactivity, despite being a significantly poorer procedure at reducing BOO. Furthermore, Van Melick et al, in a randomized trial comparing TURP, contact laser prostatectomy and electrovaporization, noted a 50% resolution of preop DO on 6 month postop UDS in all groups.

However, OAB/DO may be an adverse risk factor for post-BPH surgery outcomes, especially when not associated with BOO. Dybowski et al evaluated 76 patients who had PVP for UDS proven BOO using IPSS and noted that while the incidence of moderate or severe storage LUTS decreased over time, the presence of preop urgency was predictive on multivariate analysis of persistent storage symptoms 6 months postop (OR 5.7, 95% CI, 1.41-23.16;

P=0.014). Seki et al also found that greater preop storage symptom score (IPSS) and presence of preop DO were negative predictive factors for QOL improvement after TURP. Kim et al compared patients with high preop storage symptoms (IPSS storage score ≥8) to those without (IPSS storage score <8) who underwent TURP and found that at 12 month follow-up, those with high preop storage symptoms were more likely to have persistent symptoms and significantly worse QoL. Bae et al[302] noted that preop OAB issues predisposed patients to transient postop *de novo* UUI after Greenlight PVP. They reported that *de novo* UUI occurred commonly early in the early postop period (43% of patients at 1 week) but improved over time such that by 1 year 0 patients had it. On multivariate regression, they identified older age, higher symptom scores (including higher total OABSS), small volume at first desire to void and smaller cystometric capacity on preop UDS were independent predictors of *de novo* UUI. Machino et al[341] reported less favorable efficacy after TURP in patients with preoperative DO without BOO. They noted more persistent DO postoperatively in patients without preop BOO (60%) than in those with BOO (27%). Choi et al, on multivariate analysis, identified worse initial storage symptoms (OR=8.32), impaired detrusor contractility (OR=2.96), small bladder capacity (OR=4.31) and age (OR=1.05) were significantly associated with persistent (at 6 months) storage symptoms (IPSS storage score >7) after TURP. Zhao et al identified that the pattern of DO may play a role in persistent OAB symptoms after TURP. Preoperative terminal DO (as opposed to phasic DO) was associated with worse postop OAB symptoms (including UUI).

3.2.2.5. Prostate Size

Xu et al[328] and Hirasawa et al[297] reported prostate volume to be an independent predictor of transient urinary incontinence after endoscopic enucleation of the prostate (PK, bipolar). In addition to prostate volume (>81g) being an independent predictor of post-HoLEP TUI (SUI), Elmansy et al[339] found that a postop PSA reduction of >84% was a significant associated factor. Recently, Das et al reported that prostate volume >100g was associated with an increased risk for TUI after HoLEP and on multivariate analysis, resected prostate weight was predictive of any SUI. Hirasawa et al[297] explain that with increasing prostate volume, there will be a larger prostatic fossa following enucleation (they did transurethral bipolar enucleation) and this may cause urine trapping and leakage with stress maneuvers in the short-term. Furthermore, they postulate that the longer surgical time associated with larger prostates results in a longer period of stretch induced injury of the internal sphincter at the prostatic apex.

3.2.2.6. Preop Sphincter Function

Baseline MUCP was identified as an independent predictor of *de novo* TUI after HoLEP.[301] Furthermore, preoperative pelvic floor muscle function may help hasten the resolution of TUI. A recent randomized trial found that a regimen of preoperative pelvic floor muscle exercises (in addition to postop PFME) significantly reduced the post-HoLEP UI (any pad usage) rate at 3 months from 26% to 3%, (*P*=0.01) compared to just postop PFME although by 6 months postop there was no difference.

3.2.2.7. Prior XRT

XRT for prostate cancer before BPH surgery appears to be a risk factor for UI and is addressed in XRT section. Please see Table 2.

3.2.3. Incontinence After Orthotopic Neobladder

Urinary diversion after radical cystoprostatectomy for bladder cancer may take the form of an orthotopic neobladder (ONB) constructed from intestine (small or large). Various techniques for neobladder construction have been described and in general detubularization of the bowel and reconfiguration into a spherical pouch has been the main principle. Urinary continence after neobladder creation depends on both an intact urethral sphincter as well as a reservoir of adequate capacity and low storage pressure.

As with radical prostatectomy, radical cystoprostatectomy transects the urethra distal to the prostate and is thus similarly prone to sphincteric deficiency postoperatively akin to post-prostatectomy. In addition, depending on the bowel segment used and how it is configured, elevated storage pressures are possible, and this could impair urinary continence. Unlike after prostatectomy where in theory the guarding reflex is still intact (reflex sphincter contraction as the bladder fills, particularly overnight), after cystoprostatectomy and neobladder formation, the guarding reflex no longer exists since the bladder is made from bowel. This has ramifications particularly with respect to nocturnal continence.

ICI 6 noted daytime continence after ONB to range between 85-100% and nighttime continence between 51-100%. However, continence may deteriorate with time. Madersbacher et al published longer term results (> 5 years) of the Studer ONB using a continence definition of complete dryness or loss of no more than a few drops of urine once or twice a month on patient completed questionnaire, as well as frequency volume charts. They reported that daytime continence plateaued at 12 months with 92% being continent but there was a deterioration at >5 years: after 5 and 10 years 82% and 80%, respectively used 0-1 pads during the day. Nocturnal continence was not as good and similarly deteriorated over time: it peaked at approximately 85% at 3 years, but at 5 years, 31% were incontinent at night and at 10 years 45% had nocturnal incontinence. However, the magnitude of incontinence in most patients was no more than a few drops. Ahmadi et al, in a prospective randomized trial of T pouch neobladder vs Studer neobladder, used BCI questionnaire as well as reported pad usage at ≥12 month follow up (mean 4.5 yrs). They noted that 40% of patients had daily urinary leakage and 17% reported no control/frequent dribbling during the day. 55% of patients noted nighttime urinary leakage, 53% reported no control/frequent dribbling at night. 78% of patients used pads: 47% of patients used at least 1 pad during the day with 23% of patients using diapers. 72% of patients used nocturnal pads with 39% wearing diapers at night. However, overall, 47% of patients noted minimal wetness to their pads day and night and around 80% of patients noted no/minimal bother by incontinence and no/minimal limitation with daily activity. More recently Kretschmer et al,[217] using questionnaires and pad testing (continence equals 0-1 safety pad and ≤10g of urine loss), with a median followup of 61 months after ileal ONB, reported continence rates of 54.3% and 36.3% during the day and night respectively. Median daytime pad use was 1 pad (range 0 to 9) with median daily urine loss (pad weight testing) of 8 g (range 0 to 2400). Median nocturnal pad use was 1 pad (range 0 to 7) with median nocturnal urine loss of 28.5g (range 0 to 1220).

The etiology of ONB incontinence, similar to post-prostatectomy can be sphincter related (ISD) and/or reservoir related (hyperactivity). Koraitim et al did UDS in men after ONB (tubularized ileocecal, detubularized sigmoid detubularized ileum) and noted: MUCP showed statistically significant correlation with daytime continence whereas nocturnal continence was significantly positively correlated with MUCP and negatively correlated with maximum reservoir contraction amplitude and baseline pressure at mid and max capacity. MUCP, maximum reservoir contraction amplitude and baseline pressure at capacity were significant predictors of continence on multivariate analysis. Keszthelyi et al studied 28 patients with incontinence after ileal ONB (mean follow-up 43 months) and compared those with daytime and nighttime incontinence (total incon-

tinence) to those with nighttime incontinence only (partial incontinence). They noted significantly higher urethral resting pressures and maximum voluntary sphincter contractions in the partially incontinent patients. Furthermore, totally incontinent patients were more likely to have neobladder hyperactivity with higher pressure and longer duration contractions, and lower neobladder compliance and capacity. Thus, they had a mixed picture of sphincteric and reservoir dysfunction.

Given that intestinal contractility is mediated via the parasympathetic cholinergic system (similar to the bladder), it is not surprising that medical treatment of pouch hyperactivity (anticholinergic medication) has been shown to improve neobladder storage (including nocturnal enuresis) presumably via anticholinergic suppression of the neobladder motility. Both El-Bahnasawy et al and Zahran et al demonstrated improvement in ONB incontinence using anticholinergic OAB medication in randomized crossover studies. Furthermore, the medication was shown to significantly increase the neobladder volume (at first desire, at normal desire and at the maximum enterocystometric capacity) on UDS and decrease neobladder hyperactivity (frequency and amplitude).[361]

Decreased urethral sensitivity after radical cystectomy has also been suggested to play a role in neobladder incontinence. Hugonnet et al demonstrated that the sensory threshold in the membranous urethra is lower in incontinent patients and it was suggested that this may impair the conscious or unconscious sensation of urine leakage in the membranous urethra that would otherwise result in a reflex or voluntary contraction/increased tone of the external urethral sphincter. The higher nighttime incontinence rate that has been reported after ONB has been attributed to several factors including the absence of the guarding reflex, decreased rhabdosphincter tone and increased diuresis at night.[357] In fact in a recent study, nocturnal polyuria was found in 58% of ONB patients at a median of 3 years postoperative.

Incomplete emptying of an ONB in males has been reported on average to be about 5% but up to 43% of patients may end up catheterizing for residuals of >100mL.[365] Depending on the degree of retention, the ONB capacity may be reached in short time intervals and coupled with weakness of the urethral sphincter may result in incontinence.[365] This may especially be the case with respect to nocturnal incontinence in that the residual urine will cause the ONB to reach volumes at which pouch contractions occur (typically after 50% of actual ONB capacity) earlier during sleep and this coupled with lower urethral pressure during sleep (in part related to loss of the guarding reflex) results in NE.[365]

As with RP, both surgical and patient related risk factors for incontinence after ONB have been identified.

3.2.3.1. Surgical Factors

3.2.3.1.1. Bowel Segment (and Length)

Both small bowel (ileum) and large bowel (sigmoid) may be used to create an ONB. However, there may be an advantage to ileum. In a meta-analysis of 12 cohort studies comparing ileal ONB to sigmoid ONB, Tao et al noted that both daytime and nighttime continence rates were significantly better in IN group than in SN group: incidences of daytime continence in patients with ileal and sigmoid ONB were 74.1-97% and 66.7-90% respectively (RR=0.87, 95% CI: 0.81-0.94) and nighttime continence were 57.1-90% and 23.8-65.2% respectively (RR=0.73, 95% CI: 0.60-0.90) although SN patients were more likely to have spontaneous voiding. Furthermore, when looking at UDS results, ileal neobladders had larger capacity (WMD=-84.93, 95% CI: -160.36 to -9.50), lower pressure at capacity (WMD=11.18, 95% CI: 4.29-18.06), and better compliance (WMD=-25.55, 95% CI: -32.45 to -18.64) although post-void residual volume was also larger (WMD=-23.48, 95% CI: -36.75 to -10.21). On the other hand, El-Helaly et al recently compared sigmoid ONB to ileal ONB and found no significant differences in the continence status and spontaneous voiding between both groups. Sigmoid ONB patients had higher nocturnal voiding frequency. MUCP was significantly higher in ileal neobladder patients.

Given that adequate ONB capacity is considered essential for urinary continence, one might speculate that using a longer bowel segment to construct the ONB would be associated with better continence. However, this is not necessarily the case. Yadav et al used a modified W shaped ileal ONB made from only 25cm of ileum and reported good or satisfactory daytime (up to 1 pad per day) and nighttime (up to 1 pad per night) continence in 100% and 93.8% respectively at a mean follow-up of 27 months. All but one patient had good ONB compliance on UDS by 1 year and the mean capacity was 588mL at 3 years. Nesrallah et al, in their comparative study of 40cm small J-pouch and 60cm larger spherical pouch, found that large initial volume does not result in better continence rates at 12 months and instead predisposed to urinary retention (0% vs 19%) due to neobladder atony and progressive emptying failure.

3.2.3.1.2. Detubularization

Of major importance to ONB continence is a low-pressure reservoir of adequate volume. Detubularization of the bowel helps to achieve this.[367] By preventing transmission of myogenic activity from the intestinal longitudinal smooth muscle to the inner circular muscle, detubularization limits the intestinal contraction and intraluminal pressure elevation.[356] The pressures within tubularized neobladders are 1.8 times those of detubularized spherical reservoirs. Given that nocturnal continence depends on low internal reservoir pressure, it is no surprise that Koraitim et al[359] reported better nocturnal continence rates in ONB with detubularized compared to non-detubularized bowel.

3.2.3.1.3. Nerve Sparing

Similar to RP, nerve sparing may help post-ONB continence. Turner et al reported that daytime continence rate was significantly higher in men with attempted nerve sparing (94%) versus no nerve sparing (83%) cystectomy technique (*P*=0.003). Furrer et al reviewed 180 ONB patients with >10 year follow-up, reporting that 89% were continent during the day and 69% at night and on multivariable analysis, any degree of attempted NS was significantly associated with daytime continence (odds ratio [OR] 2.08, 95% CI 1.05-4.11; *P*=0.04) and night-time continence (OR 2.51, 95% CI 1.08-5.85; *P*=0.03). On the other hand, el-Bahnasawy et al compared NS to non-NS cystectomy + ONB in preoperatively potent patients younger than 65 using standardized questionnaires to assess daytime and nighttime continence (complete dryness without need for pads) as well as UDS. They found no difference between groups in daytime or nighttime continence. However, they did find that the NS group had significantly longer functional urethral length although there was no significant difference in maximum urethral pressures between groups. Interestingly, there was no difference between postoperatively potent and impotent patients in the NS group with respect to continence or UPP measurements which suggests meticulous apical dissection, rather than actual nerve preservation may be the key to postop continence (similar to what has been reported after prostatectomy).

3.2.3.1.4. Open vs. Intracorporeal

Palleschi et al evaluated 30 pure laparoscopic ONB (40cm ileum, U shape) patients with UDS at 180 days postop. They reported that 80% of patients were continent during the day and 64% at night. On UDS, the mean maximal capacity was 287mL and while all had residual peristaltic activity, 30% of patients had reservoir contractions exceeding 35cmH_2O and overall, 67% of these (20% overall) experienced incontinence with these contractions. 5/30 (17%) of patients had demonstrable SUI at neobladder capacity on UDS with a VLPP ranging between 44 to 82cmH_2O. 20% of patients needed CIC for PVR>100mL. Satkunasivam et al retrospectively compared open ONB to robotic intracorporeal ONB using BCI and SF-36 questionnaires and found comparable BCI scores for urinary function and bother between groups. Rates of 24-hour pad use were comparable between iONB and open ONB groups (pad-free 17% vs. 19%; ≤2 pads 84% vs. 79%). However, pad size and daytime wetness were worse in the iONB group. This might be explained by the significantly shorter follow-up in the iONB group (9.4 months vs 62 months) that may not have allowed enough time for spontaneous improvement in the iONB group.

3.2.3.2. Patient Factors

3.2.3.2.1. Age

Similar to RP, several studies have reported that increasing age may be associated with neobladder incontinence.[357,358] This might be in part due to age related decline in sphincter function, although a negative correlation between reservoir capacity and age has also been reported.[357]

3.2.3.2.2. DM

Ahmadi et al[358] noted that after ONB older patients and those with DM scored significantly poorer with respect to urinary function on the BCI questionnaire, although there was no correlation with pad usage. Kessler et al reported a lower nighttime continence rate in patients with DM which remained significantly different from that of patients without diabetes even 2 years after surgery. Furthermore, the patients with DM took longer to achieve daytime continence. It is possible that diabetic neuropathy affects autonomic nerve fibers supplying the urogenital diaphragm/sphincter or intrapelvic afferent fibers from the membranous urethra, which can lead to decreased urethral closure pressure or decreased voluntary sphincter contraction.[378]

3.2.3.2.3. BMI

Palleschi et al[375] noted that patients with a higher BMI and lower mean cystometric capacity were more likely to experience SUI after lap ONB. They suggested that the higher BMI results in less bladder expandability and more pressure on the pelvic floor.

3.2.3.2.4. Prior Prostate Surgery

De Arruda et al, using a >1 pad per day definition of incontinence, reported a 13% incidence of incontinence after ileal ONB with median follow-up of 53 months. Previous prostate surgery appeared to be associated with a greater incidence of ONB incontinence (33% vs 7%, OR=6.5, *P*=0.023).

3.2.4. Incontinence After Pelvic Fracture/Urethral Injury/ Posterior Urethroplasty/Pelvic Extirpative Surgery

Urinary incontinence after pelvic fracture/urethral injury and/or its management is uncommon, but does occur. In a systematic review/meta-analysis of the different forms of initial PFUDD management (primary realignment [PR], early endoscopic realignment [EER], initial suprapubic catheterization with delayed urethroplasty [SCDU]), Light et al reported that UI affected 8.5% of PR patients, 5.8% of EER patients, and 8.2% of SCDU patients. They noted no statistically significant difference in the rate of UI between PR and SCDU (fixed effects model; OR: 0.94; 95% CI: 0.49–1.79; *P*=0.86) or EER and SCDU (fixed effects model; OR: 1.10; 95% CI: 0.48–2.53; *P*=0.82).

Owing to the tethering of the posterior urethra to the pubic arch by the puboprostatic ligaments proximally and perineal membrane distally, this region is vulnerable to injury when there is a pelvic fracture. The proximal tethering is thought to be tighter and thus urethral disruption, if it occurs, tends to occur more distally; in fact most commonly just distal to the external sphincter at the level of the bulbomembranous junction.[17] It has commonly been thought that either the initial trauma itself or posterior urethroplasty may result in damage to the rhabdosphincter resulting in continence depending on the BN and supramontanal urethra (i.e., proximal part of the internal sphincter/lissosphincter).[17] Given this, the presence of an incompetent BN is considered a risk factor for incontinence after posterior urethroplasty. BN incompetence related to PFUDD is present in approximately 4.5% of patients. The mechanism typically involves direct injury to the BN by the sharp edge of the fractured and displaced pubic bone and typically there are fractures of both superior and inferior pubic rami on same side.[384] Boys younger than 15 years old may be at greatest risk because their small prostates provide less protection from pubic bone fragments.[384] However, while an open bladder neck on preoperative cystography can be an indicator of increased risk for postoperative incontinence (especially with a longer open bladder neck), most patients who are found to have an open BN do not experience postoperative incontinence. This may be related to varying severity of the BN injury as well as the possibility that the rhabdosphincter function may actually be preserved to some degree (probably due to the urethral disruption occurring more distally at the bulbomembranous junction). In fact, several studies have confirmed the presence of rhabdosphincter function after posterior urethroplasty.[17] Furthermore, some patients have intact support of the posterior urethra by the levator ani complex (despite the trauma and surgery) and therefore can have a pelvic muscle contribution to urinary continence.[388]

Similar to a BN injury at the time of pelvic fracture being a risk for incontinence, a history of BPH surgery such as TURP is a risk factor for incontinence after posterior urethroplasty. Given that TURP destroys the internal sphincter/lissosphincter, there is reliance on the external sphincter for continence. If posterior urethroplasty is needed for a proximal bulbar/bulbomembranous urethral stricture, the external sphincter will be at risk for damage and consequently sphincteric incontinence.[17] Because of this concern, it has been suggested that one avoid anastomotic urethroplasty that involves urethral transection and instead use substitution urethroplasty with grafting (typically buccal mucosa).[390] A recent multicenter retrospective study of posterior urethroplasty in continent patients with a history of BPH surgery used a ventral onlay of buccal mucosa, avoiding urethral transection, and reported a stricture free success rate of 84% and incontinence (defined as a subjective incontinence or use of pads reported by the patients) in 4%. The authors felt that by avoiding urethral transection and injury to dorsal urethral tissues, they were able to preserve external sphincter function bulbar urethral blood supply. On the other hand, anastomotic posterior urethroplasty has been reported successful with relatively low risk for incontinence in patients with a history of BPH surgery. Favre et al reported on their results of anastomotic posterior urethroplasty in 77 patients with a history of BPH surgery and noted 6 (7.8%) with UI: 4 had moderate UI (defined as <4 pads/day) while 2 were severe. Interestingly, the majority of patients with UI had a history of open prostatectomy. Gómez et al recently identified a connective

tissue plane between the membranous urethra and external sphincter muscle that allowed them to mobilize the external sphincter muscle off the membranous urethra to the level of the prostate via a dorsal, bulbar artery sparing approach in order to perform anastomotic urethroplasty. With a mean follow-up of 53 months, they reported that 90% of their patients were free of stricture recurrence and 85% were continent (0-1 pad).

The corollary to this is that BPH surgery in patients with a history of PFUDD/posterior urethroplasty may similarly place patients at risk for incontinence. While there is limited data on this issue, recently a modified TURP technique involving conservative resection of the median lobe (or one of the lateral lobes if no median lobe was present) with avoidance of resection of the circular fibers at the bladder neck was reported to maintain continence in 5 patients.

3.2.4.1. Pelvic Extirpative Surgery

Radical non-urologic pelvic surgery (e.g., for rectal cancer) may affect genito-urinary function. This is typically attributed to anatomical changes within the pelvis or autonomic nerve injury leading to an impairment of the parasympathetic innervation to the detrusor muscle or the sympathetic innervation to the bladder neck, trigone, and urethra. Damage may result from ischemic injury, nerve stretching, thermal damage, local inflammatory effects, and ligation of sacral splanchnic plexus or hypogastric nerve. When parasympathetic nerves are damaged the bladder may become non-contractile (detrusor hypoactivity) and this may result in urinary retention with overflow incontinence. Sympathetic denervation may result in reduced closure/resistance of the bladder neck/internal sphincter that may contribute to SUI. In addition, damage to the pudendal nerve or its branches may compromise the striated external sphincter and similarly contribute to SUI.[397] In many publications, the issue of bladder dysfunction after colorectal surgery refers to incomplete bladder emptying/urinary retention and this has been noted in 30-60% of patients after APR or LAR.[395] Most cases are short lived. In a non-systematic review, Panteleimonitis et al reported that urological function tends to deteriorate in the early postop period but recovers with time (6-12 months) irrespective of surgical modality (open, lap/robotic). In a systematic review of 89 studies from 2005–2015, Dulskas et al reported that sexual function is more commonly affected after rectal surgery than urinary function with urinary dysfunction (mainly urinary retention) occurring in approximately one-third of patients after rectal cancer surgery. They noted that the main cause of the dysfunctions is damage to the pelvic nerves that can occur during rectal mobilization from adjacent structures as well as indirect injury via traction. The preservation of autonomic nerves has been associated with a reduction in the incidence of postoperative urinary dysfunction.[395] Surgical experience/learning curve (*P*=0.019), male gender (*P*=0.006) and T stage (T1-2 vs T3-4) independently impacted identification of pelvic nerves intraoperatively and thus impacted postoperative function.

There is conflicting data as to whether or not lap/robotic surgery result in better nerve preservation and urinary functional outcomes compared to open surgery.[395,399]

3.2.4.1.1. Climacturia

Climacturia is incontinence that occurs with orgasm and was first reported in 1996 by Koeman et al. It has been most commonly associated with radical prostatectomy; although, it has also been reported after cystoprostatectomy with neobladder. In a recent literature review of orgasmic dysfunction after radical pelvic surgery (RP, cystoprostatectomy with neobladder, colorectal surgery), Haney et al noted that climacturia has been reported after RP in 20-93% whereas after cystoprostatectomy the rate is 6-45% and it has not been quantified after colorectal surgery. Clavell-Hernanez et al, in their review similarly noted a wide range in post-RP prevalence of climacturia but most data suggested 30%. Climacturia is a separate entity from SUI and UUI and it often bothers patients with up to 48% of patients with climacturia experiencing significant bother from it. Mitchell et al evaluated 1459 men who underwent open RP and using UCLA-PCI questionnaire noted that 44% of patients reported bother from sexual incontinence (not specified if this was orgasm associated) at 3 months postop and this decreased to 36% at 24 months. While bother from incontinence during sexual activity and from SUI were strongly associated at all times (~ 50% of patients with bothersome sexual incontinence also had bothersome day to day incontinence), 10% of sexually incontinent patients had no daytime incontinence at all. Similarly, Nilsson et al assessed postop climacturia using a questionnaire in 691 sexually active men post RP (open or RARP) and found that 39% had climacturia but 86% of these patients were otherwise continent. Furthermore, 28% of patients who had daytime incontinence, did not have climacturia. Prior TURP (RR 1.4 [95% C.I. 1.0–2.0]), self-assessed loss of penile length (RR 1.4 (95% C.I. 1.1–1.7) and postop erectile dysfunction (RR 1.3 [95% C.I. 1.1–1.6]) were risk factors for climacturia. Choi et al similarly reported that postop penile length loss was a predictor of climacturia as was orgasm associated pain.

Surgical approach (open RRP vs RALP) does not appear to matter with respect to the incidence of climacturia, but RALP is associated with a greater and faster recovery from climacturia over time (8.5% vs 5% at 24 months, 48% vs 15% at 84 months, *P*<0.01).

The pathophysiology of sexual incontinence is very similar between men and women and is influenced by injury to the pelvic and pudendal nerves, pelvic floor and external sphincter incompetence, and detrusor overactivity. It has been suggested that removal of the internal sphincter (ie BN) during RP combined with external sphincter relaxation that normally occurs with ejaculation might be responsible for climacturia.[401] However, arguing against this being the sole mechanism is the fact that climacturia is not as common as one would expect after RP (since the BN/internal sphincter is affected on all RPs) and furthermore, while a history of TURP (which involves resection of the bladder neck) has been implicated as a risk factor for climacturia after RP, there is a paucity of data reporting climacturia after TURP alone.

Damage to the external sphincter and support structure of the membranous urethra during RP has also been a suggested etiologic factor,[407] but the aforementioned lack of a consistent association with daytime SUI suggests other issues are relevant. Pudendal nerve/neurovascular bundle injury (direct or stretch) could also play a role in compromising sphincter function and a stretch injury could be consistent with the fact that climacturia can improve over time.[409] The fact that climacturia has also been reported with XRT suggests another process beyond surgical anatomic disruption may play a role: O'Neil et al reported climacturia in 28.3% of sexually active patients after RP alone, 5.2% after XRT alone and 28.6% after RP+XRT, while Jimbo et al[411] recently reported climacturia in 39% of patients after RP alone, 14% after XRT alone, and 52% after RP + XRT.

A study by Manassero et al reported urodynamic findings in patients with climacturia. They noted that of 84 patients who underwent BN sparing RP and were potent and continent at least 1 year postop, 24/84 (29%) experienced climacturia (at least 3 episodes of urinary leakage at moment of orgasm). Compared to 5 non-climacturic controls, climacturic patients had significantly lower functional urethral length on UDS (20 vs 35mm, *P*=0.02) and daytime con-

tinence recovery for them took significantly longer (mean 21 vs 0 weeks, *P*=0.02). While MUCP was lower in the climacturic group, it and other VUDS variables (presence of DO, Qmax, VLPP, fluoro appearance of vesicourethral junction), as well as pad testing and symptom scores were not significantly different between groups. They concluded that residual sphincter function, related to functional urethral length, may be enough for daytime continence in climacturic patients, but not for continence at orgasm. The fact that slings have successfully alleviated climacturia is consistent with a sphincteric mechanism.[409]

IV. POST PROSTATECTOMY SURGICAL OPTIONS

1. MALE SLINGS

In recent years, the synthetic male slings (MS) have gained significant popularity because of their relatively low cost, less invasive nature, as a relatively simple procedure and since patient can void normally without the need to manipulate a pump. The ideal candidate should have a mild to moderate degree of SUI with an adequate residual sphincter function and can generate a strong detrusor contraction to overcome the fixed resistance of the sling to void.

Although Berry was first to describe MS surgery, it was Kaufman who popularised one of the earlier external bulbar urethral compressive devices to treat male SUI. Nonetheless, this urinary device had poor success and high complication rates and was subsequently abandoned. Around a decade later, Schaeffer described a bulbourethral sling with Dacron bolsters placed under the urethra and suspended to the anterior rectus fascia by sutures with mixed outcomes where a third of patients required revision surgery. Poor outcomes were reported in patients who had radiation. By the early 2000s, several bulbourethral composite slings were designed and marketed with limited commercial success. John described a retropubic bulbourethral composite suspension using a porcine dermal graft secured to the bulbospongiosus muscle and a separate 1cm wide polypropylene sling that had a reported 69% cure rate but this device was associated with high intraoperative bladder perforation rate. Xu et al reported the use of a suburethral polyester patch plus a narrow polypropylene tape with around 85% successful outcome, while Wadie et al showed that revision surgery was necessary for 25% of patients who received polypropylene bulbourethral sling suspended by nylon sutures and fixed to rectus sheath.

Bone anchor sling fixation became popular in 2000 and the bone-anchored male sling (BAMS) obviated the need for any suprapubic incision for suture passage and fixation. In 2001, Madjar et al described this technique with a synthetic or cadaveric fascial sling and 86% of the 14 patients were “cured” wearing none or 1 pad at 12 months follow-up. Comiter reported a 76% cure and 14% “substantially improved” rate in 21 men with post-prostatectomy incontinence using polypropylene mesh with a mean follow up of 12 months. Follow-up study by the author showed that 65% of patients remained pad free and 15% required 1 pad per day at a median of 48 months follow-up. In a study comparing various materials for the MS (allograft dermis, allograft fascia lata, porcine small intestine submucosal (SIS) graft, synthetic mesh, and a composite of synthetic and dermis), Onur et al reported 41% of patients (46 men) were dry and 35% reported a 50% reduction in the number of pads after a mean follow-up of 17 months (6–26). The InVance male sling (American Medical Systems, MN, USA) was marketed for a short time in the early 2000s with a reasonable success rate (around 50% patients were dry, 25% improved and 25% failure rate).[409] However, the morbidity related to bone screws such as pubic bone osteitis and bone-anchor dislodgement, coupled with the emergence of more effective alternatives decreased the popularity of these BAMS resulting in discontinuation from the commercial market.

The modern MS can be divided into adjustable or non-adjustable types and repositioned under the bulbar urethra either through a retropubic or transobturator (TO) approach. Commercially available adjustable MS include Argus (Promedon, Cordoba, Argentina), ReMeex (Neomedic, Barcelona, Spain) and ATOMS (AMI, Feldkirch, Austria) while the current non-adjustable MS are I-STOP TOMS (CL Medical, France), AdVance (Boston Scientific, Minnetonka, USA) and Virtue (Coloplast, Minneapolis, USA) slings. The adjustable MS has a theoretical advantage over non-adjustable MS because the sling can be revised easily to provide further urethral compression in the event of persistent and/or recurrent urinary incontinence without the need for another MS or salvage AUS surgery. Over the years, the TO sling technique has largely replaced retropubic placement of MS as the preferred approach for sling placement due to the low intraoperative risk of bladder injury. It is thought that newer generation of modern MS not only provides direct compression of the bulbar urethra, but it also allows for proximal urethral relocation by realigning the mobile sphincter complex to provide further urethral sphincter complex coaptation.[45]

More recently, there has been increasing interest in the role of MS surgery to treat climacturia following radical prostatectomy.[409] This condition is often underdiagnosed and undertreated.[409] The role of “mini-sling” sling in treating climacturia has gained some interest recently. The use of Mini-Jupette graft was popularised by Andrianne. Yafi et al reported that Andrianne mini-jupette is a feasible surgical adjunct to inflatable penile prosthesis placement in subsets of patients with post-RP climacturia and/or minimal incontinence with subjectively improvement noted in 92.8% and 85.7%, respectively at a mean follow-up of 5.1 months. In a different approach using a modified Virtue mesh, Valenzuela et al[414] showed that climacturia resolved in 28 of 30 (93%), and SUI improved in 23 of 27 (85%). The mean (SD) number of pads per day for those patients with SUI decreased significantly from 1.4 (1.1) before surgery to 0.4 (0.6) after surgery *P*=0.02). However, 1 patient required sling removal for urethral erosion after prolonged postoperative catheterization.

There are very few studies comparing the nonadjustable vs the adjustable MS procedures. Whereas the adjustability does not appear to increase the overall efficacy of the continence surgery, it does, by definition, also increase the need for surgical revision/tightening to ensure on-going urinary continence. Furthermore, it does not appear that mechanical adjustability improves continence compared to a fixed male sling placed with proper tension and/or adequate fixation. Chung et al reported that more men chose adjustable over non-adjustable MS when given the options despite no significant difference observed in the clinical outcomes and similar patient satisfaction rate.

1.1. Argus sling (Promedon, Cordoba, Argentina)

1.1.1. Manufacturer and Commercial Data

The Argus male sling was first released by Promedon as a retropubic MS in 2004 before the TO version known as Argus-T was introduced several years later.

1.1.2. Device

The Argus suburethral sling consists of a silicone foam pad for compression of the bulbar urethra, two silicone columns of multiple conical elements and silicone washers that allow for regulation of the desired tension on the bulbar urethra (Figure 1 and 2).

1.1.3. Surgical Techniques

The original Argus sling arms are implanted in a retropubic approach while the newer Argus-T arms allow for a TO sling placement (Figure 3).

The Argus sling is usually tensioned to a recommended maximum intra-operative retrograde leak point pressure of 45 cmH_2O, and in the event of persistent or recurrent SUI, the sling can be tightened through a small non-invasive incision and the silicone washers can be readjusted over the silicone arms to provide further urethral compression (Figure 4).[436]

1.1.4. Clinical Outcomes

Romano et al reported that 31 out of 47 patients (66%) were dry at 3-year follow-up with 6 patients improved to 1 pad per day and 10 patients had failures (2 or more pads per day). Of the 10 patients who failed, nine had their sling removed; six because of erosion and three were related to infection.[437] In 2011, three other studies analysed short-term outcomes of the Argus male sling showed similar device explantation rates around 16% (37 of 225 patients across three studies), with the majority due to erosion (19 out of 37 devices) followed by infection (11 out of 37 devices). The continence rates varied considerably depending on the exact definition but 17–79% of patients were reported dry at follow-up and most of the complications were transient and minor (Clavien grade 1/2). A larger multicentre series published by Siracusano et al[439] found that the success rate decreased with worsening baseline incontinence from 95% in mild incontinence, 78% in moderate incontinence and 70% in severe incontinence, with up to a third of patients required at least one adjustment surgery. More recently, Cotugno showed that readjusting of the tension of the sleeve is not uncommon where 5 patients required a 3 months adjustment and 4 needed 2 adjustments to improve stress incontinence.

Longer-term data by Casteleijn reported that after 5 years of follow-up, 53.3% of patients were completely dry, 71.5% reported an improvement greater than 90% and 79.6% reports an improvement greater than 50%, while the patient's satisfaction rate remained high (70 ± 21 vs.16 ± 9, $P<0.001$) and similarly, the patient's quality of life (85 ± 20 vs. 88 ± 13, $P=0.1$).

A more recent comparative study between retropubic and transobturator Argus sling showed better continence rates (33.3% vs 11.8%, $P=0.114$) with superior functional outcomes and decreased explantation rates after Argus classic compared to Argus-T. Figure 5 shows cutaneous erosion of the Argus sling.

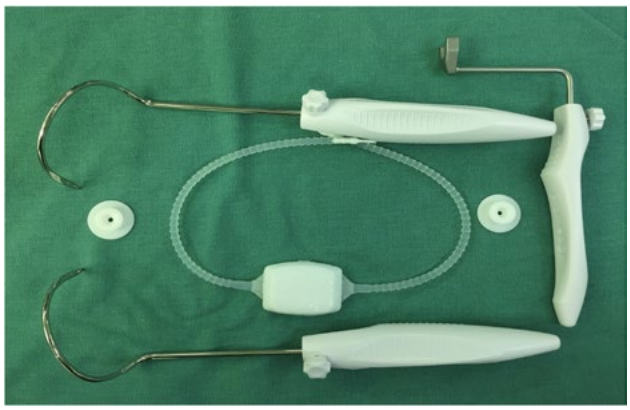


Figure 1. Argus-T Male Sling – surgical kit. Courtesy of Dr. Luís Gustavo Morato de Toledo.

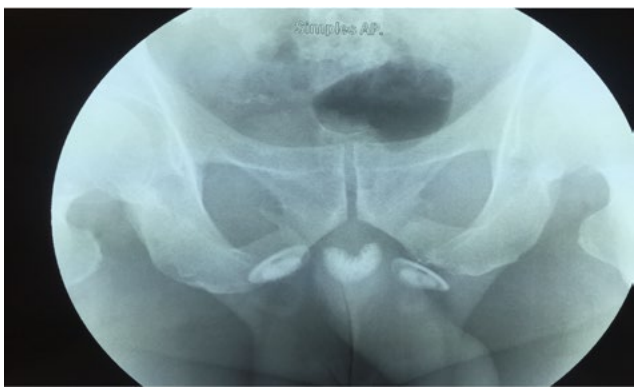


Figure 2. Plain Xray showing the Argus sling in place. Courtesy of Dr. Luís Gustavo Morato de Toledo

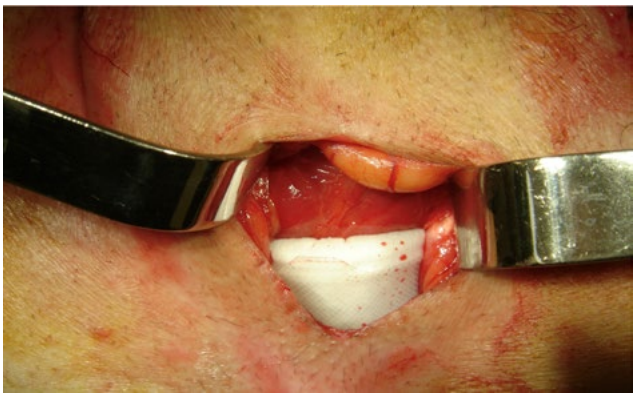


Figure 3. Argus silicone foam pad in place. Courtesy of Dr. Luís Gustavo Morato de Toledo

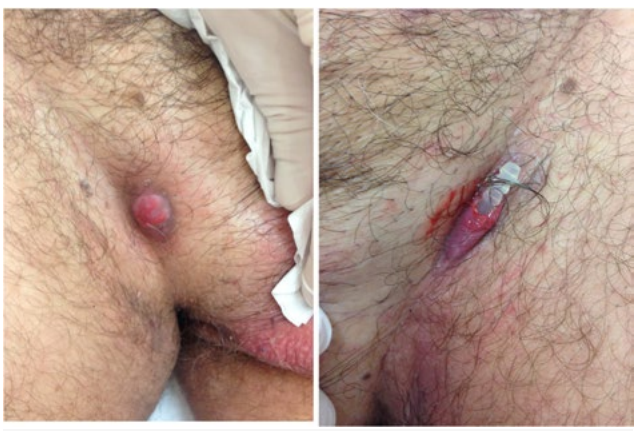


Figure 5. Cutaneous erosion of the Argus arm silicone tip. Courtesy of Dr. Luís Gustavo Morato de Toledo

Comparing inguinal-perineal incision to single-perineal incision for the Argus-T, Cornel et al showed greater infective complications in the inguinal approach compared to the single incision approach, and four patients required device explantation (three inguinal vs one single incision). Comparing Argus to Advance MS, Chung et al[435] found that 25 out of the 44 patients preferred adjustable Argus MS over the non-adjustable AdVance MS despite 6 out of 25 patients required revision surgery to tighten the Argus MS, and 23 out of 25 Argus patients were socially continent vs. 16 out of 19 with AdVance sling at 2 years postoperatively with similar improvements in quality-of-life domains. In a smaller study, Lima et al showed a slightly superior outcome for Argus-T compared to AdVance MS but this was at the expense of an increased rate of explantation of Argus-T in four patients (3 erosion, 1 pain) compared to none from the Advance group. In a different study, Lim et al demonstrated relatively high success rate (one safety pad or less per day) of 85% for Argus compared to 73% in the AUS group at 2-year follow-up. Salvage surgery with AUS following failed Argus sling appears to be relatively straight forward.[445]

A recent retrospective analysis from a large cohort study by Husch with the following patient distribution of 294 (62.6%) patients received a fixed MS (109 AdVance and 185 AdvanceXP) and 176 (37.4%) had an adjustable MS (127 Argus classic or Argus-T and 49 ATOMS), persistent or recurrent incontinence occurred in 17 (5.8%) patients with fixed and 16 (9.1%) patients with adjustable MS. While there were no differences in ICIQ-SF or PGI-I detected between adjustable and fixed slings, significantly more intraoperative complications occurred in adjustable slings (P<0.001, 0.3% vs. 10.2%).

1.2. Remeex Sling (Neomedic, Barcelona, Spain)

1.2.1. Manufacturer and Commercial Data

The Remeex sling which stands for Readjustable Mechanical External device was introduced by Neomedic around 2004 and is another adjustable MS inserted under the bulbar urethra.

1.2.2. Device

The Remeex system involves a 1.5 × 3 cm polypropylene suburethral sling connected to a mechanical regulator via traction threads (figure 6A and 6B).

The mechanical regulator is a subcutaneous permanent implant (known as varitensor) and allows for adjustment of suburethral pressure from outside the body using an external manipulator.[447]

1.2.3. Surgical Techniques

The Remeex sling is inserted via a retropubic approach and a transverse suprapubic incision, for the passage of a modified Stamey needle. The two monofilament traction threads are then drawn through the passage created with the needle until the polypropylene sling mesh is in full contact with the bulbocavernous muscle without pressure. The threads are attached to the varitensor device which is implanted subcutaneously over the abdominal rectum fascia 2 cm above the pubis. The morning after the surgery, the sling is tensioned appropriately with the external manipulator (Figure 7).[447]

1.2.4. Clinical Outcomes

There are only a few studies thathave reported clinical outcomes for this device. In a prospective multicenter Phase II trial of the Remeex adjustable sling, Sousa-Escandon et al[448] reported a continence rate of 64.7% with an additional 19.6% of patients reporting improvement over baseline, but 90% of patients requiring at least 2 adjustments. More recent but smaller studies have also shown

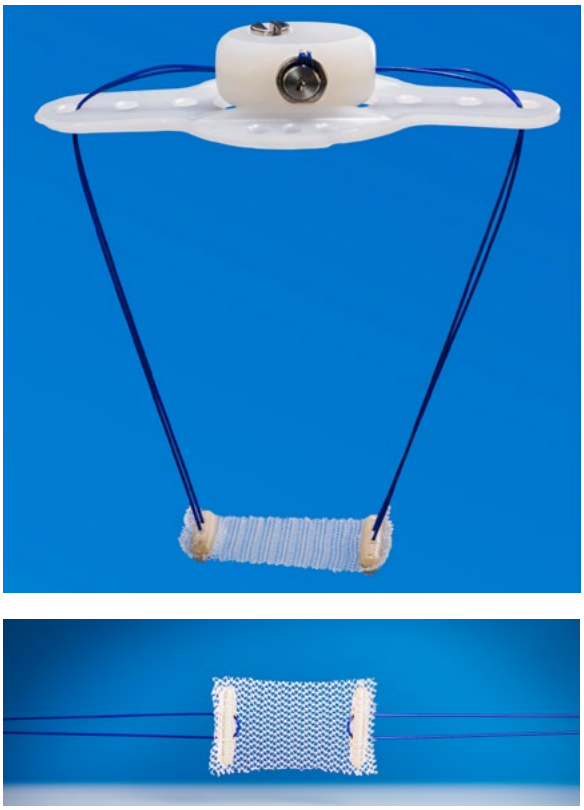


Figure 6A and 6B: Reemex system

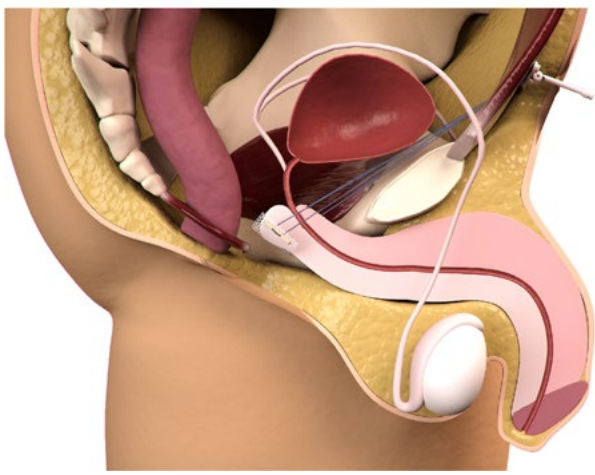


Figure 7. Illustration showing the Reemex system in place

similar outcomes.[447,448] Navalon Verdejo et al found that 3 of 5 men were dry but 4 of 5 patients experienced recurrent SUI, which was resolved after surgical re-adjustment via the varitensor, while Jimenez Parra et al reported 42% of the patients were dry and 33% reported improvement at an average of 18.6 months postoperatively. However, complications such as bladder perforation occurred intraoperatively in 29%, sling explantation was required in 21%, urinary retention occurred in 36%, and sling readjustment was necessary for 83% of patients.

1.3. AdVanceSsling (Boston Scientific Formerly American Medical Systems, MN, USA)

1.3.1. Manufacturer and Commercial Data

The AdVance MS is a non-adjustable male sling which was introduced by American Medical Systems around 2006. The AdVance XP is a second-generation TO sling released in 2010 and it incorporates several new features such as tensioning fibres, chevron anchors to limit sling slippage and altered trochars to aid placement in larger patients.

1.3.2. Device

This male sling is made of polypropylene material with 2 (outside-in) arms for TO surgical placement.

1.3.3. Surgical Techniques

The placement of the AdVance involves a midline perineal incision with dissection continued to expose the underlying bulbospongiosus muscle, which is then opened. The corpus spongiosum is mobilized from the perineal body by dividing the central tendon allowing anterior and cranial relocation of the bulb by around 2 to 3 cm when the sling is appropriately tensioned. The trochars are passed in an out-to-in fashion through the obturator foramen from a point, just below the adductor longus tendon to a point as high as possible in the triangle formed by the inferior pubic ramus and urethra. Following appropriate sling tensioning, the bulbar urethra is relocated proximally, by a distance of 2 to 3 cm, into the higher-pressure pelvic outlet, functioning as a "backstop" during straining Membranous urethral rather than bulbar urethral placement of the sling was introduced with the TO sling to relocate the urethra in a more proximal direction. This approach relies more on the rotation of the dorsal surface of the proximal bulbous urethra and indirect support of the sphincteric urethra, rather than on direct compression of the urethral lumen. The sling arms can then be pulled back to the groin wounds; the central portion of the mesh is secured to the bulb, and the sling then tensioned before wound closure under direct cystoscopy examination. Figure 8 (A, B and C) demonstrate the Advance Male Sling mechanism of action, as proposed by Rehder et al.

1.3.4. Clinical Outcomes

The original publication on AdVance sling by Rehder and Gozzi in 2007 reported an increase in retrograde leak point pressures >60 cmH_20 following appropriate tensioning of the sling along with a mean 14mm increase in membranous urethral length based on cadaveric placement and a small clinical series of 20 men. Over the past few years, there have been several case series reporting greater than 2-year follow-up. Success rates are generally between 50 and 80%, with cure/dry rates averaging 50%.[450] While an early report from the Cleveland Clinic showed a diminished efficacy over time, with patient-determined success rate decreasing from 87.3% to 62.5% with the average daily pad use more than doubling over 2 years postoperatively,[451] others have shown reasonably sustained efficacy over time.

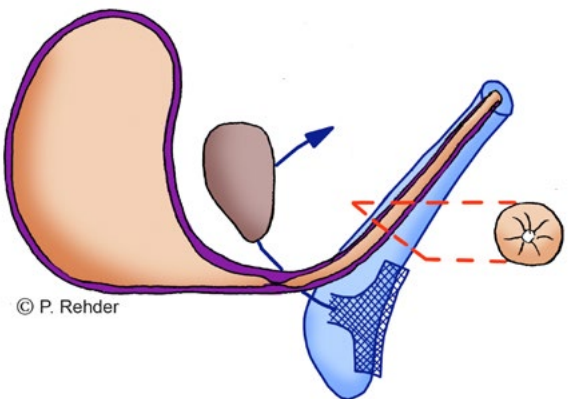


Figure 8B This figure demonstrates the relative position of the middle portion of the sling on the urethral bulb. Note the short distance of urethral sphincter closure. When scoped a half open sphincter is seen endoscopically. Courtesy of Dr. Peter Rehder

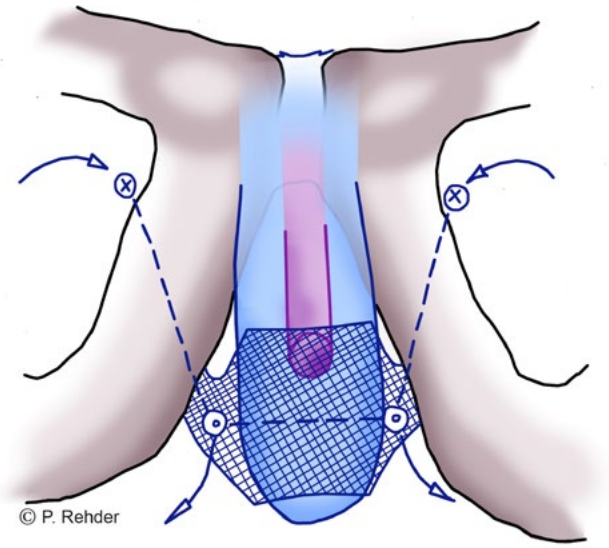


Figure 8A The arrows indicate the outside-in transobturator trocar placement. Note the retroluminal (subluminal) trocar exit site. When the sling is finally tensioned, the middle portion of the sling will double-fold in a position below the distal membranous urethra. There is no direct obstruction of the urethral lumen. Courtesy of Dr. Peter Rehder

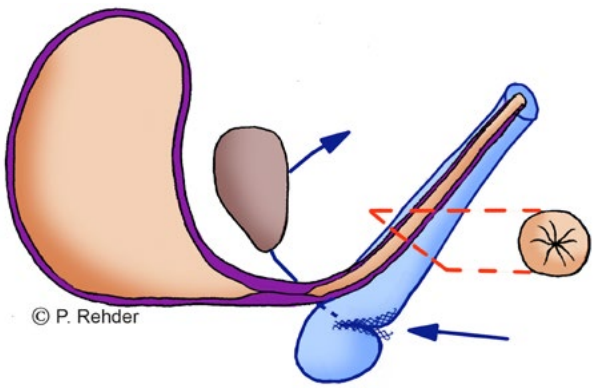


Figure 8C After tensioning of the sling, the middle portion double-folds, and in the process indenting the urethral bulb. This functional suspension, supports the distal aspect of the membranous (sphincteric) urethra. During physical activity this suburethral suspension enables better sphincter function and closure. The endoscopic view confirms better sphincter closure, and an increase in retrograde leak-point pressure. Courtesy of Dr. Peter Rehder

Over the past decade, the AdVance has become the most implanted male sling device with the largest body of literature supporting its use. In a multicentre European series, Rehder et al[456] reported results with 53.8% cure rate (dry) and 23.1% improved (using 1–2 pads with 50% reduction in pad use from baseline) at 12 months which was maintained at 3-year-follow-up with cure and improved rates of 53% and 23.8%, respectively. Using a similar definition of success (dry and 50% reduction in pad use), Zuckerman et al were not able to show similar durability of efficacy with success rates declining from 74% at 12 months to 63% at 2 years and 62% at final follow-up (mean 36 months). This finding was replicated by Li et al[455] where a progressive decrease in efficacy from the initial follow-up to 2 years with mean pad use rising from 0.8 to 1.7/day and the number of patients using two or fewer pads/day falling from 87 to 62.5%.

In another multi-centre study, Mascle et al reported 39.4% (of 66 patients) achieved continence, with an additional 40.5% improved at an average of 3 years follow-up study. Interestingly, success related strongly to the degree of preoperative leakage, with 94%, 74% and 56% achieving surgical success with mild (1 pad per day), moderate (2-3 pads per day) and severe (>3 pads per day) leakage. In another report, Serra et al found similar efficacy around 80% success rate depending on the degree of incontinence, with 86% success was achieved in those with < 100 g/d leakage, vs only 40% success in those with > 400 g/d leakage. Kowalik et al also showed a 60% cure rate and 13% improvement rate in 30 patients with median 39 months follow-up, with the finding that higher pad weight (in this report > 200 g/d) predicted surgical failure. The risk of poor durability of success with AdVance placement has been reported as particularly high in those patients with a history of radiotherapy or storage dysfunction on urodynamics with a recent series reporting a return to baseline levels of incontinence at 3 years of follow-up.[81]

Published data from the MASTER trial[6] with randomisation of 134/154 (87.0%) for male sling versus 133/158 (84.3%) for AUS showing non-inferiority (difference 3.6% [95% CI -11.6 to 4.6, PNI=0.003]), with incontinence symptoms (ICIQ-UI SF) reduced from scores of 16.1 and 16.4 at baseline to 8.7 and 7.5 for male sling and AUS, respectively (mean difference 1.4 [95% CI 0.2-2.6], *P*=0.02). Furthermore, all secondary and post-hoc analyses were in favour of artificial urinary sphincter versus TO male sling.

With the newer AdVance XP device, Bauer et al reported 66% of patients cured (no pads) and 23.4% improved at 36 months study period. Direct comparison of mid-term results between AdVance and AdVance XP has been reported by three authors[,] showed no significant differences in outcomes were seen although, in one study.[464] There was a higher rate of urinary retention observed with AdVance XP. Marzi reported that even after external beam radiation therapy, Advance XP male sling can be effective with 12 patients (21.4%) using 1 safety pad and 15 (26.8%) wearing no pad, without a significant increase in failures and complications when compared to those without previous radiation therapy. A recent long-term report on Advance XP by Mumm found that at 60-month follow up in 59 patients, there were 57.6% cured and 25.4% improved continence rate.

Reported adverse events are generally mild with transient urinary retention and groin pain being the most frequently encountered. The need for explantation is exceedingly low. In patients with a failed AdVance sling, the implantation of a second AdVance sling has demonstrated relatively good and safe outcomes with more than a third of patient requiring no pad and only 10% (3 of 29 patients) considered as treatment failures. Failure of AdVance sling can also be salvaged with AUS or prostate adjustable continence therapy.[43] However, patients with a failed primary sling who underwent a secondary sling procedure were up to 6 times more likely to have persistent incontinence compared to those who underwent salvage AUS placement. Similarly, men who suffer from recurrent UI secondary to cuff compression atrophy can be made continent by the placement of an MS without an AUS revision surgery. The advantages of using AdVance to salvage recurrent SUI in AUS patients include a lower risk of postoperative infection due to non-violation of AUS pseudo-capsule and avoiding the need to rely upon the use of the AUS to maintain continence.

1.4. Virtue Sling (Coloplast, Humlebaek, Denmark)

1.4.1. Manufacturer and Commercial Data

The Virtue quadratic “adjustable” sling manufactured by Coloplast was introduced in 2009.

1.4.2. Device

This quadratic ventral elevation urethral sling consists of monofilament polypropylene mesh that measures 5.5 cm x 7 cm with four mesh arms, 2 (inside-out) TO arms and 2 (outside-in) prepubic arm. This sling was designed to provide both urethral relocation and prepubic compression.

1.4.3. Surgical Techniques

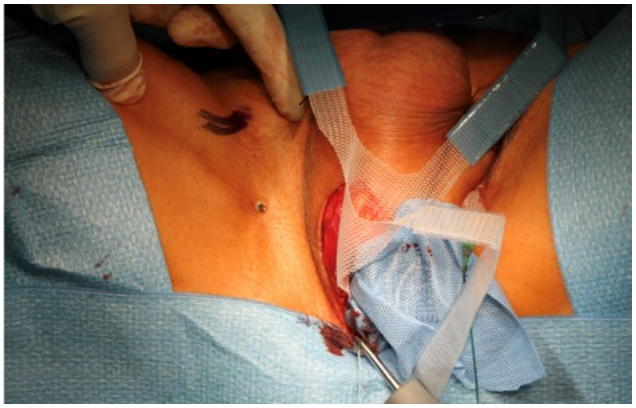
The surgical technique is similar to other TO sling surgeries. With the patient in lithotomy position a vertical perineal incision is made, dissection then proceeds to the bulbospongiousus which is retracted superiorly to allow division of the perineal body attachments and permit mobilisation. Then, the J-hook passer is used to pass through the TO space, and the TO sling arms are passed through the TO space with an inside-out technique. This is repeated on the opposite side. Next, requires the prepubic sling arms to be passed, so two small suprapubic stab incisions are made, two fingerbreadths lateral to the midline. Then, the J-hook passer is moved through the prepubic space to the perineal surgical area just lateral of the urethra. The sling is then attached and pulled through the prepubic space with the J-hook and repeated on the opposite side. The sling is then tensioned via the TO arms, then prepubic arms by using the retrograde leak point pressure, with a target pressure of 60 cmH_2O.

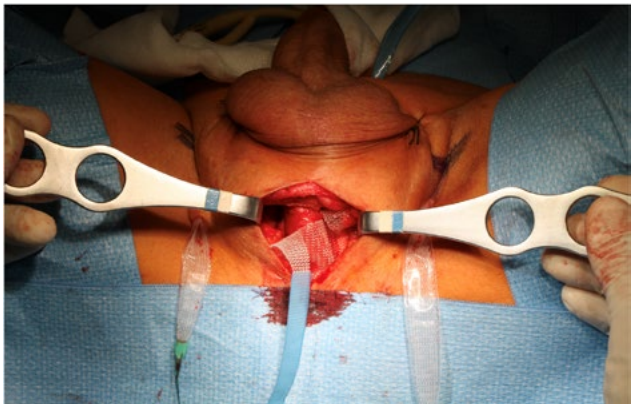
Figure 9 (A, B and C) illustrates the surgical steps for implantation of the Virtue Male Sling.

Following a lower than anticipated success rate, the surgical technique on Virtue sling placement was updated in the early 2010s with proposed tensioning of the TO arm laterally to elevate the bulbous urethra and the prepubic arms superiorly similarly to compress the bulbous urethra. Additional fixation sutures are placed onto the prepubic mesh arms to the underlying pubic bone to provide further distal urethral compression, similar to InVance sling mechanism of action.[472] The retrograde leak point pressure system is completed intraoperatively at 60 cm water pressure closure to visualise compression of the urethra as the prepubic arms are tensioned and fixated with a nonabsorbable suture.[470] The TO sling arms can be re-routed back into the perineal wound to be fixed to their opposite side to secure the mesh in place.

1.4.4. Clinical Outcomes

Comiter published the first Virtue MS study in 2012[470] followed by a larger multicentre trial in 2014[473] which compares the original sling fixation as described above and the modified technique where the prepubic and TO sling arms were fixed to their opposite side. Around 42% of the original fixation group achieved either objective





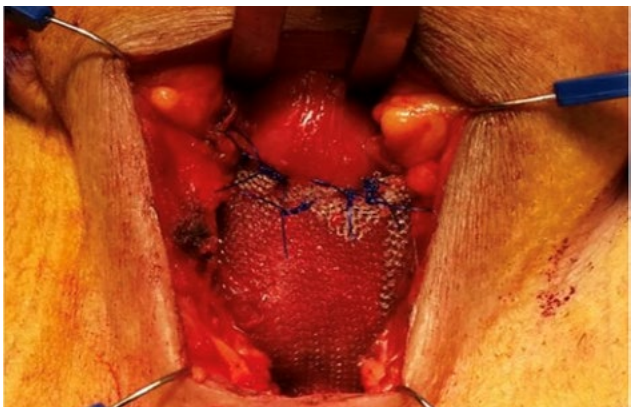


Figure 9 (A, B and C). Virtue Male sling – surgical technique

or subjective success (defined has reduction > 50% pad weight or "much" or "very much" better on the Patient Global Impression of Improvement respectively) compared to 70.9% subjective and 79.2% objective success rates in the group undergoing the additional fixation steps. Neither group developed any complications greater than Clavien grade 1 in the 12-month follow-up period.[473] Smaller studies with longer-term clinical outcomes[456,457] showed similar continence rate between 30 to 40% with relatively high failure rates requiring subsequent continence surgery. Cystoscopy-guided sling tensioning gave significantly worse continence outcome compared to sling tensioning based on retrograde leak point testing (39% vs 70%). Prior radiation therapy was strongly related to treatment failure while patient age and severity of incontinence were not significant factors. This was confirmed in a retrospective study by Abdullah et al with clinical success at 83% in 35 men. A history of radiotherapy, low bladder compliance, and severe incontinence were associated with negative result. More recently, Ferro reported significant improvement in 24-hour pad test (128.6 vs. 2.5g), number of pads per day (2 vs. 0) and ICIQ-SF score (14.3 vs. 0.9) and outcomes remained stable at 36 months, in 29 patients, most of whom had mild to moderate incontinence.

In terms of revision or salvage surgery, imbricating non-absorbable sutures can be placed into the dense fibrous mesh and tied down onto the bulbospongiosus muscle, with further tensioning based on retrograde leak point pressure of 60 cm water pressure.[472] The potential adverse events include wound infection, perineal pain and urinary retention. At the time of this review, there is no reported pubic bone osteitis in the literature.

1.5. I-STOP TOMS sling (CL Medical, France)

1.5.1. Manufacturer and Commercial Data

The I-STOP TOMS sling was developed by CL Medical in 2009.

1.5.2. Device

The I-STOP TOMS is a monofilament polypropylene 4-arms sling (2 arms on each side) measuring 4.5 cm × 1.4 cm, with a 2.8-cm central part placed over the urethra. This device was developed from the female I-STOP TO sling. Grise et al described it initially as a two-arm sling, but subsequently, the larger four-arm was released. It was proposed that the larger surface area, in addition to the fact that the sling was designed to be placed more distally, over the bulbar and post-bulbar urethra, which has bulbospongiosus coverage, would reduce the risk of erosion.[478]

1.5.3. Surgical Techniques

It is placed via a TO approach in the lithotomy position with a vertical perineal incision.[478] The perineal aponeurosis and superficial fascia are then incised, no muscle dissection is undertaken and the central tendon is not divided. The sling allows for either an outside-in or inside-out approach with the helical needle used along with blunt dissection to guide the passage through the TO space for the passage of the two arms on each side. Once in position, the sling is tensioned symmetrically after being sutured to the bulbospongiosus muscle.[479]

1.5.4. Clinical Outcomes

An early publication by Grise et al[478] based on ISTOP-TOMS (2 arms) reported that 30% of patients were dry with 32% using one pad per day with the global improvement of quality-of-life scores at 12 months follow-up.[479] In a later study, Grise et al[479] showed that patients after the ISTOP TOMS (4 arms) have higher continence outcomes with 59% dry and 20% using one pad per day at 12-month follow-up. Similar outcomes were also reported in other studies. A longer-term follow-up study by Ej-Jennane et al showed lower dry rates of 47% and 17% on total continence and one pad per day use respectively, with no report of any significant complications. Similarly, Malval et al demonstrated 40% dry rate with 77% of patients using one pad or less per day at 1 year; these figures decreased to 15% and 22% respectively at 5 years post-insertion. Furthermore, 18 patients required further surgical procedures for recurrence of incontinence, with the majority opting for AUS (12 out of 18 patients). Apart from device failure, the only other reported complication was persistent pain in one patient that lasted for more than 2 years.

1.6. ATOMS Sling (A.M.I. GmbH, Feldkirch, Austria)

1.6.1. Manufacturer and Commercial Data

The adjustable TO male system (ATOMS) sling was developed and marketed by Agency for Medical Innovations, an Austrian company that manufactures medical technology, in 2010.

1.6.2. Device

The ATOMS system is composed of a TO-placed mesh tape with an adjustable soft inflatable silicone cushion, connected to a refillable port. Adjustments are made via inflation of the silicone cushion rather than by manipulation of the sling arms. Three models have been released with different port arrangements. The original design utilised an inguinal port and the current design utilizes a scrotal port.

1.6.3. Surgical Techniques

The surgical technique involves a single perineal incision. The tunneller is placed outside in. The ATOMS device is secured in place by two mesh arms of polypropylene, which are drawn on either side through the obturator foramina and then back to the central cushion component of the implant (figure 10).

The arms are then attached to the cushion, creating a firm, 4 points fixation point. The implant is connected by a silicone tube to a silicone covered titanium port, which is placed in the scrotum; this allows for adjustment of the system's pressure postoperatively by altering the filling volume of the cushion. The suburethral substitute sphincter cushion is left in deflated state postoperative and normal saline can be injected into the port to inflate the cushion appropriately, often initially at 4 to 6 weeks post-implantation and adjusted every 6 weeks until the pressure is optimal.[484]

This is an adjustable sling that has similar components and aims to replicate a similar principle to that of the AUS, but with two major differences. It does not create a circular compression of the urethra, and secondly, it is designed for postoperative adjustment. Similar to the AUS, it is implanted in the region of the bulbar urethra, however, the bulbospongiosus is left intact as an additional protective layer between the implant and the urethra. Figure 11 shows a cross-sectional image of Atoms sling.

1.6.4. Clinical Outcomes

In one of the early studies, Seweryn et al reported that 60.5% of patients were using one pad or less per day following ATOMS insertion. Hoda et al[484] showed that 63% of their 99 patients were dry at 18-month follow-up with an additional 29% of patients reporting improvement in continence. The mean adjustments per patient were 3.8 and 4 patients had device removal due to inguinal port infection.[484] Krause et al reported a lower success rate with 38.9% achieved "social continence" and 11 (30.6%) patients underwent device removal, the majority due to infection. More recent publications with longer-term outcomes[,] have confirmed similar findings. In one of the largest studies to date, Muhlstadt et al[487] found an overall 50% of men were dry, and 32% reported improvement in continence by at least 50% with an average device adjustment rate of 3.4 ± 2.1 per person at follow-up of more than 3 years. Interestingly, similar continence and quality of life outcomes were reported but there were significantly higher complications requiring explantation in the inguinal port group compared to the scrotal port option with late infection or erosion occurred in 30 out of 37 cases (24 out of 30 from the inguinal port group alone). The pre-connected scrotal port had the lowest complication rate overall. While Friedl et al showed similar continence rates with 64% of men being dry and 26% improved, there was a 20% (56 devices) explantation rate. The majority of the removals were described as being due to titanium intolerance (41%, 23 patients), device leakage (21%, 12 devices) at the port or cushion, and infection (21%; 6 early and 6 late device infection), with device failure, reported in 8 devices.

More recently, a systematic review and meta-analysis comparing ATOMS and Pro-ACT device[7] reported a higher continence (68 vs. 55%, *P*=0.01) and improvement (91 vs. 80%, *P*=0.007) rates for ATOMS than ProACT device based on a combined data from 41 observation studies. Furthermore, the satisfaction rate was higher for ATOMS (87 vs. 56%, *P*=0.002) and explantation rate was higher for ProACT (5 vs. 24%, *P*<0.0001); although, significant heterogeneity was evidenced due to variable factors such as incontinence severity baseline, difficulties in common reporting of complications, different number of adjustments and time of follow-up and the absence of proper randomised studies.

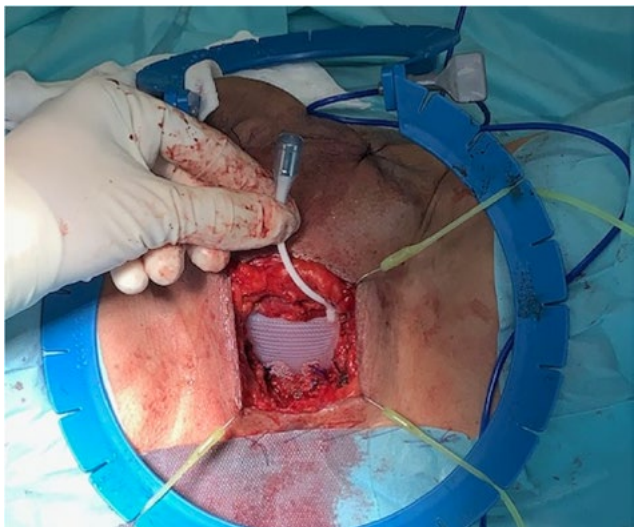


Figure 10. Atoms Male Sling. Courtesy of Dr. Argimiro Collado Serra.

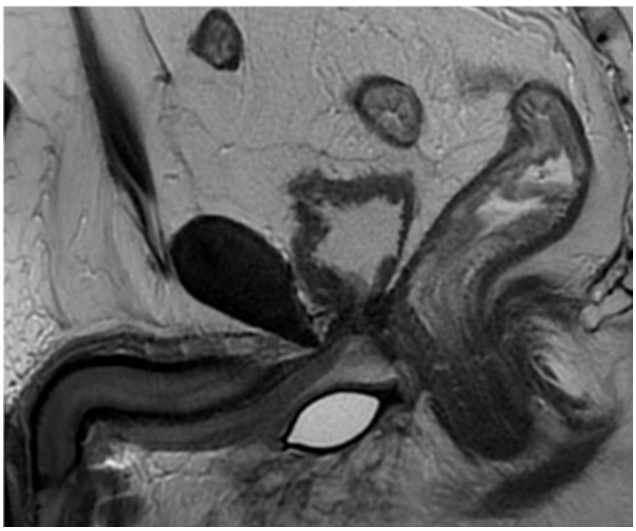


Figure 11. Magnetic resonance imaging showing the Atoms sling. Courtesy of Dr. Argimiro Collado Serra

1.7. Predictors of MS Success

The literature evaluating the efficacy of MS in patients with mild to moderate SUI is marked by heterogeneous study population, variable definitions of incontinence prior to treatment and characterizations of "cure" or "improvement" following treatment, inconsistent use of validated and non-validated outcome measures and relatively short follow-up study, as well as lack of direct comparisons among devices, making it difficult to accurately evaluate currently available MS devices. Nonetheless, in a carefully selected group of men who received MS for mild to moderate post-prostatectomy SUI following failed conservative measures, published literature shows that a majority of patients achieved cure or at least 50% improvement in social continence (as defined as at least a 50% improvement in pad weight or pad use).

There is an increasing volume of evidence in the literature pertaining to patient factors that predispose to sling surgery failure. The presence of prior urethral stricture, pelvic radiation, or prior incontinence surgery can compromise sling efficacy. These factors are associated with poorer MS outcome, probably due to urethral fibrosis, inadequate urethral coaptation and lack of proximal bulbar urethral relocation.[435,495] The presence of a more complex prior history and neurological disease can result in poorer clinical outcomes. Critical success factors for MS are good mobility of the urinary sphincter region and a good residual sphincter function.[45,429] Radiotherapy, PUBA, prior TURP, failed stem cell therapy, previous AUS placement and urethral fibrosis are all compromising factors.[429,494]

Urodynamic predictors of surgical failure include the presence of a short functional urethral length, a low maximal urethral closure pressure and abdominal leak point pressure,[61] and a negative repositioning test.[70] Preoperative incontinence severity as measured by the degree of leakage also appears to adversely influence sling outcomes. Several studies support a strong correlation between those with more severe preoperative incontinence and poorer continence outcomes.[58]

In terms of MS composition, the use of organic (resorbable) material is less efficacious than synthetic (permanent) sling material. Furthermore, failure to adhere to strict surgical principles such as poor suture fixation of the TO sling and failure to adequately tunnel TO sling arms could contribute to an inferior outcome.[473] Similarly, for the quadratic sling, improper fixation of the arms can result in a substantially lower success rate compared to sling with properly fixated prepubic and TO sling components.[473]

1.8. Conclusion

In men with mild to moderate degrees of SUI, or for patients demanding a less invasive procedure or non-mechanical device, the MS has established itself as an effective viable alternative to the AUS. When given a choice of surgery, patients have been reported to overwhelmingly choose the MS over an AUS.[59] Although high-level comparative evidence is lacking, it is generally accepted that MS shows good efficacy in mild to moderate incontinence that may be comparable to an AUS but MS represents a less favourable alternative to AUS placement in men with severe incontinence, previous radiotherapy or urethral stricture surgery. The MASTER trial is a UK multi-center randomized, non-inferiority trial comparing male sling surgery to AUS in men with any degree of SUI who are suitable for surgery may provide higher-level evidence relating to the comparative effectiveness of MS surgery. Published data showed that both surgical options result in fewer symptoms and high satisfaction, despite most men not being completely dry.[6] Secondary outcomes measures were in favour of AUS in terms of operative and postoperative details, patient-reported measures and adverse events.[6]

In the intermediate-term, the MS appears to be a reasonable option. At present, there is no conclusive evidence to suggest that one type of male sling is better than another, and there is no evidence that adjustability of the male sling offers an additional benefit over other types of sling.[435] We recommend that going forward a standard set of outcomes measures be decided upon and utilized so that future studies can be more readily compared. While the ideal MS is probably yet to be developed, continued scientific advances in slings design, mesh technology and more refined surgical techniques will improve continence rate and deliver better safety records. As clinical data mature from each of the sling designs, adequate preoperative counselling and the ability to select the optimal MS for a particular patient will hopefully improve. Strict patient selection and counselling, selection of MS with proven clinical records, and safe surgical practice are paramount to ensure high continence rate, good patient satisfaction and low postoperative complications.

(Level of evidence 3; Grade of recommendation B).

2. THE ARTIFICIAL URINARY SPHINCTER (AUS)

The first description of an AUS dates back to 1947. The modern AUS was designed by F.B. Scott, W.E. Bradley and G.W. Timm in 1974. Their original model has undergone numerous modifications, ultimately resulting in the current AMS 800 (Boston Scientific, Marlborough, MA) released in 1983 (See Figures 12 and 13).

For more than three decades, the AUS was the most popular surgical treatment for post RP incontinence due to intrinsic sphincter insufficiency, with more than 200,000 devices implanted worldwide, only recently surpassed in popularity by the male sling. The current model consists of three components: a narrow backed urethral cuff, a pressure regulating balloon (PRB), and a scrotal pump. The three components must be connected through their tubing with the help of connectors. The components are prepared free of any air bubbles and connected tightly. Since 2009, the only major change to the AUS has been the addition of a 3.5 cm cuff option.

The PRB is filled with 22-23 mL of saline or contrast and transmits pressure to the occlusive cuff. It is available in six pressure ranges from 41 to 100 cmH_2O. The most commonly used pressure is 61-70 cmH_2O. The goal of this pressure regulation is to occlude the urethra by increasing the resting urethral pressure.

The control unit or pump consists of two parts. The lower part is a bulb which transfers the fluid out of the urethral cuff to the PRB to allow micturition. The upper part contains the resistor valves and deactivation button which allows the cuff to be placed into a locked open position.

2.1. Indications

The AUS remains the most reliably effective surgical treatment for all degrees of stress urinary incontinence due to sphincter insufficiency in men resulting from various etiologies, which may include prostate cancer surgery, surgery for benign enlargement of prostate, pelvic XRT, neurological disease, trauma or congenital anomalies. Prior to 1985, a significant proportion (17–50%) of AUS devices were placed for neurological disease. However, since 1985, with increasing number of radical prostatectomies, post-prostatectomy

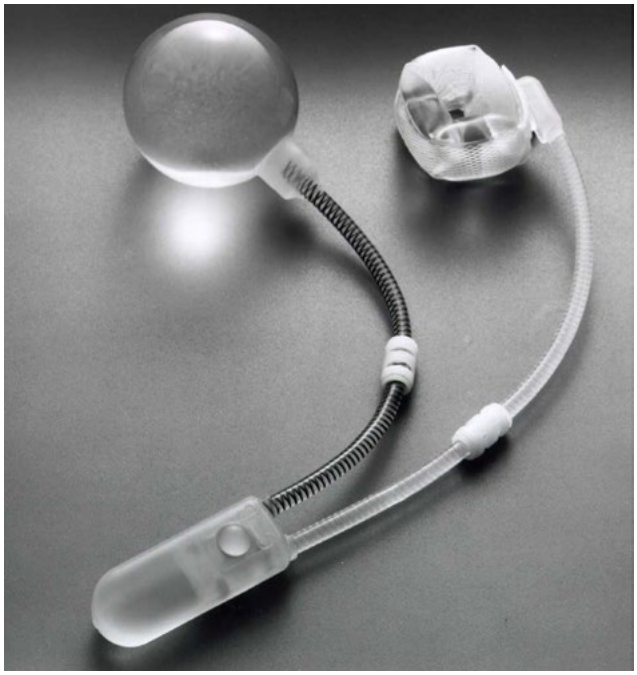


Figure 12. AMS 800. The urethral cuff is available in various sizes ranging from 3.5 to 11 cm. The narrow- backed cuff was introduced in 1987 [504,505] to improve transmission of cuff pressure to underlying tissue and to decrease the incidence of cuff erosion.[506] The cuff was later coated with InhibiZone (rifampicin and minocycline coating) in 2008 aiming to reduce the infection rates. However, a decrease in infection rates with the InhibiZone coating has not been demonstrated. [507, 508, 509]

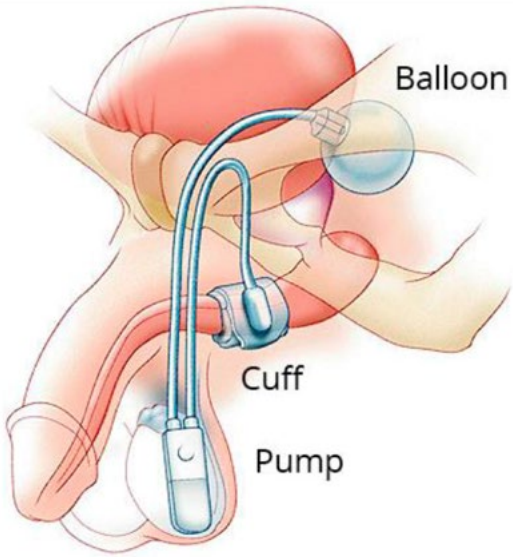


Figure 13. Artificial urethral sphincter

incontinence (PPI) has been the most common indication, representing 39%-69% of AUS placed through 2005.[513,] Indications for spinal cord disease are more common in the pediatric population with myelodysplasia.

In the era of robotic-assisted radical prostatectomy, the 12-month incidence of urinary incontinence rate varies between 4% and 31%. However, only a portion of these patients (4–6%) will have enough bother to pursue AUS placement.[,] Currently, approximately 11500 AUS are placed annually worldwide. In 2005, only 13% of US urologists performed AUS surgery, with only 4% considered high volume surgeons performing at least 20 AUS implantations per year.[513] Traditionally, active conservative management with pelvic floor muscle exercises for at least 12 months following prostate cancer treatment has been suggested in men with bothersome SUI. However, per the new American Urologic Association guidelines, patients with severe symptoms that have not improved with conservative treatment can be offered an AUS as early as six months postoperatively.[16]

The recent development and widespread adaptation of alternative surgical approaches such as the various male slings (described elsewhere) have given patients alternative surgical options. Ultimately, choice of AUS will be based upon patient dexterity, patient preference, severity of incontinence, previous incontinence surgery, history of pelvic radiation and expectations from surgery. Kumar et al[59] reported that most patients chose a male sling over an AUS and when advised to undergo a specific continence surgery, when given a choice 92% chose a sling.

2.2. Contraindications

The ability of the patient to understand and manipulate the device is of paramount importance. Patients who are unable to comprehend or lack sufficient dexterity to manipulate the scrotal pump should not be offered implantion of an AUS. Advanced age is not a contraindication to AUS placement. A recent analysis by Ziegelmann et al demonstrated that while patients over 80 years of age were more likely to experience device erosion or infection compared to men under 60, overall device failure rates were noted to be acceptably low in properly selected octogenarians. Patients with poor bladder compliance, low bladder capacity or high grade vesicoureteral reflux may be at increased risk for upper tract deterioration after AUS placement as the device increases bladder outlet resistance that would otherwise be low and protect the upper tracts.[16,82] While not necessarily a contraindication to or predictive of adverse outcomes after AUS implant,[86,88] it has been recommended that patients receive appropriate treatment for their detrusor storage pressures prior to AUS implant and be followed closely postoperatively[16,82]

2.3. Preoperative Evaluation

The evaluation should start with a detailed history and physical examination, with attention paid to duration and severity of incontinence, detailing stress versus urge symptoms, any previous surgical or non-surgical treatments, history of pelvic radiation, change/improvement in continence over time, ability to interrupt urinary stream, other associated urological disease including bladder neck or anastomotic stricture, urothelial malignancy and urinary stone disease. All patients should have urinalysis to rule out urinary tract infection, measurement of post void residual urine volume to assess for incomplete bladder emptying, and cystoscopy (or other urinary contrast studies, such as video-urodynamics) to rule out anastamotic disease (Figure 14). Further testing with multichannel urodynamic studies may be indicated in patients with suspicion of altered compliance (history of radiation, underlying neurological disease or severe voiding dysfunction)[18] or to rule out low volume detrusor overactivity in patients with mixed incontinence.

2.4. Surgical Technique

Preoperative prophylactic intravenous broad-spectrum antibiotics covering both gram negative and gram positive organisms should be administered preferably 60 minutes before skin incision. For a perineal approach, the patient is positioned in dorsal lithotomy position for bulbar urethral cuff placement. In transcrotal AUS placement, the patient is placed in frog-leg position. While traditional dictum required a five to ten-minutes surgical scrub with chlorhexidine or povidone-iodine, contemporary literature showed the use of alcohol-containing chlorhexidine or povidone-iodine preparation is effective and avoids the need for preoperative surgical scrub.

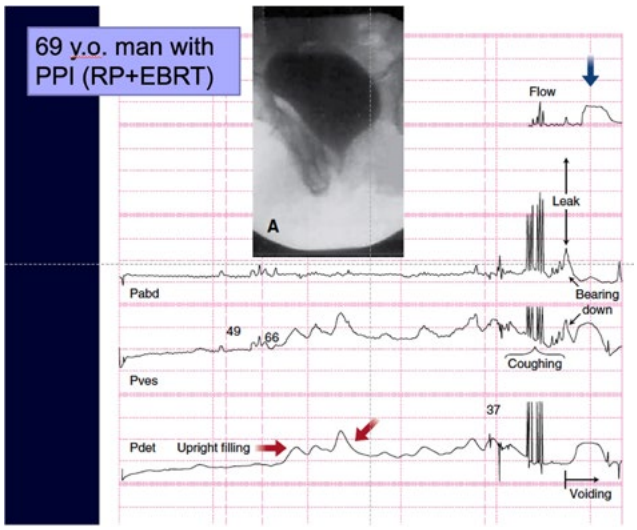


Figure 14: Videourodynamics showing an open bladder neck in a male patient that underwent radical prostatectomy (RP) and and external beam radiation therapy (EBRT)

However, another study showed that chlorhexidine scrub is more effective and is associated with lower device infection rate than a povidone-iodine preparation. The anus is isolated by covering with a sterile drape or towel to prevent any fecal contamination during surgery. A "no-touch" technique using Loban™ may be considered for draping the area. A size 14 or 16 Fr Foley catheter is inserted in the bladder to facilitate urethral palpation during urethral dissection.

The recommended initial approach for a single cuff initial device placement is via midline perineal incision (Figure 15).[18]

A lone star retractor with skin hooks is helpful for adequate exposure. The bulbo-spongiosus muscle is exposed and divided sharply or with electrocautery. The proximal bulbar urethra is dissected circumferentially off the overlying corporal bodies and a 2cm window is created on the dorsal aspect of the urethra. This should accommodate the measuring tape, which is used to measure urethral circumference, and an appropriately sized cuff is selected; the urethral catheter may or may not be left *in situ* for this measurement.

Bladder neck cuff placement is not required in patients with incontinence after prostate surgery or radiation. This surgical approach is reserved in salvage female stress incontinence cases or those with neurogenic bladders.

The pressure regulating balloon reservoir (PRB) is typically placed in the space of Retzius either in the midline or to one side, via a second incision. However, a high sub-muscular location (under the rectus) has been espoused as it avoids the scarring in the space of Retzius and/or inguinal regions related to prior surgery (RRP, inguinal hernia repair) while yielding comparable functional outcomes in comparison to traditional placement within the space of Retzius. The PRB is filled with 22-23mL of fluid, some of which will fill the cuff once connected. The fluid can be isotonic saline or a contrast mixture, the latter having the advantage of being radio-opaque and thus easily identified on plain x-ray, while the former can still be imaged via ultrasound.[67]

The pump is placed in the anterior scrotum on the side of the patient's dominant hand in an effort to avoid difficulty with pump manipulation. This is achieved by passing a long Kelly clamp subcutaneously from the abdominal wound and transferring the pump into scrotum. The cuff tubing is transferred into the abdominal wound with a needle passer in the reverse direction. The quick connector system is recommended to complete connections between the three components. At the end of the procedure, the device is left deactivated for a period of four to six weeks to allow for any scrotal swelling to decrease and minimize the risk of cuff erosion that can occur with immediate activation.

Another surgical approach has been described using an upper transverse scrotal incision for placement all of 3 components through the same incision. It also allows simultaneous placement of a penile prosthesis through the same incision. While this approach has the benefit of fewer incisions, a few reports have revealed that surgical outcomes are less favorable compared with the perineal approach. The perineal approach allows more proximal cuff placement than does the transcrotal approach, which permits the cuff to be placed on the area of the urethra with a thicker spongiosum. A multicenter retrospective study by Henry et al in 158 patients reported that patients undergoing perineal approach had higher completely dry rates as compared to trans-scrotal approach (44% vs 28%, $P<0.03$) and had much higher rates of social continence. The cuff sizes were also typically larger in the perineally placed AUS patients. Thus, the perineal approach appears to control stress incontinence better than trans-scrotal approach, and is therefore the recommended technique for initial AUS placement when penile prosthesis is not concomitantly planned.

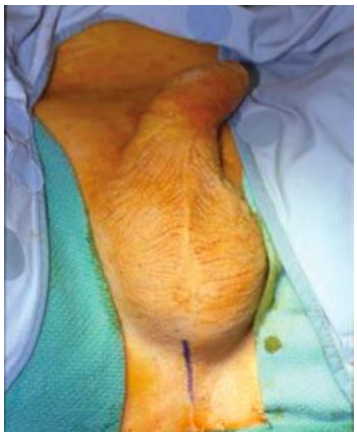
2.5. Outcomes

The AUS has the longest track record of success for the surgical treatment of PPI and appears to be efficacious regardless of the degree of leakage. There are more than 400 articles that have been published reporting outcomes of the AUS. As most are retrospective small series, it remains difficult to compare outcomes among reports. This is due to the fact that, in the literature, there are many different methods for reporting the degree of incontinence and numerous criteria to define success. Despite variation in definition and length of follow up, the current literature consistently demonstrates high long-term success rates and patient satisfaction for primary AUS implantation[37,88,...]

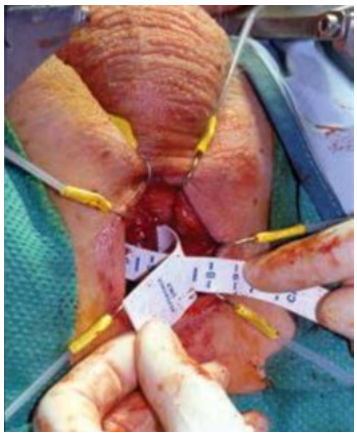
The success rates for AUS as defined by social continence of 0-1 pad ranges from 59% to 90%.[88,528,529] While actual pad free rates are somewhat low (10% to 72%), there are, nevertheless high satisfaction rates (87% to 90%).

In a systematic review of 623 patients from 12 series, social continence (0-1 pad) was reported at 79% (range 61–100%) with follow-up ranging from 6 months to 192 months. The dry rates varied widely between 4% and 86%. In this pooled analysis, overall, re-intervention rates were 26% (range 14.8–44.8%), with 5-year device survival ranging from 59% to 79%.[37,88,528,529,530,531,533]

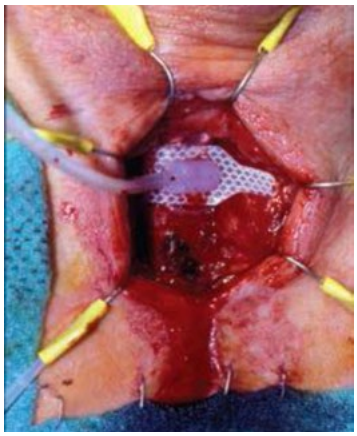
FIGURE 15. Artificial sphincter technique



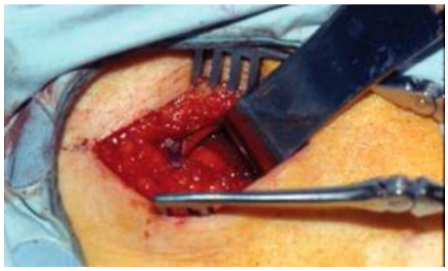
A. With the patient in lithotomy position, a perineal incision is made behind the scrotum to expose the bulbar urethra.



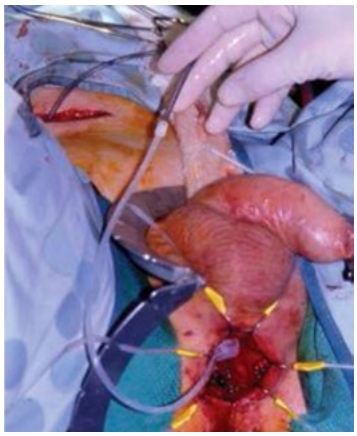
B. The urethra is mobilized circumferentially within the bulbospongiosus muscle and the measuring tape is used to obtain the cuff size.



C. The belt-like cuff is positioned around the urethra.



D. A right lower quadrant (RLQ) abdominal incision is made and the extraperitoneal space is entered lateral to the rectus muscle for insertion of the reservoir.



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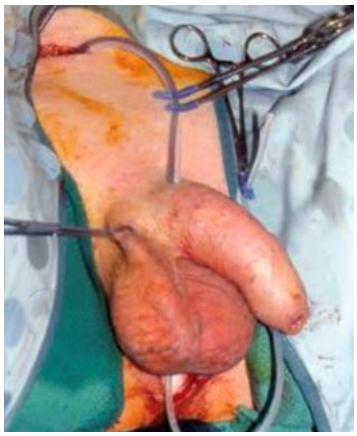

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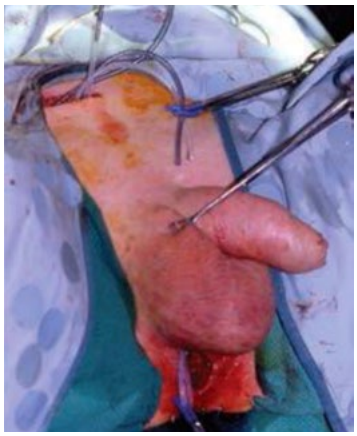
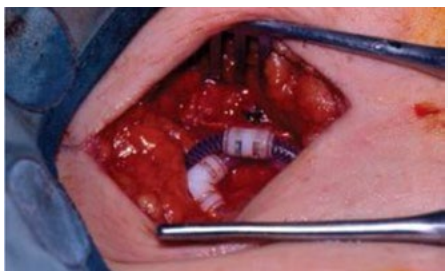


G.



H. Connectors are placed to join the tubes from the cuff and reservoir to the corresponding tubes from the pump in the RLQ incision.

A number of studies reported 10-year device survival rates ranging from 28% to 64%.[527,529,,] In Webster et al's report of 554 implantations over a 10-year period, 21.4% required at least one revision surgery, while 78.6% did not. Of the119 patients who required re-operation, 76.5% required no further treatment, while 23.5% required another re-operation for either mechanical or non-mechanical failure.[536] Five-year durability of the AUS following primary or secondary implantation was comparable, with 80% for the initial placement, and 88% following revision surgery. Similarly, continence rates were comparable, with 90% of primary and 82% of revision patients achieving 0-1 pad per day.

In a retrospective series reported by Singla, in 79 patients with 10-year follow-up, 62% required no revision while 12% required one revision and another 12% underwent 2 revisions.

Data regarding outcomes beyond 10 years is sparse. In a few series, 15-year device survival rate was 15% and 41%.[527,534] Leon et al[527] reported on 57 patients who underwent AUS with median follow up of 15 years, AUS survival rates without revision were 59%, 28%, 15%, and 5% at 5, 10, 15 and 20 years respectively. No patient was lost to follow up in this series. In another large series of 1082 patients who underwent primary AUS implantation at the Mayo Clinic, the 5-, 10-, and 15-year device survival rates were 74%, 57% and 41%.[534] High patient satisfaction (94%) was also reported.[534,]

It is important to note that patients undergoing AUS should be properly counseled regarding outcome and provided with realistic goals. Patient expectation is not the same as Surgeon expectation and are not equivalent to surgical outcomes. They should be advised to expect to wear a thin social pad as 100% dryness may not be guaranteed.

2.6. Complications and Troubleshooting

Despite excellent continence outcomes and high patient satisfaction reported in the literature, AUS implantation is nevertheless associated with potential risks. The complication rates are generally low; however, the need for revision remains high. As experience with AUS has grown and the total number of cases performed at high volume centers (>20 cases in a year) has increased, the overall revision rate has decreased.[513] What follows are general recommendations for managing some of these complications as there are no detailed descriptions available in the literature dealing exclusively with their management.

The complications may be divided into early versus late.

2.6.1. Early complications

Early complications in post-operative period include: urinary retention, scrotal hematoma, hematuria, inability to activate the device, device infection and urethral erosion.

The most common immediate post-operative complication is urinary retention: This may occur in up to 31% of cases as reported by Linder et al, and is generally due to urethral edema, improper cuff sizing, urethral erosion or inadvertent device activation. It is usually transient in nature and resolving without surgical intervention and may be more common with a 3.5 cm cuff and/or transcorporal cuff placement. With early postop retention, one needs to make sure the AUS pump is in fact in the open deactivated state. When in doubt, the device should be deactivated again and no fluid should be left in the pump. If retention persists, the patient may be instructed on self catheterization or have a catheter left indwelling for 48-72 hours. Generally, a small size catheter should be used (12 Fr or less). If retention persists, then suprapubic tube diversion should be considered. In patients with ongoing retention despite suprapubic catheter drainage, office cystoscopy should be performed. Persistent retention usually results from an error in cuff sizing (cuff too small) or a urethral erosion. In these situations, patients should undergo immediate surgical exploration. Prolonged urinary retention has been reported to be associated with adverse overall device survival and significantly high rates of infection/erosion.[539]

Scrotal hematoma can be managed conservatively with rest, ice packs, scrotal support and prophylactic oral antibiotics. Patients should be observed for signs of infection. The presence of scrotal and perineal wound swelling along with cellulitis should alert the surgeon to the possibility of infection or urethral erosion leading to urinary extravasation. This may be secondary to unrecognized intra-operative urethral injury or error in cuff sizing. A tight urethral cuff may cause urethral wall ischemia. Urethral erosions occurring early in post-operative period (within first 2-3 months), are likely due to an unrecognized urethral injury.

2.6.1.1. Unable to Activate AUS

After an initial period of postoperative deactivation, one may occasionally be unable to activate the AUS. If this occurs, first try compressing the deactivation button and/or entire surface of the pump forcibly for a longer period of time. If unsuccessful, squeezing the narrow sides of the upper portion of the pump should be tried. If again unsuccessful, press hard with a Q-tip on the back side of upper portion of the pump. In refractory cases, patients should undergo open exploration to assess for fluid loss or for air lock.

2.6.2. Late Complications

2.6.2.1. Urethral Erosion

Late erosions present at a median time of 19.8 months at a rate of 5–10%.[528] Late erosions may be related to constant cuff compression that may cause tissue atrophy/ischemia and eventual erosion. The incidence of erosion and/or infection varies widely between 0% to 24.6%.[529,,,,,,,,,] Most recent large series report an incidence less than 8%.[73,528,533,535,,,,,] In a retrospective series reported by Singla,[537] erosion/infection occurred in 8.9% at a mean duration of 1.9 ± 1.1 months (range 0–3 months) after implantation. Lai et al reported that patients undergoing a "secondary" implant, following a prior explant for erosion or infection had a four-fold higher rate of erosion as compared to "primary or virgin" cases.[545] Other risk factors for erosion include urethral catheterization or blind manipulation with an activated sphincter. It is of paramount importance to educate patients to inform healthcare providers regarding the presence of an implant and the need for deactivation prior to any urethral manipulation.

Erosion is suspected in patients with a history of new onset incontinence, hematuria or retention. It is confirmed by office cystoscopy demonstrating exposed cuff material within the urethral lumen (Figure 16).

If confirmed the entire device should be removed. In some cases of sterile asymptomatic erosion, only the cuff may be removed while the tubing is plugged with an available steel button. A new cuff is replaced at a later date and connected to existing tubing with a connector. A urethral catheter is left in place for a few weeks to allow healing. A retrograde urethrogram may be performed to rule out extravasation before removing the catheter. A period of three months wait is recommended before re-implantation of a new AUS particularly if erosion is associated with infection. There are no clear guidelines regarding removal of entire device versus only the cuff in sterile late erosions. However, a recent AUS consensus panel

noted that the decision to remove the cuff alone or the entire device mainly depends on time since original AUS implantation.[16] Erosions occurring many years after surgery may require removal of the entire device, as a new balloon reservoir and scrotal pump are generally recommended if they are more than two years old.

The necessity of surgical repair of the urethra (urethroplasty) versus allowing the erosion to heal spontaneously over a catheter is debatable and left to the discretion of the surgeon at the time of explantation. A recent study in 26 patients by Rozanski et al found that the incidence of urethral stricture formation was significantly lower when patients underwent an in-situ urethroplasty with re-approximation of urethral edges (38%), compared to patients treated with Foley catheter alone (85%) with a mean follow-up of 24 months (range 8–69). This facilitates healing and expedites time to re-implantation. Urethral repair in these patients added an additional 8 minutes to the total operating time. Those patients treated with in situ urethroplasty had a much higher rate of undergoing secondary AUS implantation (54% vs 15%) compared to those with cuff erosion treated with Foley catheter only. In another retrospective study by Chertack et al, 75 patients with AUS erosion were treated with either Foley placement or urethroplasty. With a mean follow-up of 13 months, they concluded that Foley catheter drainage alone may be suboptimal management for a large erosion. There was no difference in probability of re-implantation between primary urethral anastomosis, catheter-only placement, or abbreviated urethroplasty (63% vs 69%, 63% vs 33% respectively).[559]

2.6.2.2. Infection

As with any prosthetic implant, infection can be a significant concern and requires early recognition and prompt action. Infection usually presents with scrotal edema, cellulitis and induration/skin fixation at the pump site (Figures 17 and 18).

The incidence of implant infection is generally low. The rate of infection in most series is reported as between 1% and 8%.[541,552] The rates at high volume centers are less than 2%6.[37] Not all series report erosion and infection separately. Gram positive organisms such as *Staphylococcus aureus* and *Staphylococcus Epidermidis* and *Enterococcus* account for majority of infections, while Gram negative bacilli such as *Escherichia Coli* and *Pseudomonas aer*uginosa infections account for 26% of infections.[533]

In cases of overt infection, the standard of care is removal of the entire device. A subsequent device may be re-implanted at least three months later to allow the infection to clear and inflammation to subside. It is preferably implanted at a different location along the urethra.[18] Good results have been reported in these patients undergoing repeat implantation. It has been demonstrated in a single small series, that a salvage technique with immediate re-implantation of a new device, after the removal of infected, but not eroded AUS is possible, with a reported success rate of 87%. Coating of the device with Inhibizone (minocycline and rifampicin) did not result in reduced infection rates but did increase costs.

2.6.2.3. Urethral Atrophy and/or Inadequate Compression

Urethral atrophy is the most common sequela following AUS implantation, and is unavoidable as aresult of constant urethral compression leading to ischemia. The urethra loses tissue bulk over time and the original cuff may become relatively loose and provide suboptimal urethral coaptation resulting in recurrent incontinence. The incidence of urethral atrophy requiring revision varies from 3% to 9.3%.[528,537,542,546,547,548,549]

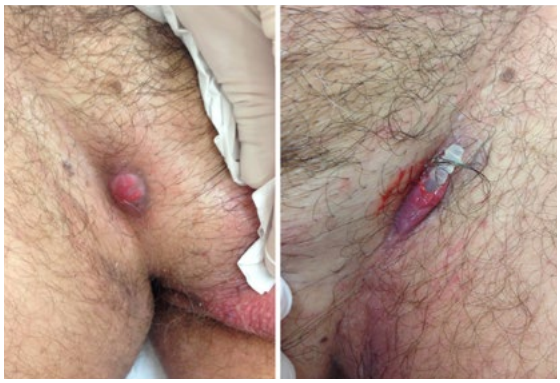


Figure 17. Pump erosion. Courtesy of Drs. Luis Augusto Seabra Rios and Márcio Augusto Averbeck and by permission of Urologia Essencial.

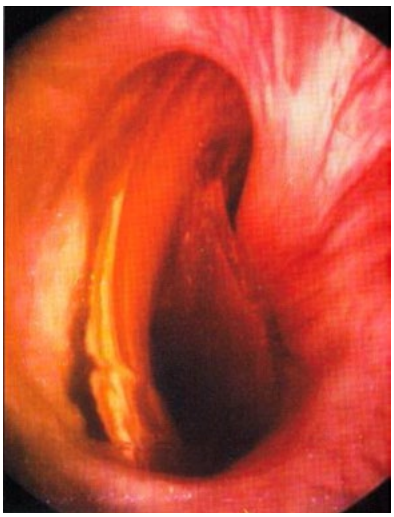


Figure 16. Endoscopic view of AUS cuff erosion into the bulbar urethra. The patient had undergone radiation after radical prostatectomy

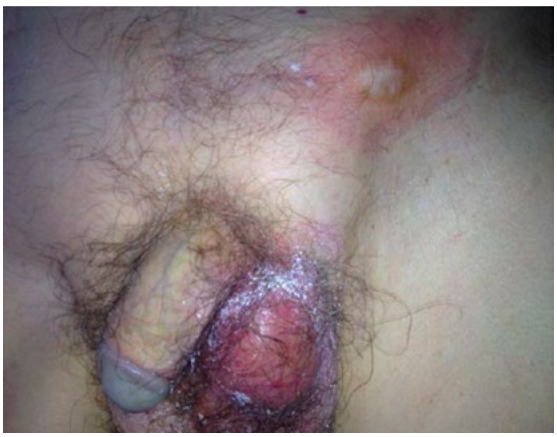


Figure 18. AUS infection. Courtesy of Drs. Luis Augusto Seabra Rios and Márcio Augusto Averbeck and by permission of Urologia Essencial.

Urethral atrophy typically presents as new onset stress incontinence following a prolonged period of surgical success. Such "sub-cuff atrophy" typically presents many years after the primary AUS implantation. Diagnosis is confirmed by office cystoscopy demonstrating inadequate urethral wall coaptation. Fluid leak should be ruled out by pelvic ultrasound (to confirm a full reservoir) or plain xray (in patients whose device was filled with contrast). Several options exist to manage recurrent incontinence, including downsizing the cuff, increasing reservoir pressure, placement of a tandem cuff to increase the area of urethral resistance, transcorporal cuff placement or interposition of a biologic graft as a urethral wrap.[69,,,] The most common and easiest approach is downsizing the cuff size, while the latter 2 options provide additional bulk of tissue to the urethra.[536] The use of a 3.5 cm cuff in smaller urethras may lessen the incidence of sub-cuff atrophy as cause for surgical revision.

However, there are some who question the entity of urethral atrophy and instead have noted constriction of the sub-cuff urethra by the pseudocapsule, that can be released via incision of the pseudocapsule resulting in increased urethral circumference.[,] This would allow for replacement of the original sized components with satisfactory outcomes. There is limited data on performing this.

2.6.2.4. Mechanical Failure

As with any prosthetic implant, mechanical failure can be expected with AUS and is typically a late complication. It is believed to be due to wear-and-tear of the tubing or components of the device. This includes loss of fluid from the system, malfunction in the pump, leak in the reservoir or tear and/or kink in the tubing. Introduction of "kink-free" tubing has virtually eliminated this last tubing problem although tubing break next to the pump can occur over time if the device is not situated properly within the subdartos pouch. The current implant design of the AMS 800 has significantly lowered the device failure rates secondary to mechanical issues. The incidence varies widely and ranges from 0%[547]to 52.5%. In a study with long follow-up ranging from 10–15 years,[569] the authors reported the cuff being the most vulnerable component of the system (22 cuff failures in 18 patients), most of them occurring in first 2-3 years following implantation, followed by pump failure (6 times in 4 patients). Blockage only happened once in 61 patients.

In a 13-year review by Lai H,[528] mechanical failure occurred at an average of 68.1 months following implantation.

Malfunction can be identified on physical exam with improper device cycling and lack of coaptation during office cystoscopy. The loss of fluid should be ruled out first with a quick office pelvic ultrasound to check the amount of fluid in the pressure regulating balloon. The bladder ultrasound is readily available in urology clinics.[67] Plain abdominal x-ray can be utilized if contrast was used to fill the reservoir.[69] There is limited data on the management of this sort of failure available in the literature. There are no guidelines or recommendations regarding management in cases of malfunction. Some suggest replacing the individual component only if the device has been in place less than 5 years. On the other hand, others recommend replacing the entire device in all cases regardless of duration of implanted device due to minimal added surgical risk.[67,,]

Unusual mechanical complications may occur which included displacement of the locking tab into the cycling portion of the cuff preventing fluid transmission into the cuff or even a persistently open locking tab.

Figure 19 illustrates the case of a young spina bifida patient in whom an artificial sphincter has been implanted with the cuff around the bladder neck. After more than 10 years, he became suddenly incontinent. Comparing the second KUB to the original one clearly demonstrated fluid loss from the system. Contrast studies include cystography which may demonstrate an open bladder neck when bladder denervation is sus-pected20 (e.g., following abdominoperineal resection of the rectum). CT or MRI may be useful as well particularly in cases where there is concern that components of the AUS have shifted or herniated (Figure 20 A and B).

2.6.2.5. Complications in the Long-Term

More recently, Schillebeeckx C et al presented their 30-year experience with AUS implants in a tertiary referral center during the ICS 2021. All patients who underwent artificial urinary sphincter implant for non-neurogenic stress urinary incontinence between June 1989 and January 2020 were included in this single-centre retrospective consecutive series. All implants were AMS 800® (Boston Scientific) and performed by two experienced surgeons. A total of 263 patients were included in this retrospective series with a mean follow-up of 61 months. The median patient age was 69 years. 86.7% of the patients became incontinent due to radical prostatectomy. Twenty-two early postoperative complications were registered (5 retentions, 12 scrotal hematomas, 1 infection, 2 wound problems and 2 hematuria cases). A total of 294 sphincters were implanted; 249 patients received one implant, 40 patients received a second implant and 5 patients underwent a third AUS implant. Of these implants, 71 (24%) were explanted. Explants were mainly due to urethral erosions (51%) and infection (39%). Explant-free survival

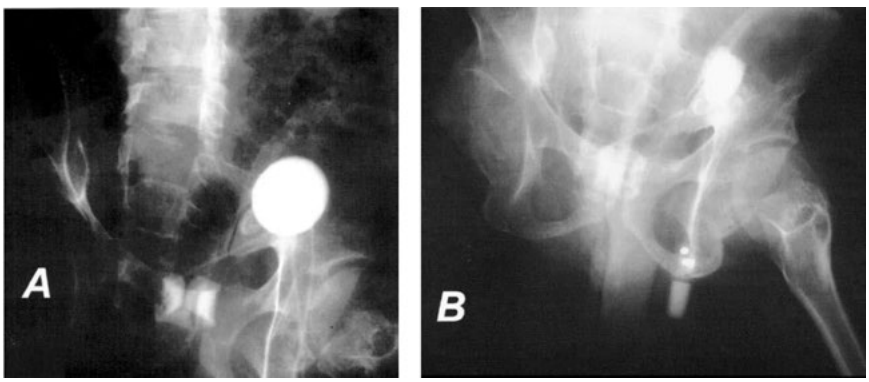


Figure 19. Young spina bifida patient who had a bladder neck artificial sphincter implanted. After more than 10 years, he become incontinent. Early abdominal plain film, A, shows a full reservoir. After leakage started abdominal plain film, B, demonstrates loss of fluid from the reservoir.

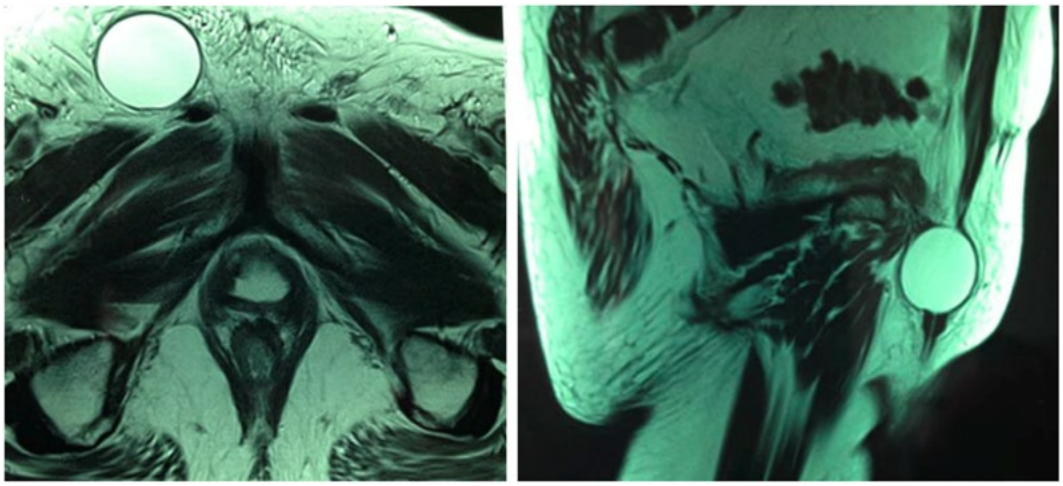


Figure 20 A and B: MRI demonstrating reservoir displacement through an inguinal hernia. Courtesy of Drs Luis Augusto Seabra Rios and Márcio Augusto Averbeck and by permission of Urologia Essencial

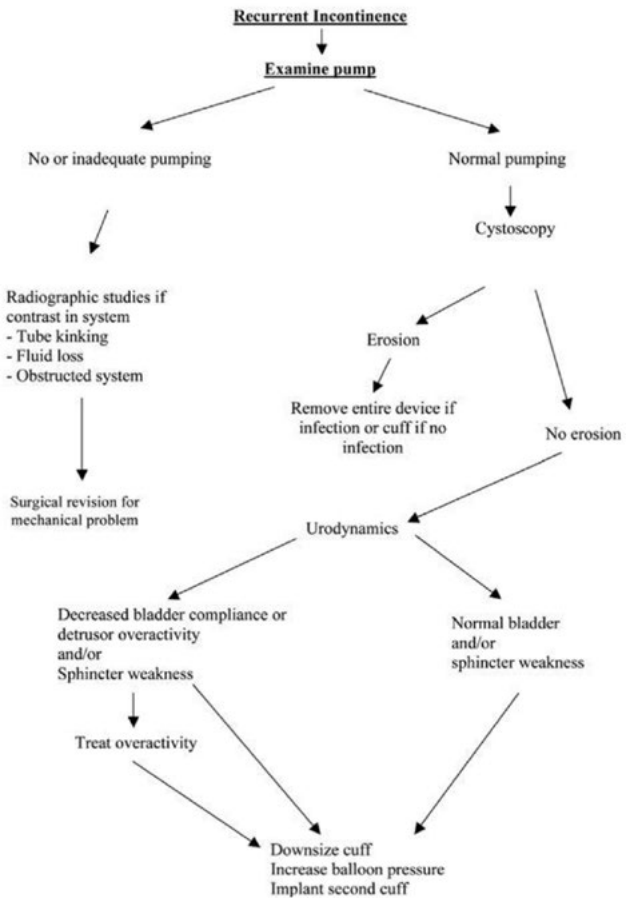


Figure 21 shows an algorithm to investigate and treat the male patient with a previously functioning AUS who becomes incontinent.

after 5 years was 75.3% (CI 68.8% - 80.7%) with a median time to explant of 16.2 years (CI 12.2 – 28.1). A total of 73 patients (24.8%) underwent revision or maintenance surgery. Overall revision-free implant survival was 62.1% (CI: 55.0%-68.4%) after 5 years with a median revision-free implant survival rate of 10.8 years. Previous pelvic irradiation, a history of stricture disease and previous artificial urinary sphincter implants were independent risk factors for decreased implant survival. Overall social continence rate (i.e. needing no more than 1 pad/day) after 5 years was 60.3% (CI: 53.2% - 66.7%) and after 10 years social continence rate decreased to 37.9% (CI: 30.1% - 45.6). Prior radiation therapy, anticoagulation therapy, previous AUS implant and other previous anti-incontinence surgery were associated with a higher incontinence risk.

2.6.2.6. Alteration in Bladder Function

Patients undergoing AUS can develop *de novo* OAB. Lai and Boone reported the need for anticholinergics medication in 23% of patients for OAB symptoms. More reports of bladder dysfunction are available in the pediatric neurogenic population. These include decrease in bladder compliance, development of high detrusor pressures resulting in hydronephrosis and even renal failure.[543,,,,,] Changes in detrusor pressure with upper tract dilation were reported in up to 57% of patients with bladder dysfunction.

Ideal candidates for AUS implantation are patients with adequate bladder capacity and normal vesicalcompliance. It has been reported that even those with “unfavorable” urodynamic parameters may have a good outcome after AUS implantation.[82] It is recommended to re-train small capacity bladders for several weeks prior to implantation and to treat such patients with anticholinergic medications as necessary.

2.6.2.7. Role of Tandem Cuff

In an effort to improve efficacy and continence, some authors have proposed using two cuffs in a tandem fashion. This is based on a concept of increasing resistance over a greater surface area. While placing a tandem cuff, it is recommended to leave 1-2 cm of normal urethral tissue between the two cuffs to avoid a long segment of possible urethral ischemia. The 2 cuffs are connected using a Y connector. It is estimated that approximately 15% of total AUS are placed as tandem cuffs.[559] Brito et al was the first to describe successful tandem cuff placement with success reported at 95%. Multiple reports recommend it as a primary procedure in totally or se-

verely incontinent patients,[580,] or as a salvage procedure by adding a second cuff following a failed previous single cuff.[580,581,] Despite initial enthusiasm and favorable outcomes following tandem cuff, subsequent reports with longer follow-up demonstrated a higher rate of complications. O'Connor et al[556] reported their experience in 28 patients who underwent double cuff placement, noting that with longer follow up there was no difference in continence compared to 28 men who underwent single cuff placement.

2.6.2.8. Role of Transcorporal Cuff Placement

Guralnick et al[564] first reported the transcorporal cuff technique in an attempt to improve continence in patients with recurrent incontinence due to urethral atrophy, urethral erosion, inadequate urethral coaptation, small urethral circumference (less than 3.5 cm), or multiple previous revisions to prevent future erosions. The urethra itself is not circumferentially mobilized but instead incisions are made into the tunica albuginea of the overlying corporal bodies and a tunnel created dorsal to the urethra, between these tunical incisions. This provides added dorsal bulk to the urethra and helps to avoid an inadvertent dorsal urethrotomy and further devascularization of the dorsal urethral tissue that could lead to cuff erosion. Initial success was reported in 84% of patients. In a prospective series, dry or socially continent rates were reported to be 76% at a median follow-up of 20 months.[583]. Many authors believe that transcorporal cuff placement affects erectile function and patients should be cautioned regarding this concern. Despite this concern, a small series report that a majority of patients (5/6, 83%), maintained their erectile function even after transcorporal cuff placement.

Despite conflicting reports, violation of the tunica albuginea is widely considered a contraindication in patients who have normal erectile function and/or desire a penile prosthesis for their erectile dysfunction.

Alternatively, in this complex patient population, a circumferential urethral wrap using biologic graft may be interposed between the urethra and the cuff as a salvage procedure. The graft materials used are either cadaveric dermis (personal experience, unpublished data) or small intestinal sub-mucosa (SIS). In a small retrospective study by Trost and Elliott[565] in eight patients with mean follow-up of 12 months, 38% (3/8) patients were dry requiring no pads, three patients had AUS explantation for erosion and infection and two patients developed recurrent incontinence.

2.6.2.9. Special Populations

2.6.2.9.1. AUS Following Sling Placement

For patients with persistent or recurrent stress incontinence after male urethral sling placement, AUS implantation as a secondary procedure is utilized.[42,43,] It is believed that the resultant fibrosis from sling limits the urethral compression and/or urethral mobility needed for sling efficacy.[163,] This will decrease overall sling efficacy with time and even a second sling will not be effective. Following sling surgery, recurrence of incontinence ranges from 20% to 35%. The outcomes of primary AUS placement are comparable to those performed after prior failed sling placement. An AUS may be placed following bone anchored sling, transobturator sling or quadratic sling. Usually a transobturator sling is not seen during AUS placement and may be left in place. If a sling is encountered, it may simply be incised to expose the urethra. AUS outcomes following sling placement are high, with success rates reported between 79–83% without increase in the complication rates.[42,469] Few reports suggested a repeat urethral sling surgery after a prior failed sling with reasonable success.[467] In another study in 28 patients undergoing AUS after a failed urethral sling, similar high success rates were reported when compared to a control group without prior urethral sling surgery.[43] Similarly, in a comparative analysis of patients with SUI after a failed urethral sling, patients undergoing repeat transobturator urethral sling placement were six times more likely to have persistent incontinence than those who underwent AUS.[468] Unfortunately, these reports are small series, retrospective in nature and with a short follow-up. Due to lack of long-term outcomes, it is strongly advised to offer AUS placement following failure of male urethral sling.

2.6.2.9.2. Pelvic Radiation and AUS

It is believed that post-XRT patients constitute a group of high risk patients with a substantially increased risk of complications. Radiation is associated with endarteritis and chronic vascular changes that may lead to decreased blood flow making urethral tissue vulnerable to higher complications.[16] Several series have found higher rates of urethral erosion and atrophy necessitating higher rates of revisions in patients with prior history of radiation.[228,512,537,] A recent report showed that the relative risk of erosion is significantly higher in those who underwent radiotherapy compared to those who did not – RR 4.05, 95% CI 1.1-15.3 – and this risk is not diminished despite the improvement in radiation techniques. There are conflicting reports in the literature regarding increased complication rates and lower continence rates. Some series contradict these reports and show comparable complication rates and continence rates with or without a history of radiation.[,] In a recent meta-analysis of 15 series, including 1886 patients, men with history of radiation in addition to prostatectomy had higher rates of AUS revisions than those treated with surgery alone.[228] Most of the studies included in this meta-analysis were small retrospective series, but when analyzing the four largest series, the relative risk of revision was not significantly different between those with and without prior radiotherapy.[228] Because of the concerns in these compromised urethras, some surgeons recommend using a lower pressure regulating reservoir (51-60 cm of water) and a longer period of deactivation time (6 weeks) instead of standard pressure of 61-70 cmH_2O and 4 weeks of deactivation.[537,]

Despite these conflicting reports, it should be noted that patients with history of radiation should not be excluded from receiving an AUS implant. These patients should be counseled accordingly and given realistic expectations of a lower continence rate and increased need for revision.

Regarding timing of the AUS insertion in patients who may need salvage radiation, there are scarce evidences in the literature, which preclude definitive conclusions. DeLay et al assessed 306 men, 292 (95.4%) received radiation before AUS placement (group 1) and 14 (4.6%) received radiation after AUS placement (group 2). Median follow-up was 30 months after AUS placement. Group 1 had 32 of 292 (11.0%) patients suffer from erosion, compared with 0 of 14 (0.0%) patients in group 2 (P=0.191). None of the patients in group 2 had infection or mechanical failure. The number of patients who received revision in group 1 was 91 of 292 (31.2%) and in group 2 was 2 of 14 (14.3%) (P=0.180). The number of pads used per day in group 1 before and after AUS placement was 5.24 ± 3.12 and 1.13 ± 1.31, respectively (P<0.001). In group 2, the number of pads used per day before and after AUS placement was 6.09 ± 1.97 and 1.53 ± 0.99, respectively (P<0.001). There was no significant difference in the average number of postoperative pads used per day between group 1 and group 2 (P=0.907). It is noteworthy that there were zero erosions in the group that had AUS first, then radiation. Nevertheless, the "N" was too small to achieve significance. Thus, future research is still needed.

2.6.2.9.3. AUS Implantations Following Radical Cystectomy

A significant proportion of patients will suffer from SUI following radical cystectomy with neobladder reconstruction. Only a few studies exist in the literature evaluating clinical outcomes in patients with orthotopic neobladders who have undergone an AUS. In one of the largest series reported, 72% (21/29) of patients noted an improvement in incontinence at a mean follow up of 40 months. However, 60% of patients underwent a revision or explantation due to device erosion, infection, device malfunction or recurrent SUI at a mean of 28 months after initial implant. It should be noted that a significant minority of these patients (28%) received adjuvant or salvage pelvic radiation. In comparison, these outcomes are inferior to outcomes in PPI.

2.6.2.9.4. AUS in Neurogenic Population

In a series of 30 males with spina bifida, Spiess et al found that the mean lifetime of AUS was4.7 years with no statistically significant difference in device survival of those inserted at the bladder neck versus the bulbar urethra (4.6 and 4.9 years, respectively). Significant decline in device survival was observed at 100 months with only 8.3% of the original sphincters still functioning beyond this point.[596] In a series of adolescents with neurogenic voiding dysfunction implanted with a bladder neck cuff over an 11-year period, with an average follow up of 5.5 years, Lopez Pereira and colleagues reported 20% mechanical failure rate with an additional 8.6% erosion rate. Adverse bladder storage changes developed in 31.8% of patients, necessitating augmentation cystoplasty to improve bladder function although urinary continence was achieved in 91.4% of patients.

2.7. Other Devices

For futher information on technologies under development, please see Section 4.6 Future Directions.

2.7.1. Zephyr Surgical Implant (ZSI 375)

The ZSI 375 (Zephyr Surgical Implants, Geneva, Switzerland) is a more recently developed device. It is a one-piece device and pre-connected. It has no reservoir, but has an adjustable urethral cuff which is connected to a chamber which hosts the pump and a pressure regulating tank. It obviates the need for any abdominal incision, thereby reducingd operative time. In comparison to AUS 800, the smaller device should also have a lower overall cost.

Since its introduction, there have been a few reports confirming the safety and efficacy of the device. Staerman et al reported a retrospective study in 36 patients with moderate to severe incontinence following radical prostatectomy, TURP or bladder replacement. The median follow-up was 15.4 (6–28) months. Complications were noted in 4 patients requiring removal for erosion/infection. Social continence (0-1 pad) was achieved in 73% at 6 months after activation.

Another series with a longer follow-up of 4 years was reported by Ostrowski et al in 50 patients. In their series, the majority of patients suffered from severe incontinence. The median follow-up was 21.04 (1–50) months. Complications leading to revision or device removal occurred in 24%. These included erosion and/or mechanical failure. Social continence was achieved in 58% and 30% of patients improved significantly.

More recently, Ostrowski et al reported a large multicenter study in 10 European centers. A total of 109 patients with severe urinary incontinence underwent ZSI 375 device implant. The average follow-up was 43 (24–78) months. Complications leading to device removal were noted in 11% urethral erosions in 8.25% and mechanical failure in 2.75%. Total continence was observed in 19.27% and social continence was reported in 65.14%. Another 8.25% of patients noticed significant improvement. The authors concluded that the ZSI 375 is highly effective in treating severe incontinence with acceptable low complication rates. The ability to adjust the internal pressure via in-situ trans-scrotal applicator in an office setting makes this device an attractive option for men with severe incontinence.

2.7.2. VICTO and VICTOplus AUS

A new AUS called VICTO hase been recently introduced into Europe and South America. Manufacturers have introduced two configurations of this new AUS called the VICTO and VICTO plus. This device comes pre-connected with minimally invasive adjustments required. VICTO is a single unit pre-connected adjustable device with an occluding cuff (OC). The filling procedure is performed by inserting the needle into the port and filling the system with 13 mL of saline solution. In theVICTO plus the initial filling is 20 mL.

The pressure regulating balloon is placed intraperitoneally and with the VICTO plus, the stress balloon is be placed under the fascia. After passing the cuff through a subcutaneous channel from the abdominal incision to the perineum, the cuff is placed around the urethra. Finally, the pump is placed in the scrotum.

Four different cuff sizes are currently available (3.7, 4.0, 4.5, 5.0 cm).

Only one center reported outcomes of 51 patients (VICTO N=22, VICTO plus N=29) with a mean follow-up of 14.1 months. The pad per day usage improved from 6.2 (±3.3) to 1.4 (±1) and the continence rate (max. 1 pad per day) was 58.8%. There were on average 1.7 (median=2) adjustments needed and in two patients cuff revisions were required to achieve continence. An overall high patient satisfaction of 86.4% was reported. No erosions or device explants were reported by the authors.

2.8. Follow-up Protocol Of Patients Undergoing AUS Implant Surgery

No standardized recommendations are available in the literature regarding post-operative follow-up of patients after AUS implant surgery. Recommendations are based on expert opinion own protocol.

1. Peri-operative intravenous broad spectrum antibiotics are given to provide coverage for both gram positives, specifically *Staphylococcus Epidermidis*, and gram negative bacilli like *E.Coli.*
2. At the conclusion of the surgery, the device is deactivated and the Foley catheter may be left in place to drainage.
3. Patient is either discharged same day or may be kept overnight in hospital under observation and is discharged following morning based on surgeon's preference.
4. Foley catheter is removed in the recovery room or the following morning and a voiding trial is given to ensure complete voiding or leaking by the patient. A post void residual is checked with bed side bladder ultrasound before discharging patient.
5. The AUS device is kept deactivated for 4–6 weeks following surgery. Patients with a history of radiation are kept deactivated for a longer period, usually 6 weeks and 4 weeks for patients without history of radiation. Patients should avoid strenuous activity during this time.
6. Patients are seen in the clinic for the AUS activation by the surgeon and taught how to squeeze the pump for urination. Nocturnal deactivation of the device should be considered in high-risk patients (e.g., prior radiation or urethral erosion) and those who are comfortable deactivating the device themselves.

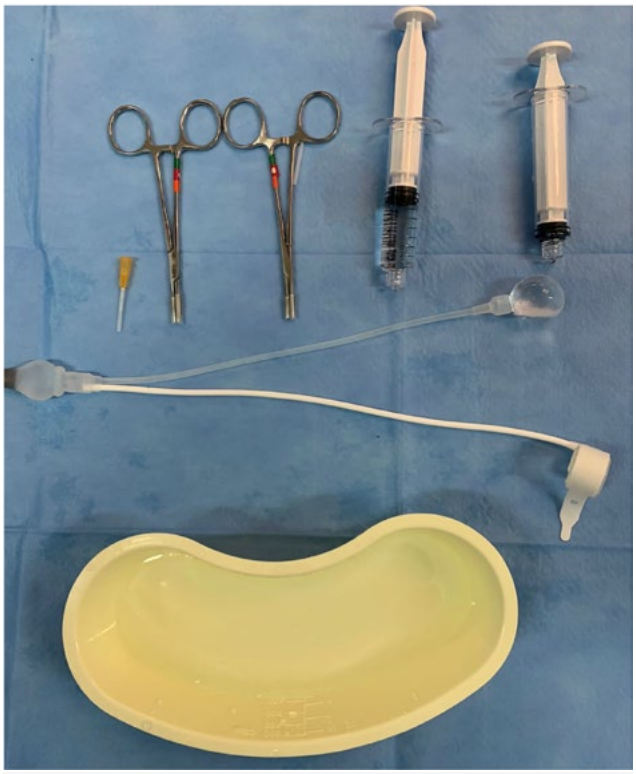


Figure 22. Victo artificial sphincter Courtesy of Dr. Luis Seabra Rios.

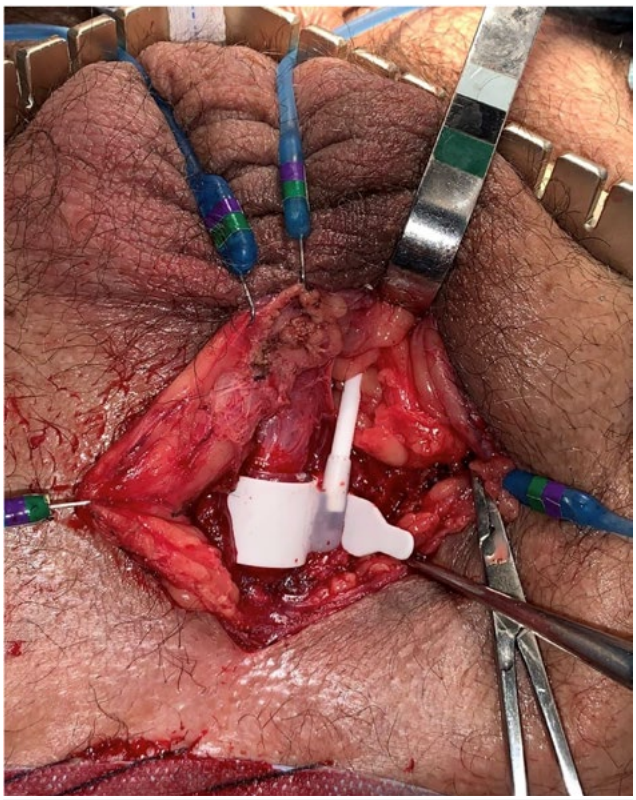


Figure 23. Victo cuff implanted around the bulbar urethra. Courtesy of Dr. Luis Seabra Rios.

7. Patients are reviewed around 3 to 6 months after activation to ensure proper functioning of the device and to assess continence status.
8. Patients are instructed to contact the physician in case of hematuria, pain, redness, new onset of incontinence or any difficulty manipulating the device.
9. Long-term follow-up is different in the neurogenic and non-neurogenic patient. With time alteration in bladder function may compromise the upper tracts and overall renal function in the neurogenic patients. As such these patients should be monitored with periodic assessment of renal function/renal imaging.
10. If changes are observed or patients complain of worsening incontinence, urodynamic evaluation may be necessary to rule out detrusor overactivity or poor bladder compliance.
11. Office cystoscopy may be required in patients with a history of new onset of hematuria or difficulty in emptying the bladder to rule out cuff erosion.

3. MALE SLINGS VS. AUS

3.1. Introduction

Post-prostatectomy incontinence is multifactorial. Adequate sphincter function depends on the ability of the urothelium and urethral wall to properly coapt and seal, functional smooth and striated muscle, and sufficient support of the membranous urethra and the pelvic floor. As these factors can change over time, before embarking on surgery, one must be sure that the patient´s symptoms are stable, that conservative treatment has been fully undertaken, and that bladder function is assessed. Careful clinical history and evaluation is mandatory, since the pathophysiology of "post prostatectomy incontinence" may include **stress urinary incontinence**, **urgency incontinence**, **nocturnal enuresis**, i**nsensible urinary incontinence** and p**ostural urinary incontinence**.[35] The key to a successful treatment is to determine the presence/absence and impact of each type.

It is difficult to compare surgical techniques that are based on differing mechanisms of action: the **compressive nature of annular systems** around the urethra (artificial urinary sphincter);[533,600] **non annular compression of the bulbous urethra** of a compressive sling (quadratic and adjustable slings)[484] or **urethral re-positioning** (transobturator retroluminal sling).[453] Choice of surgical procedure depends on the patient's degree of incontinence, history of prior incontinence procedure or prior XRT, bladder function, and the goals of treatment. This shared decision-making between patient and surgeon is based on the principle that treatment poses risks and confers benefits for the patient. Shared decision-making is a process in which providers and patients work together to make decisions about tests, interventions, and care plans. The physician provides the clinical evidence and the patient is free to express his preferences and values. The surgeon should honor the patient's preferences for treatment goals and consider those preferences when giving a treatment recommendation, including long-term continence and long-term complications when we compare sling (loss of continence, perineal pain) with AUS (risk of erosion, mechanical failure, and loss of compression in urethra). In the case of adjustable systems (e.g., ATOMS™, Argus™, Reemex®), the need for any postoperative adjustments should be explained to the patient. Furthermore, AUS is a mechanical device requiring pump manipulation with the potential for mechanical breakdown, and it has been reported that some patients prefer to avoid the mechanical nature of an AUS and choose a sling even when their surgeon recommends an AUS over a sling.[59] Shared decision-making produces better

health outcomes by decreasing anxiety, promoting faster recovery, and improving compliance.[,,,]

In the patient who has failed conservative management, the two main choices for surgery to restore urinary continence are the artificial urinary sphincter (AUS) and the male sling. There are few comparative studies of the artificial sphincter and the various male slings, and only one prospective randomized trial comparing the devices. However, there are several recent cohort studies comparing outcomes of the AUS with those of specific male slings in certain patient populations. While no one device is preferred in all patients in all clinical situations, there are some recommendations made in the literature regarding the preferred treatment in certain patient populations depending on prior radiation, prior incontinence surgery, prior treatment of urethral stricture,[31,] degree of urinary incontinence, and degree of residual sphincter function.

While it can be difficult to measure bladder contractility in these patients, detrusor hypocontracility is a relative contraindication to a potential obstructive sling. However, most series have not included men with known detrusor hypocontracilty in their cohort. In the setting of detrusor underactivity in the group with moderate incontinence, AUS is preferred, as it is cycled to an open (nonobstructed) state during voiding (a potential advandage of the AUS is the ability to open the cuff to allow valsalva voiding.). On the other hand, the compressive sling is designed to prevent leakage with straining and may therefore interfere with voiding in those patients unable to produce an adequate bladder contraction. In the patient with detrusor underactivity who does not want implantation of a mechanical device, a non-compressive sling such as the transobturator male sling, is an option. Han et el,[93] in their retrospective review, show that patients with post-prostatectomy urinary incontinence with urodynamic findings suggesting impaired contractility or Valsalva voiding can be safely treated with sling surgery if they have normal preoperative emptying. Thus, in the man with a poorly contracting detrusor, the transobturator sling may be preferred versus a compressive sling, given its non-compressive mechanism of action.

3.2. Specific Patient Factors

3.2.1. Degree of Incontinence

Success for sling surgery appears to relate to the severity of leakage (by pad weight). The success rate in men who leak more than 200g per day were lower than those with milder leakage, and in those with 400g per day incontinence, failure rate was 80% higher than in those with less than 200g per day on pad weight. Averaged out, for each 1g increase in 24-hour pad weight, success rate declines by 0.4%.[60,498,] Similar data was shown for the bone-anchored sling, where the AUS was recommended over sling implantation for those with greater than 450g per day urine loss.[585] Whereas the international trial of the quadratic sling with fixation (a modification of the initial technique with the attachement of the retropubic arms over the pubic rami) showed equal efficacy for those with mild (up to 100g per day), moderate (100–400g per day) and severe (more than 400g per day) leakage, a more recent report indeed demonstrated higher failure rates with greater degree of incontinence.[476]

In the MASTER RCT (Sling vs AUS),[6] 24-hour pad test baseline was 256g (range: 89–545) in the sling group and 267g (range: 130–554) in the AUS group. While non-inferiority was reported for the primary endpoint (any self-reported urinary incontinence at 12 months after randomisation), subgroup analysis of the primary outcome suggest that the male sling is indeed less efficacious tan the artificial sphincter for men with greater incontinence at baseline (pad weight >250g); although, the difference does not reach statistical significance.

3.2.2. Prior Radiation

Adequate urethral compliance is necessary to allow sufficient urethral compression with a non-circumferential sling implantation. Similarly, prior radiation has been shown to limit the mobility of the bulbar urethra, often preventing adequate proximal urethral relocation. Moreover, it has been described the damaging effects of XRT on the structure and function of the pelvic floor muscles of patients with cancer in the pelvic area.

Debates exist whether men with urinary incontinence post-prostatectomy should receive continence surgery prior to XRT, or to wait post-radiation to ensure tissue fibrosis has settled.

It is not surprising, therefore that a history of radiotherapy correlates with a higher rate of sling failure.[419,500,611] Radiation was the most significant predictive factor for sling failure for both the Northwestern pubourethral sling[419] and for the bone-anchored sling.[500] Torrey et al[492] reported that only 29% were improved (none were cured) with the transobturator sling in men with a history of XRT, versus a 90% cure/improved rate in those without prior radiation. Bauer et al[611] showed similar findings, with TO sling success of 80% in non-radiated men compared to only 50% in those with prior radiation.

3.2.3. Prior AUS

Similarly, prior AUS implantation and explantation can result in a fibrotic and poorly compressible urethra that fares poorly with a non-circumferential sling placement.[425,] On the other hand, reimplantation of the AUS is associated with a high success rate. In a comparative study of men undergoing salvage sling placement versus AUS re-implantation after prior AUS surgery, AUS patients were three times more likely to achieve adequate continence than were sling patients.[586]

3.2.4. Prior Sling

The data regarding prior sling surgery generally favors AUS over sling revision, with the exception of late sling failure with a persistently positive repositioning test. It is well-established, that following sling surgery, recurrence of incontinence occurs in a significant minority of patients (20–35%). There is a growing body of literature regarding the choice of repeat sling surgery versus AUS following sling failure. The history of prior sling failure does not adversely affect the success of AUS implantation, which can be implanted via a standard perineal approach distal to the membranous urethra and proximal bulb, unencumbered by the *in situ* sling. The efficacy of a repeat sling depends on the time to sling failure, and the degree of residual sphincteric function. With early sling failure (less than 6 months postoperatively), the efficacy of repeat sling surgery was lower (20% cure, 20% improved) than men with late sling failure (greater than 6 months postoperatively). Late failure patients realized a 63% cure and 13% improvement rate 1 year post sling revision.[38] Similarly, in the cohort reported by Soljanik et al,[467] 46% of patients were cured at 6 months following repeat sling surgery. However, only men with a positive repositioning test were offered repeat sling implantation. Singla's group, who did not discriminate based on the repositioning test, found a low success rate with repeat sling, noting a 55% failure rate, which was seven times higher than the likelihood to fail with AUS implantation.[468]

Recently, a pelvic MRI has been proposed to correlate the postoperative position of the sling and the success of the surgery. MRI can show proper positioning of the sling (successful surgery) based on our quantitative analysis of MRI parameters. A strong relationship was found between proper positioning of the sling (a complete sling indentation on the urethral bulb profile and a small sling backward distance, defined as the distance between the prolongation of a line through the major axis of the pubis) and the continence outcome. According to these data, only in cases where the sling is poorly lo-

cated postoperatively would a second mesh surgery be indicated.[39] Given the high success rate of salvage AUS, and the relatively high failure rate for repeat sling (with the exception of late failure and positive repositioning test), AUS is the procedure of choice in men who have failed primary sling.

Approximately 13% of men who undergo male sling surgery will ultimately have AUS implantation. AUS placement after failed sling has a high success rate (80–90%) without an increase in the expected complication rate.[422,423,424,425,426] The TO sling may be left *in situ* while the AUS is placed distal to the sling in the normal bulbar urethral location, whereas the quadratic sling must be divided to allow access to the bulbar urethra for AUS cuff placement. The sling is readily identified via a perineal incision, and is easily dissected off the underlying bulbospongiosus muscle, which should be left intact over the urethra during quadratic sling placement.

3.2.5. Pre-Existing Comorbidities

In patients with comorbidities or a history of previous incontinence surgeries, these should be evaluated to decide between a sling or an AUS. It is, however, difficult to draw conclusions due to bladder neck contractures or urethral strictures treated and previous surgery are usually exclusion criteria for all published studies (i.e,. patients were excluded if they had had previous male sling or AUS surgery in RCT MASTER study).[6] AUS implantation seems to be a viable, safe and effective therapeutic strategy for incontinence treatment despite previous buccal mucosa graft urethroplasty (BMGU) beforehand.[609] Although, AUS implantation in patients with former urethroplasty can provide satisfying results, compared to patients without the previous urethroplasty, the higher risk of cuff erosion and AUS explantation has to be addressed during preoperative consultation.[31] Related sling surgery, anastomotic stricture treated has not been demonstrated as a risk factor for successful after 49 months median follow-up sling surgery.

Endoscopic surgery after the placement of an AUS should be considered, mainly in patients with previous nonmuscle Invasive bladder cancer (AUS might be difficult if need to undertake TURBT). *De novo* detrusor overactivity must also be considered; although, it is feasible treatment with botulinum toxin injection with flexible cystoscopy in men with AUS.

3.3. Sling vs. Sphincter Based on Non-RCT

In a retrospective review of 124 patients with mild to moderate PPI (≤ 5 pads per day), 76 of whom underwent TO sling surgery vs 48 who underwent AUS placement, Hoy et al showed relative equivalence in surgical outcome. Specifically, there was no statistical difference in continence (88.2% vs 87.5%), satisfaction (93% vs 92%) or complication rate (19.7% vs 16.7%). However, those complications associated with the AUS were more severe than those following sling surgery.[618] In a comparison of men with mild-moderate PPI receiving AUS (N=20) or adjustable TO sling (N=20), Lim et al[445] reported no statistically significant difference in efficacy (72.7% vs 85% success). However, there was a greater rate of pain reported in the adjustable sling group (30% vs 7.7%), and sling explantation was required three times more often in the sling group.

3.4. MASTER Trial

More recently, the MASTER trial was a prospective noninferiority randomized trial assessing of the transobturator male sling versus the AUS.[6] The primary outcome measure was based on patient reported urinary incontinence at 12 months. Based on the strictest definition of “any leakage”, 87% and 84% of men had some degree of incontinence postoperatively in the sling and AUS groups, respectively (confirming non-inferiority of sling vs AUS). When a less strict definition of incontinence was used (“small amount” and “less than once a week”), 66% and 65% of men in the sling versus AUS group were incontinent (again confirming non-inferiority). Preoperative and postoperative pad use was not statistically different between the groups. Satisfaction via ICIQ questionnaire was higher in the AUS group than the sling group (90.6 vs 72.2%). Despite the primary outcome showing that the TO sling is not inferior to an AUS (with urinary incontinence being greatly reduced after surgery in both groups), there were differences in secondary outcome measures at 12 months postoperatively including incontinence symptoms (using ICIQ-SF), self-reported amount of urine leakage, self-reported pad use, and the impact of incontinence on everyday life, with greater improvements in the AUS group. Furthermore, at 12 months after surgery, significantly more sling patients needed additional incontinence surgery (7.2% vs 1.2%) and the overwhelming majority of sling failures ended up having an AUS placed.

Adverse events were generally rare, with the male sling group having a higher rate of catheter problems which is not surprising considering catheterization is almost never indicated after AUS placement with deactivation. As device-related complications do not always occur in the first 12 months (the data currently published are at 12 months of follow-up), and longer-term data acquisition has been advised for all surgical devices, the authors will continue with a 5-year follow-up of the established MASTER trial cohort.

This well-run clinical trial did not show a statistically significant difference in continence or pad use at 1 year. However, it must be taken into account the baseline characteristics of the patients. The median of the 24-hour pad test result was 256g in the sling group and 267g in the AUS group and the range was 89–545 in the sling group ant 130-554g in the AUS group. Although, all the subgroup analyses forest plot (primary outcome) show a large amount of uncertainty around the effect sizes, baseline pad weight subgroup study suggest that the male sling is inferior to the sphincter for men with greater incontinence at baseline (pad weight >250g). This corresponds to it has been previously published that success for sling surgery appears to relate to the severity of leakage.[60,498,611] Furthermore, the strict definition of incontinence and the omission of postoperative pad-weights makes it difficult to compare the outcomes of this trial with those of the non-randomized cohort studies that typify the majority of the literature regarding surgery for PPI. Regarding the preoperative status, a 20% of sling group patients and 20.5% of AUS group patients had received radiotherapy for prostatic disease. As mentioned previously history of radiotherapy correlates with a higher rate of sling failure and therefore this data should also be evaluated. The subgroup analyses also suggest that the male sling may perform better than the AUS for men with pure SUI at baseline

3.5. Conclusion

The Committee’s conclusions should be evaluated accepting that there is no strict consensus in the degree of incontinence (with classification of pad weight and category of incontinence). In men who have not been radiated and have not had prior incontinence surgery, factors such as degree of leakage, proximal urethral mobility, and detrusor contractility can help determine the preferred surgical approach.

The Committee’s recommendation in those with mild to moderate leakage (with 24-hour pad test below 400g per 24 hours) and a positive repositioning test or adequate urethral mobility on video urodynamics, a retroluminal (transobturator) or compressive (quadratic or adjustable) sling is a reasonable approach, with lower complication rates compared to AUS placement and without an adverse effect on future AUS placement. Nevertheless, data from the recent RCT MASTER study show no evidence of difference between male sling and AUS.

With leakage > 400g per day (moderate to severe), AUS is the recommended option, due to a general demonstration of superior efficacy than the male sling in non-comparative studies and in the MASTER subgroup analyses suggest that the male sling is inferior to the sphincter for men with greater incontinence at baseline (pad weight >250g). The recently published MASTER trial does not support this finding of AUS superiority in those with higher preoperative pad weights due to the range in both groups was below (the range was less than 554g in both groups,89–545g in SLING group and 130–554g in AUS group).

In the patient who will not or cannot have an AUS, a compressive sling is also a reasonable alternative as long as he has urodynamically demonstrable normal bladder contractility and understands the higher risk of sling failure.

The Committee's recommedations in patients with persistent mild to moderate SUI following prior sling, AUS implantation is the treatment of choice for persistent PPI because it can provide the circumferential urethral compression necessary for adequate coaptation even in the setting of diminished urethral compliance. Even though the mechanism of action is quite similar in both AUS (AMS-800® and Zephyr®), nowadays the track record of AMS 800® is much longer.

It has the largest body of literature reporting long-term success and this success and high patient satisfaction seem to outweigh the need for periodic revisions in some patients with AUS. Intermediate-term data with the male sling demonstrates that the sling is equally efficacious with a lower rate of severe complications in patients with mild-moderate SUI, provided that those patients have not failed previous AUS surgery, have not had radiation treatment, and have normal bladder contractility.

The Committee's propose there exist a need for further study (multi-institutional) to evaluate the grey zones (i.e., leakage > 400g per day, prior radiotherapy, pre-existing comorbidities, bladder, hypocontracility) due to clinicians need to adequately counsel patient and have back-up plan if intended clinical outcome is suboptimal.

4. PERIURETHRAL BULKING AGENTS

Periurethral bulking agents (PUBA) offer men with stress urinary incontinence (SUI) a minimally invasive surgical option to restore urinary continence by increasing the urethral resistance to urinary flow and augmenting urethral coaptation at the level of the bladder neck and/or distal sphincter. In contrast to male urethral sling which is predominantly utilized in the setting of post-prostatectomy, PUBA has been used in post TURP and neurogenic SUI patients, some with relative success rate. PUBA has received considerable attention for the treatment of SUI in women; however, their role in male SUI is more uncertain with the optimal agent, patient selection, and technique(s) still yet to be defined. Published literature shows suboptimal clinical outcomes compared to other surgical continence options, with the need for multiple periurethral injections and the risks of subsequent deterioration and/or migration of bulking particles over time.

4.1. PUBA Classification

PUBA can be divided into two major classes: those made from solid microparticles in an absorbable liquid or gel carrier (particulate agents) and those comprising a homogenous gel (non-particulates) that resists absorption. The two types of bulking agent achieve their effect of urethral coaptation in slightly different manners. In the case of the particulate bulking agents, they induce a foreign-body reaction around the particles resulting in fibrosis formation. Current and previously marketed particulate bulking agents includes Macroplastique® polydimethylsiloxane (Uroplasty Ltd, Reading, Berkshire, UK), Durasphere® carbon-coated zirconium oxide (Carbon Medical Technologies, Saint Paul, Minnesota, USA), Coaptite® calcium hydroxyapatite (Boston Scientific, Marlborough, Massachusetts, USA) and Tegress® and Opsys® polyacrylate/polyalcohol copolymer (Promedon, Córdoba, Argentina). With the exception of calcium hydroxyapatite, these particles are non-degradable with each agent achieving its long-term bulking effect through reactive changes around the persisting particles while the carrier volume is lost. Non-particulate PUBA are Bulkamid® polyacrylamide hydrogel (Contura Ltd, London, UK), Contigen® glutaraldehyde cross-linked bovine collagen (CR Bard, Covington, USA) and Deflux® dextranomer hyaluronic acid (Q-Med, Uppsala, Sweden).

Contigen has served as the standard by which all other injectables are compared for the treatment of SUI. Contigen was FDA approved as a urethral bulking agent in 1993 but its production was discontinued in 2011. There are a significant number of studies published on the role of Contigen as PUBA with reported clinical "success rates" around 36–69% in post-prostatectomy incontinence, with 4-20% of patients reporting no pad use postoperatively.[,,,,] In these studies, multiple injections were required to achieve subjective improvement in the continence rate. There was no reported advantage between retrograde and antegrade periurethral injection techniques.[627] The presence of extensive bladder neck scar or urethral stricture formation, previous radiation, and severe SUI and low abdominal leak point pressure (ALPP) adversely effect the success postoperatively.[624,627] Comparing treatment outcome in those with SUI following transurethral prostatectomy as opposed to radical prostatectomy, it was shown that the presence of residual prostatic tissue was associated with more favourable continence postoperatively. The use of PUBA did not appear to adversely affect the outcomes including complication rate of subsequent artificial sphincter implantation or bone-anchored male sling surgery. Some of its major drawback include biodegradability, need for retreatment, allergic reaction and the unknown long-term risk of urethral complications as well as the possibility of distant migration.

Macroplastique® is a minimally invasive silicone macroparticulate agent with global clinical literature describing its use over 20 years. In one of the early studies, Bugel et al reported an initial success rate of around 71% at 3 months but this improvement decreased to 26% at 12 months follow up. A similar observation was confirmed by a recent study that showed 43% success at 3 months following Macroplastique® injection, which declined to 32% at 6 months; lower ALPP and a history of radiation correlated with treatment failure. In a larger prospective study, Kylmala et al demonstrated that 2 injections were more ideal with short-term continence achieved of 12%, 20%, 18%, and 10% following 1, 2, 3, and 4 injections respectively. A quantitative meta-analysis review of Macroplastique supports its use as an effective, durable, and safe treatment option for female SUI, with some patients requiring reinjection. In a randomized trial of the artificial urinary sphincter (AUS) vs Macroplastique® injection in patients with minimal SUI, Imamoglu et al[57] demonstrated no significant difference in success with AUS vs Macroplastique® in the short-term. However, in patients with more severe incontinence, AUS was superior, with minimal improvement following transurethral Macroplastique. As one would expect, due to the poor efficacy of PUBAs, their use for treating male SUI had decreased dramatically over the past decade, from 80% of cases in 2004 to 60% in 2010, and less than 40% cases in 2013.[615]

Newer PUBAs have been reported in several small series publications with suboptimal clinical outcomes. Hurtado et al showed that

not only was the failure rate high, but the complication rate was also unacceptable, as 10 out of 17 patients suffered complications, such as erosion of injected material, which was reported in 41.1% of patients. Tregress has been voluntarily removed from the market due to safety concerns. Clinical utility of Opsys which is manufactured by the same company, has also shown poor outcomes with only one patient with success, one with improvement, and eight with failures after 1 month of follow-up study. Subsequently, one patient was treated with an artificial urinary sphincter and two patients with a male sling. Carbon-coated zirconium beads have been similarly reported to be inefficacious, with one recent study reporting that none of the patients achieved subjective or objective cure. Similarly, Deflux use as PUBA has been shown to be poor with a high failure rate.

Common PUBA-related complications include urinary retention, UTI, dysuria, and hematuria.[620] Postoperative retention is the most common complaint (3–17%) with most study protocols requiring satisfactory voiding as the condition for discharge. No intervention was needed in most cases, however, a few patients required temporary catheterisation. Uncommon complications such as periurethral pseudocyst and urethrovaginal fistula have been reported in women.

While it is generally accepted that PUBA works best in carefully selected men with mild-to-moderate SUI, PUBA injections may be as effective as AUS or male sling.[630] Several factors have been cited as preoperative indicators towards treatment success. A VLPP value of 60cmH_2O or higher was more likely to have a better response to PUBA.[625] There is a strong correlation among previous radiation therapy, concomitant detrusor overactivity, or bladder neck contracture with treatment failure.[620] Furthermore, previous intraoperative complications, such as excessive blood loss, scarring from multiple anastomotic incisions, and difficult prostatectomies are associated with worse clinical outcome.[623] Comparing PUBA use in post-prostatectomy vs. TURP-related SUI, more favourable outcomes were reported in the TURP group.[57] Nonetheless, there is a lack of standardized protocols and surgical techniques in the literature. The volume of injection, injection site, and even the procedure approach (antegrade vs retrograde injection) differ among published studies.[620]

There has been considerable interest in the use of novel agents such as autologous muscle cells, stem cells, and fibroblasts recently. Numerous pre-clinical studies have demonstrated the therapeutic utility of stem cells in various animal models of mechanical, nerve, or sphincteric injury, with improvement observed in terms of leak point pressure, myoskeletal dedifferentiation and urethral muscle contractility. Several clinical studies have now demonstrated the short-term safety and efficacy of stem cell therapy in treating SUI.[,] Current research has leaned towards the use of adipose-derived stem cells and muscle-derived stem cells, as they are easier to harvest with higher yield compared to autologous bone marrow-derived stem cells.[637] In a landmark publication, Mitterberger et al[645] demonstrated a 67% continence rate at an average of 1-year follow-up following transurethral ultrasound-guided injections of autologous fibroblasts and myoblasts obtained from skeletal muscle biopsies. Another study from the same group also demonstrated that men with post-prostatectomy incontinence achieved a 52% dry rate with the injection of adult autologous stem cells, which appeared superior to a similar cohort of men treated with collagen injection.[646] However, this study was subsequently retracted and was investigated by the country governmental agency for scientific data irregularities.

In another large study, Gerullis et al demonstrated that muscle-derived stem cells can achieve complete continence in 12% and improvement in 42% of 222 men at 1-year post-injection. Nonetheless the levels of stem cells viability and engraftments following periurethral injections remain uncertain at this stage with studies showing that the concomitant administration of other bioactive factors such as poly-lactic-coglycolic acid (PLGA), various growth factors (e.g., nerve growth factor, brain-derived neuropathic factor) or calcium concentration microdomains, may improve the clinical outcomes such as urinary leak point pressure, muscle mass density, and concentration of neuronal density compared to delivery of stem cells alone. While the current evidence is accruing to suggest that stem cells may be a viable alternative for PUBA, issues relating to long-term safety, efficacy, and quality of stem cell therapy remain a potential concern and pose considerable bioethical challenges before widespread clinical application.

4.2. Conclusion

PUBAs remain the most minimally invasive surgical treatment option for male SUI despite the heterogeneous study populations. In addition to its simple administration technique, injectable therapies offer men with SUI who are not able to tolerate or refuse more invasive continence surgery such as male sling. Bulking agents should be differentiated into two classes based on their mode of action and whilst few head-to-head data exist, differential safety profiles are emerging. A higher success rate is observed in patients with a higher abdominal leak point pressure, absence of scarring or stricture, and no radiation history. There are no demonstrable differences in clinical outcome with respect to a transurethral vs retrograde injection method, and similarly, no differences were seen between proximal urethral or bladder neck injection site. However, patients should be counselled regarding the modest success rates with very low cure rates and these clinical effects will deteriorate over time. The use of PUBA for the treatment of male SUI should only be utilized when other more effective treatments are contraindicated or have been rejected by patients.

(Level of evidence 3; Grade of recommendation C)

5. ADJUSTABLE CONTINENCE THERAPY (PERIURETHRAL BALLOONS)

The adjustable balloon procedure (ProACT, Uromedica, Plymouth, MN), which is performed under general or spinal anesthesia through a perineal incision and guided with fluoroscopy and urethroscopy, relies on passive compression of the urethra by two adjustable balloons located on either side of the membranous urethra.

Adjustable balloons appear to be a feasible procedure in the short to medium term for patients with mild to moderate leakage and no prior radiation. However, the potential benefits should be weighed against the need for multiple sessions of refilling the balloons, and the reported rate of peri- and post-operative complications.

Reuvers et al evaluated changes of the urethral pressure profile (UPP) after implantation of ProACT in men with PPI. Maximum urethral closure pressure (MUCP) increased significantly from median 58.0 to 79.0 cmH_2O in the successfully treated group (P=0.001). Within the subgroup of unsuccessfully treated patients, MUCP did not change significantly (P=0.715). The change in MUCP was statistically significantly different between the successful and unsuccessful group (P=0.034). The authors concluded that increased

static urethral pressure contributes to the working mechanism of the ProACT device to achieve continence.

Larson et al carried out a systematic review to assess the efficacy, safety profile and rates of adverse events associated with the implantation of adjustable balloon devices in the treatment for male stress urinary incontinence (SUI). In total, 19 studies were included with a total of 1264 patients. ProACT implantation resulted in an incontinence QOL improvement of 30.8 points from baseline. At baseline, patients on average were using 4.0 pads per day (PPD) (95% C: 2.6-5.4), which was reduced to an average of 1.1 PPD (95% CI: 0.5-1.7) after ProACT implantation. The number of patients that were considered “dry” was 60.2% (95% CI: 54.2%-65.9%) and the number of patients who were found to be either “dry” or improved greater than 50% was 81.9% (95% CI: 74%-87.8%). Across the analyzed patient populations, the average number of adjustments was 3.2, with mean reported final balloon volume of 3.1mL. A total of 18 studies had adverse event data available for analysis. The most common intraoperative complication during ProACT implantation was bladder or urethral perforation. The meta-analysis estimate for intraoperative perforation of the bladder or urethra was 5.3% (95% CI: 3.4%- 8%). Estimates for infection and urinary retention were 2.2% (95% CI: 1.1%-4.3%) and 1.5% (95% CI: 0.7%-3.4%), respectively. The estimated overall revision rate for all causes was 22.2% (95% CI: 15.2%-31.2%) with a mean follow-up of 3.6 years (range 12–118 months). The pooled estimate of either urethral or bladder erosions causing explant was 3.8%. The pooled estimate of migrations resolved by explant was 6.5%. The mean follow-up time was 3.6 years, with only one study having a mean follow-up greater than 5 years; although, many papers included patients with longer follow-up. More long-term data is needed to better determine long-term efficacy results of the therapy. Heterogeneity among included patient cohorts was a major issue. The median follow-up ranges, the number of patients per study, surgical technique, and management of complications varied greatly across the studies.

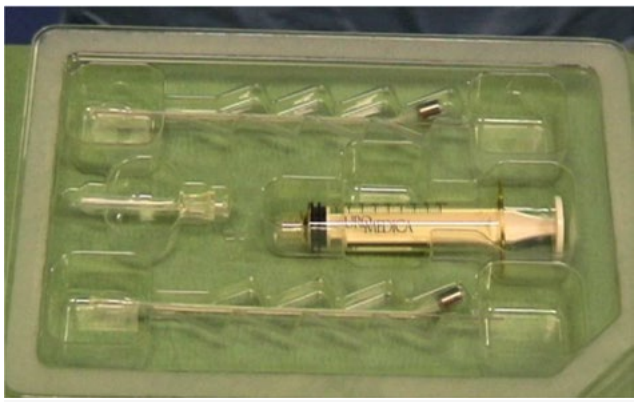
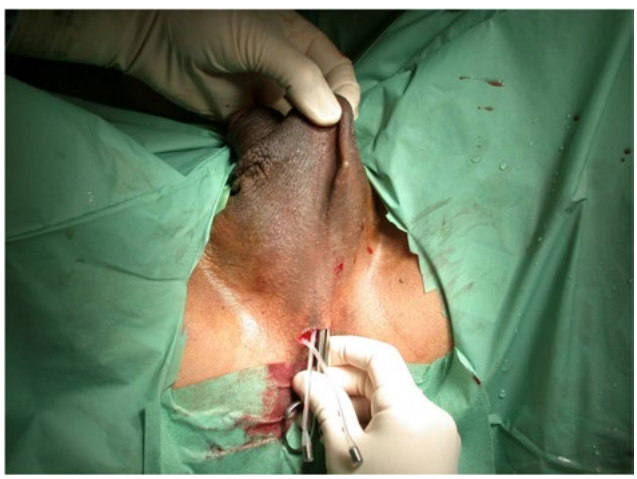


Figure 24. Adjustable Continence Therapy (Periurethral Balloons) surgical kit. Courtesy of Dr. Emmanuel Chartier-Kastler

Angulo et al[7] have also systematically reviewed the literature to compare ProACT to Adjustable Transobturator Male System (ATOMS) with respect to efficacy and safety. Combined data of 41 observational studies with 3059 patients showed that from an efficacy standpoint, there were lower dry and improvement rates for ProACT compared to ATOMS (55% vs 68%, *P*=0.01; 80% vs 91%, *P*=0.007, respectively). The decrease in mean pad usage and pad weights were significantly lower with ProAct compared to ATOMS (-2.5 vs -4 PPD, *P*=0.005; -211.4 vs -425.7 g, *P*<0.001, respectively. Furthermore, patient satisfaction was significantly higher for ATOMS (87 vs. 56%; *P*=0.002). The complication rate for ProACT was also higher, but not statistically significant (17 vs. 26%; *P*=0.07); although, the explant rate was significantly higher with ProACT (24% vs 5%, *P*<0.001). While the mean follow-up was lower for ATOMS than ProACT (20.8 vs. 30.6 months; *P*=0.02), the rate of working devices favored ATOMS at 1-year (92 vs. 76%; *P*<0.0001), 2-years (85 vs. 61%; *P*=0.0008) and 3-years (81 vs. 58%; *P*=0.0001). Significant heterogeneity was seen among the studies, thought mainly due to variable incontinence severity baseline. Other issues identified were differing criteria for reporting of complications, different number of adjustments and time of follow-up and absence of randomized studies.

Of interest while these two reviews note similar efficacy outcomes the complications rates listed are somewhat different. **Periurethral balloons are a feasible minimally-invasive option for treatment of bothersome PPI. However, high complication rates have been reported (Level of evidence 3-4; grade of recommendation C). Heterogeneous data suggest that periurethral balloons were less effective than an adjustable TO sling (LE 3, GR C).**



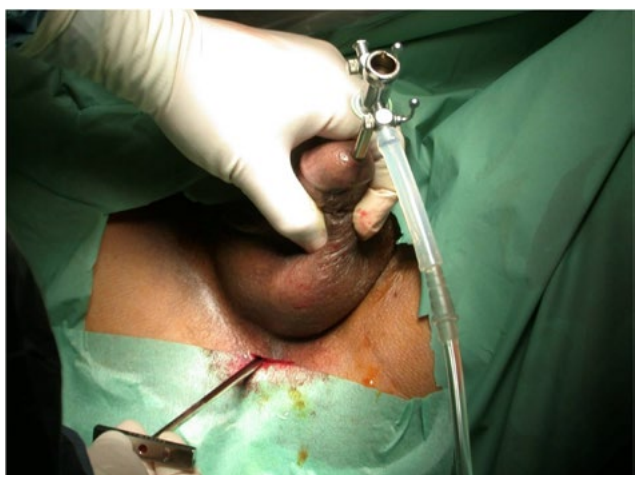


Figure 25 (A and B). Adjustable Continence Therapy (Periurethral Balloons) surgical technique. Courtesy of Dr. Emmanuel Chartier-Kastler.

Most studies focused on ProACT for post-radical prostatectomy urinary incontinence. However, one recent publication assessed the use of ProACT for incontinence after TURP. Adjustable continence balloons were implanted in 29 patients with post-TURP SUI between 2007 and 2018. Continent status was defined as no pad or one security pad. Preoperative urinary incontinence was mild in 7 (24%), moderate in 12 (41%), and severe in 10 (35%) patients. The median follow-up duration was 21 (IQR, 11–43) months. Within 30 days postoperatively, a Clavien-Dindo grade less than or equal to II complication occurred in 24% of the patients. Reintervention rate was 24%. Six and 12 months after implantation, the International Prostate Symptom Score (IPSS) quality-of-life item improved significantly from 5 (IQR, 5-6) preoperatively to 3 (IQR, 1-4.5) and 1 (IQR, 0-3), respectively. At last visit (median 21 months after implantation), the outcome on continence had improved in 76% of the patients, including, 45% dry patients. After a median follow-up of 28 months (IQR, 13-63; N=23), all but one patient reported improvement on the PGI-I scale. In detail, 10 patients reported "very much better" condition compared with before the implantation, 10 patients "much better," two patients "a little better," and one patient "no change." Daily pad use decreased from three (IQR, 2-5) to one (IQR, 0-2) pads/day (P<0.001).

Due to the paucity of data, no definitive recommendation can be made on ProACT for SUI after surgical treatment of benign prostatic obstruction.

6. FUTURE DIRECTIONS

6.1. New Technologies Under Evaluation

6.1.1. Introduction

Despite the advances in the surgical treatment of PPI, both slings and AUS present limitations in terms of continence rates and complications. With greater than 100,000 prostatectomies performed per year with a 9–20% risk of incontinence, treatment of PPI is a common clinical issue treated by urologists.[2,] This context makes room for the development of new technologies and minimally invasive treatments.

6.1.2. AMS 800 Innovations

While the AUS has not been modified or updated significantly for more than two decades, Boston Scientific and other manufacturers are working on new AUS concepts. Current research and development are focused on changes in the activation and regulation mechanism. In the future, the manual pump may be discarded in favor of a Bluetooth controlled automatic filling/emptying mechanism.

Newer engineering developments in electronics and remote-control focus on innovative activation mechanisms, which are designed to meet the needs of individual patients. For instance, if a patient needs more pressure for a specific activity as in heavy lifting or straining, the electronic actuator could be programmed to meet that need.[658] Furthermore, these electronic actuator may increase the longevity of device with the possibility of "deactivation" during the nighttime to reduce urethral atrophy from constant cuff compression. These developments are closely related to the advances in lithium battery technology with batteries rated to last up to 16 years,

Using these concepts, Biardeau et al[16] proposed different options for an electronic control system for the AMS 800 AUS. Possible working mechanisms for remote-controlled electronic artificial urinary sphincters would include:

a) "Closed" state: the cuff is inflated, and the pump is unpowered; the pressure is equilibrated between the pressure-regulating balloon and the cuff, allowing to maintain a constant predetermined occlusion closure pressure (OCP) as long as necessary;
b) Cuff deflation: as soon as a Bluetooth connection is established, the microcontroller activates the pump; the fluid is then transferred from the cuff to the balloon;
c) "Open state": the cuff is deflated, and the pump is unpowered.
d) Cuff inflation: as soon as decided via the control interface, the fluid progressively flows back to the cuff in 2–3 min thanks to the hydraulic resistor, returning to a "closed" status.

Many of these modifications, which are currently being researched by the companies, remain in development and are proprietary.

6.1.3. ZSI 375 (Zephyr Surgical Implants)

Over the past several years, the Zephyr artificial sphincter device (Zephyr ZSI 375; Zephyr Surgical Implants, Geneva, Switzerland) has been investigated and results have been recently reported. Like an AMS 800 AUS, the ZSI 375 is a hydraulic device with a fluid filled cuff that wraps around the urethra and a pump mechanism to deflate the cuff for voiding. Unlike an AMS 800, the ZSI 375 is a one-piece device with the cuff being connected by a tube to a pump and pressure regulating tank. The cuff is adjustable with a strap that can be set to different levels of tightness (like a belt) and the amount of fluid in the system can be adjusted postoperatively as needed via an injection port transcrotally. There is no abdominal reservoir. Unlike the AMS 800, the ZSI 375 allows for readjustment of cuff tightness in the case of postop urethral atrophy. However, there are only a limited number of peer reviewed publications.

Staerman et al[598] evaluated 36 patients who underwent a ZSI 375 device placement. The median (range) follow-up was 15.4 (6–28) months. Social continence (0 or 1 pad per day) was achieved in 28/36 patients (78%) at 3 months and 26/36 patients (73%) at 6 months after device activation. No patient experienced bladder overactivity, chronic urinary retention, or any other adverse effect after device activation. Complications leading to device removal arose in four patients (one case of erosion, three cases of infection).

Kretschmer et al conducted a multicenter study to assess ZSI 375 efficacy and safety in men with stress urinary incontinence. Thirteen patients underwent implantation of a ZSI375 artificial urinary sphincter device between 2010 and 2012 in three international continence referral centers. Median follow-up was 13.5 months. Mean daily pad usage decreased from 5.8 ± 1.5 to 2.4 ± 2.1 (P=0.066). One patient (7.7 %) did not use any pads. Social continence (0-1 pads) was achieved in only 15.4 % of the patients. In this period, four device defects (30.8 %) were observed, and were the main cause for device explantation, followed by device infection (15.4 %), non-resolving pain (7.7 %), and urethral erosion (7.7%). Overall explantation rate was 61.5 %. Mean time-to-explantation was 279 ± 308 days. There was no significant influence of previous irradiation or previous invasive incontinence therapy (P=0.587 and P=0.685, respectively).

Llorens and Pottek reported medium-term results and reported on 106 patients with a mean age of 72 years and followed up for 24 months. They found a 91.8% success rate with 83.6% of patients dry. There were 4 infections, 19 erosions, and a total of 24 patients required explantation. There were three mechanical malfunctions caused by intraoperative sphincter cuff damage.

Ostrowski et al reported on fifty patients followed for a median of 21.04 months. There were 12 explantations (9 erosions, 3 mechan-

ical malfunctions, and 0 infections). Outcomes were 0–1 pad per day 29/50 (58%), and there was improvement to 50% of preoperative pads per day 15/50 (30%) and failure in 6/50 (12%).

More recently, in a multicenter, retrospective review of 109 patients with "severe" incontinence (≥4 pads per day) and mean follow-up of 43 months, Ostrowski et al[600] reported daily pad usage decreased significantly to 0.84 pads per day with 19% achieving total continence, 65% social continence (0–1 pads per day), 8% improved (<less than 2 pads per day and 50% fewer pads than at baseline) and 7% failures (≥4 pads per day). Complications were noted in 12 (11%) patients with cuff erosion in 9 (8%) and mechanical failure (fluid leak) needing surgical revision in 3 (3%). There were no device infections.

This device is currently available in selected Western countries (not in USA) and is not promoted in Asia or Africa. While long-term data on clinical efficacy and safety are lacking, but the data available show some promise for the Zephyr ZSI 375.[658]

6.1.4. ContiClassic aus (Rigicon, USA)

The ContiClassic AUS (Rigicon, USA) is a new non-adjustable AUS similar to the AMS 800 in terms of design and mechanism of action. However, it has 2 potential advantages over the current AMS 800 namely a more diverse occlusive cuff sizes (increments of 0.25cm) and a hydrophilic coating on all external surfaces of the device allowing for individualized use of antibiotic and subsequent drug elution into the implant spaces. As this product is new, the data on clinical outcomes is accruing.

6.1.5. BR-SL-AS-904 Device

Another new design of the classic hydraulic AUS model BR-SL-AS-904 was recently reported from Brazil. Like the VICTO+, this modified AUS has a pressure transmission system with a reservoir placed in the abdominal cavity with connection with the inflatable urethral cuff. Any increase in pressure on this reservoir is transmitted through the hydraulic system to the urethral cuff, allowing increased pressure and preserved continence during stress-related increases in abdominal pressure. The authors have reported on 15 patients followed up for >1 year. Pad weight test had a mean change from 75.72 to 23.50g. ICQF - SF score also showed a decrease, ranging from 16.71 to 7.33. There were no infections; although, 27.2% of the devices were removed for mechanical complications with a 4% urethral erosion rate. Again, longer-term data is missing and further multicentre trials will be required to evaluate its clinical outcomes.

6.1.6. Stem Cells

Periurethral bulking using permanent injectable material has generally proven inefficacious for treating male ISD, due to non-incorporation of the injectate into functional tissue. In an effort to create a more functional urethral bulking, the use of stem cells has been studied and reported on in females with SUI. Currently, two studies looking at stem cells for male stress urinary incontinence are listed on clinical trials.org as enrolling patients. One evaluating the use of autologous adipose derived regenerative cells is run through Nagoya University and the other utilizing autologous muscle derived stem cells is run through Cook Myosite. While the use of stem cells to treat male SUI is very attractive, data collection and evaluation are still in progress and its use outside of a clinical trial cannot be recommended. Furthermore, the exact mechanisms of action and longer-term safety data are largely unknown.

V. REFRACTORY DETRUSOR OVERACTIVITY/SPECIFIC SURGERY FOR OVERACTIVE BLADDER

1. OAB

1.1. Prevalence

Overactive bladder (OAB) is a symptom complex characterized by urinary urgency, usually accompanied by increasd daytime frequency and/or nocturia with urinary incontinence (OAB wet) or with (OAB dray) in the absence of urinary tract infection or other detectable disease.[35] Quality of life is adversely affected in 65% of patients with OAB. According to the 2001 study by Milsom's group, which is a population-based study out of the United Kingdom, Sweden, Spain, Italy, Germany and France of 16776 randomly selected women and men, the overall prevalence of OAB symptoms was 16.6%. In men the prevalence was 15.6% versus 17.4% in women. Most storage symptoms were similarly prevalent regardless of gender, but urgency urinary incontinence (UUI) was more common in women than men. The 2003 National Overactive Bladder Evaluation study focused on men and women in the United States, reporting that 16% of men and 16.9% of women suffered OAB. Regardless of age, women experienced UUI at higher rates than men. Interestingly, whereas higher BMI was associated with a higher prevalence of UUI in women, no such association was found in men. The 2006 EPIC study regarding lower urinary tract symptoms and OAB surveyed 19,165 adult men and women in the United Kingdom, Canada, Germany, Italy, and Sweden by telephone. Prevalence rates of 12.8% in women and 10.8% in men were reported. Women were nearly three times more likely to have incontinence (13.1% vs 5.4%), but with respect to UUI, prevalence was similar regardless of gender. The 2011 EpiLUTS (Epidemiology of Lower Urinary Tract Symptoms) study surveying men and women from the United States, Sweden, and United Kingdom reported that 15.8% of men and 32.6% of women complained of OAB symptoms "often", with women having a higher rate of UUI. The 2018 LURN (Symptoms of Lower Urinary Tract Dysfunction Research Network) found that the prevalence of incontinence in men seeking urologic care was 51%, with post-void dribbling reported by 41% and UUI by 29%. SUI occurred in 3–4%. The inclusion of men who were already seeking urologic care, and the inclusion of post-void dribbling under the umbrella of "incontinence" skews this survey toward a higher rate of incontinence compared to previous reports. Initial management of OAB involves behavioral therapy, pelvic floor physiotherapy and/or medications (See chapter on surgical management of OAB).

1.2. Refractory OAB/UUI

In men with OAB/UUI who do not respond or do not tolerate pharmacotherapy, further treatment with peripheral tibial stimulation, chemodenervation with botulinum toxin and sacral neuromodulation should be considered (See chapter on surgical management of OAB). The possibility of occult neurogenic voiding dysfunction or undiagnosed bladder outlet obstruction (BOO) must be considered in patients with refractory OAB. Refractory OAB is the term used for patients who have failed a trial of symptom-appropriate behavioral therapy of sufficient length to evaluate potential efficacy and for those who have failed a trial of at least one anti-muscarinic medication administered for 4 to 8 weeks. Failure of an anti-muscarinic medication may include lack of efficacy and/or inability to tolerate adverse drug effects. For further information on OAB, including neuromodulation techniques and botulinum toxin, please refer to

chapter 11 (Surgery for Urinary Incontinence in Women) and 12 (Neurogenic Patients), respectively.

2. NEUROGENIC VOIDING DYSFUNCTION

Neurogenic bladder results from a variety of congenital or acquired conditions that can adversely affect the central or peripheral nervous system. Storage and voiding dysfunctions typically vary with the level of the neurological lesion. In general, UUI is more likely with a suprasacral lesion than with a sacral lesion, due to augmentation of the purinergic signaling pathway. Unlike in the bladders in neurologically intact men, where cholinergic innervation predominates, there is an increase in purinergic innervation in the setting of suprasacral neurologic insult. This abnormal elevation of P2X2 receptor density, characteristic of suprasacral spinal cord injuries, may inhibit the parasympathetic release of acetylcholine.

Neurologic disease affecting the areas of the brain associated with bladder control can cause UUI in the absence of other neurologic dysfunction. It has been generally established that the periaqueductal gray and pontine micturition center regulate voiding control in the brainstem, after receiving coordinated suprapontine signaling from the thalamus, insula, and frontal lobes.[1] The subcortical circuit consists of the hippocampal and paralimbic regions, permitting initiation of voiding when the brain judges that it is safe to void. The neurologically intact man can postpone voiding until he deems it appropriate. This inhibition may be lost in the setting of neurologic dysfunction of any of these brain or pontine regions. Part of this inhibition relies on bladder sensory information (including urgency) being properly registered in the midcingulate circuit from the periaqueductal gray to the supplementary motor area and dorsal anterior cingulate cortex. After registering urgency, pelvic floor and urethral sphincteric tone can be autonomically increased. Dysregulation of this suppression of the bladder can result in UUI.

Men with lumbar disc disease may suffer from UUI. However, unlike those with idiopathic OAB, these men will typically have lower back pain. More than half of such men will complain of storage and voiding symptoms, with nearly 50% demonstrating urodynamic abnormalities. While the most common finding is detrusor underactivity, DO may also be observed. As UUI is often a symptom manifesting from a combined abnormality of bladder activity and pelvic floor weakness, it is not surprising that perineal floor muscle innervation is often abnormal in the setting of lumbar disc disease. While chronic nerve damage typically results in bladder insensitivity and detrusor atrophy, early nerve root stretching can initially cause neurogenic DO. Detrusor overactivity with UUI can result from irritation of the sacral roots, especially with walking. Approximately half the time, the UUI resolves with lumbar disc surgery.

3. DIABETIC VOIDING DYSFUNCTION

Diabetes can also cause OAB symptoms with UUI. There appears to be a progression from DO as a cause for OAB in earlier and milder cases of diabetes mellitus, progressing to diabetic cystopathy over time, manifesting as impaired contractility and inefficient bladder emptying as a cause for bothersome urinary symptoms including overflow and urgency incontinence. Kebapci et al showed that in a group of 27 men with diabetes mellitus, urodynamic demonstration of bladder dysfunction was present in nearly 75%. Diabetic cystopathy was most common (50%) followed by an equal prevalence (25%) of BOO and DO. Diabetic cystopathy was most common in older men (> 64 years old), those with longer duration of disease (> 9 years), and with HbA1C > 7.9%. Elevated post void residual urine > 100 ml was associated with more severe disease, namely in men with autonomic neuropathy (delayed gastric emptying and cardiac conduction abnormalities) and with retinopathy and microalbuminuria.[679] In another study of 57 men, Majima, et al confirmed that more mild and early disease was characterized by DO with preserved contractility, while impaired contractility was most prevalent in men with diabetic retinopathy and nephropathy.

4. BLADDER OUTLET OBSTRUCTION

Although the prevalence of OAB symptoms in men and women is generally comparable, in men the symptoms are often attributed to bladder outlet obstruction (BOO), while in the absence of high-grade pelvic organ prolapse or prior suburethral sling, bothersome storage symptoms are rarely attributed to BOO in women. This difficulty differentiating between UUI due to detrusor overactivity (DO) with or without BOO related to benign prostatic enlargement (BPE) based on symptoms alone can lead to a diagnostic dilemma. As a significant minority of men with storage symptoms indeed do not suffer from prostatic obstruction, misdiagnosis can result in delayed and inefficient treatment, exacerbating the negative impact on quality of life caused by UUI in men. In the absence of a weak urinary stream, hesitancy, straining, and incomplete emptying, clinically relevant BOO is unlikely, yet only a minority of men with OAB symptoms are treated with detrusor-directed therapy.[11]

Men with BPO often suffer from mixed voiding and storage symptoms. Half of men with BPO complain of bothersome storage symptoms including UUI,[11] and in a significant minority (approximately 20-40%), the incontinence will persist following de-obstructive surgery.[340,343]

The use of detrusor-directed therapy in men with bothersome storage symptoms induced by BPH carries the theoretical risk of precipitating urinary retention. And with the risk of cognitive impairment in older patients taking anticholinergic medication, medical treatment has generally focused on alpha blockers with or without 5-alpha reductase inhibitors. Kaplan et al reported that the beta-three agonist mirabegron was both efficacious and safe when taken as add-on therapy in men with overactive bladder symptoms receiving tamsulosin for LUTS due to BPH. Statistically significant improvements were noted in urinary frequency, urgency and urgency urinary incontinence in men taking mirabegron plus tamsulosin versus those taking placebo plus tamsulosin. There was only 1 instance of retention requiring catheterization in the treatment group while taking the medication, and minimal change in average post void residual urine.[688] A meta-analysis of the use of mirabegron for the treatment of bothersome storage symptoms in men with BPH demonstrated the mirabegron was effective in treating overactive bladder induced by BPH in men receiving tamsulosin therapy. The number of micturitions per day decreased, urgency episodes decreased and total OAB symptoms score decreased significantly, with a clinically irrelevant increase in post-void residual urine volume of 12.02 mL (95% CI: 6.02018.04, P<0.0001).

While there are no patient-specific or urodynamic findings that can predict resolution or persistence of UUI with certainty, there are

several risk factors that are associated with a higher prevalence or persistent or de novo UUI following de-obstructive surgery: advanced age, pre-operative bladder capacity <250 mL, and DO.[344] Those patients with higher amplitude and with more frequent (repetitive) uninhibited bladder contractions were at particularly high risk of persistent postoperative UUI. Reitz et al recently showed that a novel ice water test during urodynamics can more accurately predict the persistence of storage symptoms following prostate resection. Specifically, the majority with a positive response (DO in response to bladder filling with cold water) and a minority of those with a negative response had persistent storage symptoms.[691] Interestingly, new onset urgency and incontinence is more common following laser vaporization of the prostate than after transurethral electrocautery resection, but also more likely to resolve over time. *De novo* UUI was recently reported to occur in >40%, resolving in approximately half by one month, and in all patients by 6 months following photovaporization.[302] Patients with bladder outlet obstruction should be considered for either medical or surgical therapy to decrease the obstruction.

5. URETHRAL STRICTURE

Similar to men with prostatic obstruction, those with urethral stricture disease are also susceptible to bothersome storage symptoms. Urgency or incontinence after stricture surgery may represent persistent or recurrent stricture, unrecognized prostatic obstruction, or bladder dysfunction. In a large multicenter study of over 400 men with anterior urethral stricture, 58% of men had urgency and 31% had UI preoperatively, which decreased to 40% for urgency and 12% for UI (each $P<0.01$) post stricture repair. Overall, 37% experienced improvement in urgency and 74% in UI. *De novo* symptoms were rare, with only 9% and 5% developing urgency and UI postoperatively. Risk factors for symptoms persistence were older age and stricture recurrence. In McCammon's series, nearly 90% of men had resolution of urgency and incontinence following successful stricture repair. Herschorn et al reported similar results in his review of 439 men, of whom one-third had UUI preoperatively, with only 12% complaining of persistent UUI postoperatively, and 5% developing de novo leakage. In general, those with the most severe symptoms preoperatively had the greatest improvement. For those with postoperative UUI, evaluation should include assessment of urethral patency via uroflowmetry, measurement of post void residual urine volume, retrograde urethroscopy, and cystoscopy. In the absence of a stricture, treatment should follow the OAB guidelines. Failure to improve should prompt urodynamic evaluation to rule out proximal (prostatic) obstruction, dysfunctional voiding, or DO. [Incidence and management of lower urinary tract symptoms after urethral stricture repair.[693]

6. URGENCY URINARY INCONTINENCE FOLLOWING PROSTATE CANCER TREATMENT

Following prostate cancer treatment, SUI is much more prevalent than is UUI. With respect to prostate extirpation, the most common cause of incontinence is intrinsic sphincter deficiency. However, a minority of patients will develop new onset UUI. In a recent large cohort, 29% of men developed de novo storage symptoms following radical prostatectomy, and 6% had frank UUI. The main risk factor for urgency leakage was radiation (either adjuvant or salvage) secondary to radiation-induced bladder changes.

Urinary incontinence is rare after brachytherapy for prostate cancer. Between 4% and 5% of men will have new onset leakage, with UUI occurring in 3.2% and stress incontinence in 1.2%.[259] Stress incontinence is much more prevalent in men who undergo transurethral resection of the prostate following brachytherapy, occurring in 18 to 70 % of such individuals.[263,266,] The data relates to urinary incontinence following more movel prostate cancer therapy such as proton beam or nanoknife technology is accruing and at this stage, there is very limited published data in this emerging field.

7. VOIDING DYSFUNCTION AFTER TREATMENT FOR RECTAL CANCER

Both the disease itself and the treatment for colorectal cancer can also cause urinary incontinence. In a large German case-control study of 3249 individuals with rectal cancer, the majority of whom were male, 16.7% reported UI, compared to only 5.3% of men without cancer (HR 3.59, 95% CI 2.91-4.44). Karlsson et al prospectively followed more than 1000 patients with rectal cancer. At baseline, 14% of women and 8% of men reported urinary incontinence, which doubled at 1 year to 29% of women and 14% of men.[699]

Following XRT for rectal cancer, temporary urinary dysfunction is much more common in men than in women, but typically resolves over several months. Following abdominal perineal resection, nerve damage is a common and typically unavoidable complication. During rectal extirpation, the parasympathetic nerve supply is vulnerable during deep dissection of the lateral planes, while sympathetic nerves may be injured during presacral and ventrolateral dissection of the mesorectum. Following surgery, anastomotic leak can lead to an inflammatory response causing pelvic nerve damage. While urinary leakage following rectal cancer treatment can be due to overflow or sphincteric insufficiency, UUI is typically due to DO following sympathetic nerve damage.

VI. URETHROCUTANEOUS AND RECTOURETHRAL FISTULAE

A urethrocutaneous fistula (UCF) is a connection between the urethra and skin. The fistulous opening is typically located on the penis, scrotum or perineum. A rectourethral fistula (RUF) connects the lower urinary tract and the distal rectum. Both types of fistulae can be either congenital or acquired, with the latter being much more common. Most acquired fistulae are iatrogenic in nature, and can lead to significant deterioration in quality of life including urinary incontinence if the fistula is suprasphincteric or associated with underlying sphincteric deficiency or *de novo* overactive bladder. Both conditions require a high index of suspicion for diagnosis, and can be readily identified with proper radiographic and endoscopic evaluation. Whether congenital or acquired, spontaneous closure is atypical, and most instances of UCF and RUF will require surgical repair.

It is important to recognize the varying causative factors, as the diverse etiologies (such as surgical versus radiation induced fistula) lend themselves to different surgical approaches to achieve satisfactory treatment outcome. More than three dozen distinct surgical techniques have been described in the literature, ranging from transanal to transabdominal, and from endoscopy to laparoscopy to open surgery. To date, there are no randomized studies, and

there is a lack of consensus regarding the "best" surgical approach. While the type of reparative surgery chosen is often related to the surgeon's familiarity with a specific procedure, the wide variety of approaches are characterized by different pros and cons, and should be considered in relation to the diverse etiology of UCF and RUF formation. For further information, please refer to chapter 13.

1. URETHROCUTANEOUS FISTULA (UCF)

1.1. Congenital Urethrocutaneous Fistula

Congenital anterior UCF is rare, with less than 65 reported cases in the literature. While a distinct embryological error causing UCF has not been characterized, these fistulae are thought to result from abnormal infolding of the urethral groove or from congenital urethral plate defects.

1.2. Acquired Urethrocutaneous Fistula

UCF is more typically an acquired rather than a congenital condition. With the increased utilization of gender confirmation surgery, urethrocutaneous fistula following phalloplasty or metoidioplasty is becoming more and more common. Retained vaginal remnant can lead to a urethral diverticulum, which, if untreated, can ultimately fistulize. Rarely UCF can occur following prostate cancer treatment, with an incidence of up to 0.4% after radical perineal prostatectomy, but as high as 10.7% following open perineal prostate cryosurgery. There have been case reports of UCF related to invasive fungal infection, genital tuberculosis, self-instrumentation of the urethra, urethral stones, circumferential penile strangulation by a broken condom, and even following circumcision, and penile fracture surgery gone awry.

By far, the most frequent cause of acquired UCF is related to urethroplasty and hypospadias repair. Risk factors include the length of urethral defect/location of the hypospadiac meatus, patient age, prior urethral surgery, and utilization of a single-layer closure during precedent surgery. With more proximal hypospadias, the risk of postoperative UCF formation is 1.3–1.5 times higher than with distal hypospadias repair.

Age is also a risk factor, with adolescent and adult patients having a higher risk of fistula formation postoperatively than younger boys.[739,740] This is most likely related to more frequent erections in adolescents and adults versus young children. More recently, Sheng's group reported that in their large cohort of Tanner 4 and 5 adolescents, age did not matter, nor did degree of chordee, but prior surgery and a longer defect length did indeed predispose to post-operative fistula.[741] A recent meta-analysis demonstrated that for distal hypospadias repair, the Mathieu repair had a lower risk for urethral stricture than did the tubularized incised plate repair, but the fistula rate was 13% in both groups. With repeat hypospadias repair, the fistula rate has been reported to be three times higher (18.6%) than with primary surgery (5.1%). Moreover, the incidence is substantially lower with a double-layer coverage (0.6%) compared to 5.1% with single-layer coverage only.

1.3. Management of UCF

The diagnosis of UCF is made by physical examination, retrograde urethrography or voiding cystourethrogram (Figure 26), urethroscopy, fistulography, urethral ultrasound, or color Doppler imaging. Urethral sonography provides additional information about any involvement of the surrounding tissue, location of vessels and associated abnormalities such as a periurethral abscess.

Treatment of UCF usually requires urethroplasty techniques with modifications involving fistula excision and multiple layer closure. In addition, based on a recent meta-analysis by Fahmy et al, it appears that the use of a tunica vaginalis flap rather than a dartos flap has a higher success rate, with the former having a recurrent fistula rate of only 5.1% versus 12.2% in the latter.[745]

2. RECTOURETHRAL FISTULA (RUF)

A rectourethral fistula is a connection between the lower urinary tract and the distal rectum. Rectourethral fistulae are typically grouped according to etiology: congenital, traumatic, neoplastic, inflammatory and iatrogenic. This condition can be devastating, resulting frequently in fecaluria, urinary incontinence, recurrent urinary tract infections, and pain. Congenital RUF is typically related to imperforate anus. Acquired RUF can form from penetrating trauma, but is more commonly iatrogenic.

2.1. Congenital Rectourethral Fistula

Endo et al described the results of the Japanese Study Group of Anorectal Anomalies (JSGA) to determine the relative incidence of specific types of these anomalies in Japan. They included discussion of RUF regarding the relationship between the fistula levels and the blind end of the rectum, low type deformity, rare types, and associated anomalies. A total of 1,992 patients (1,183 boys and 809 girls) registered from 1976 to 1995 were analysed according to the pathogenesis of anorectal malformation in the field of molecular genetics. They reported that more than 20% of RUF should be catego-

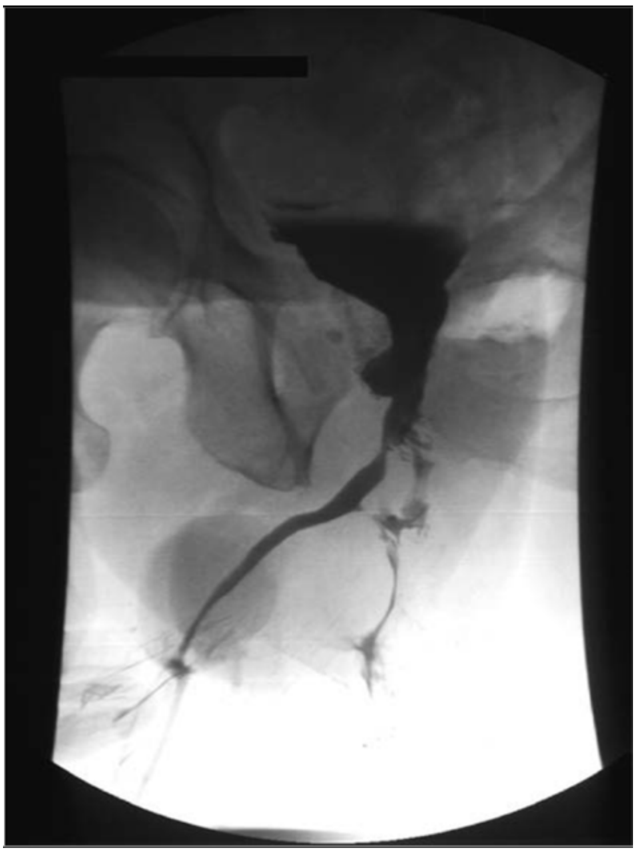


Figure 26. Voiding cystourethrogram after incision

rized as intermediate or low deformity from the position of the rectal pouch. A significant preponderance of Down´s syndrome in the deformities without fistulae suggests that investigation of associated anomalies and congenital diseases may provide further insights.[752]

With respect to surgical outcome of sacroperineal-sacroabdominoperineal pull-through (SP-SAP) compared to that of posterior sagittal anorectoplasty (PSARP), Rintala et al reported that in boys with high anorectal anomalies, PSARP was superior to SP-SAP pull-through in terms of long-term bowel function and fecal continence. More recently, the German network for congenital uro-rectal malformations evaluated postoperative urological complications in 267 patients with anorectal malformations (recto-urethral fistula in 21 cases). According to type of operation, the highest number of postoperative urologic problems was reported after abdominosacroperineal pull-through.

2.2. Acquired RUF

While there are multiple causes for acquired RUF (See Table 4), the most common causes are penetrating trauma and iatrogenic.

2.2.1. Penetrating Trauma

With penetrating colorectal or genitourinary trauma, depending on the nature of the injury, RUF can form in 0–18% of instances.[,,,,] The risk of fistulization increases as the degree of rectal wall involvement surpasses 25%, and such substantial rectal wall involvement is characteristic of the majority of colorectal injuries suffered during wartime.

A high level of suspicion is necessary to diagnose concomitant genitourinary (GU) and rectal injuries. While hematuria is generally seen in patients with bladder or urethral injuries (sensitivity > 93%),[758] rectal injury can be occult, with only 25% of cases manifesting blood per rectum. Gunshot wounds to the GU or gastrointestinal (GI) tracts are generally associated with a high rate of multiple organ injuries. With gunshots to the urinary tract, up to 60% of patients have intestinal injuries and up to 34% have rectal injuries.[757,] In trauma victims presenting with a small bowel, colonic or rectal penetrating trauma, nearly half have an associated bladder injury.[757] Meticulous evaluation is often necessary to diagnose an acquired traumatic RUF. In the stable patient, a triple-contrast CT (oral, intravenous and rectal contrast) is generally 100% sensitive and 96% specific in diagnosing concomitant GI and GU injuries, which is substantially higher than direct proctoscopy. In the case of a missed injury, RUF occurrence is typically heralded by the symptoms of pneumaturia, urine per rectum, or recurrent/persistent urinary tract infection.

TABLE 4. Etiology of Acquired RUF

External Traumatic	Iatrogenic
• Penetrating trauma (gun, bladed weapon) • Polytrauma (complex pelvic fracture with pelvic visceral injuries)	• Lesions associated with prostate cancer treatment (surgery, radiotherapy, cryotherapy, HIFU, etc.) • Lesions associated with rectal cancer treatment (surgery, radiotherapy) • Other: ◦ Prostate-related: TURP, biopsy, infection ◦ Bowel-related: inflammatory bowel disease, anorectal pathology, etc.

2.2.2. Iatrogenic RUF

RUF can relate to complications of surgery (of the prostate or rectum), radiation or other ablative energy applications to the rectum or prostate (Figure 27).

While more commonly associated with treatment of malignant disease, RUF can be an uncommon result of therapy for benign disease. RUF can occur following cautery injury during TURP, and presents with urinary leakage per rectum, pneumaturia, fecaluria, and unexplained diarrhea.[,] (Figure 28).

Following Holmium laser enucleation, RUF is believed to occur due to delayed thermal or infectious reaction. Even more rarely, RUF can result from infectious or inflammatory processes.[,,]

RUF can occur following repeated prostate biopsy,[703,] and rarely secondary to severe invasive infections, such as pseudomonas prostatitis or Fournier's gangrene with aggressive debridement of necrotic tissue.[,]

RUF can also form when the large bowel is affected by inflammatory bowel disease, with several reports of RUF in patients with Crohn's disease.[,,] There have even been reports of fistula formation following sclerotherapy for hemorrhoids, as well as following transurethral resection of the prostate for benign prostatic obstruction.[765,766]

Whereas in prostate surgery, there is intentional incision (and anastomosis) of the bladder and urethra, and accidental injury to the rectum, RUF can also complicate transanal endorectal pull-through, with intentional incision and anastomosis of the rectum and accidental injury of the urethra. The largest series of such iatrogenic RUFs was reported in 7 patients who had surgery for Hirschsprung disease.

Iatrogenic RUF can occur most commonly from complications secondary to rectal or prostate cancer treatment. The incidence of acquired RUF has increased over the past 20 years, primarily due to the increased utilization of multimodal therapy for the treatment of high-risk prostate cancer. The use of high dose radiation combined with surgery and other ablative techniques correlates with a dramatic change in RUF etiology, from primarily surgical to largely related to nonsurgical causes. Up until 1997, in 315 reported cases of RUF, only 3.8% were due to radiation.[,,,,] In contrast, in more contemporary series, approximately 50% occur following radiation or ablative therapy for prostate cancer.[750,,,,,,,,,,,,,]

2.2.3. Treatment for Rectal Cancer

In addition to radiation for prostate cancer, there are reports of RUF occurring as a complication of radiotherapy for rectal cancer.

2.2.4. Treatment for Prostate Cancer

The vast majority of acquired RUF arise from complications secondary to treatment for adenocarcinoma of the prostate. With the increasing utilization of multimodal therapy for high risk and recurrent prostate cancer, the occurrence of RUF is increasing, with a current incidence of 0.5–12% following multimodal prostate cancer treatment.[703,,] With respect to radical retropubic prostatectomy (RRP), the incidence of RUF is higher following salvage treatment than with primary surgery. The incidence of rectal injury is generally 1–2% in primary surgery,[,,,] but is double that rate with RRP after prior radiation or ablative therapy, or previous rectal surgery or transurethral resection of the prostate.[783,799,,,,,,,] The higher rate of rectal injury coupled with the ischemic changes and reduced tissue elasticity following these aforementioned treatments increases surgical failure rates for repair of recognized rectal injury, thereby increasing

the risk of RUF formation. In cases of an unrecognized rectal injury during salvage surgery in the radiated patient, a resultant fistula is highly unlikely to resolve spontaneously.[797,798,,]

Local therapy for T1-T2 non metastatic prostate cancer is associated with a greater than 90% ten-year disease specific survival.[210] Thus, potential toxicity and quality of life following treatment are principal considerations in selecting therapy. However, for the treatment of more advanced cancer, there has been an increase in the use of higher risk multimodal and salvage therapies over the past two decades. As a result of the utilization of these higher risk therapies, the incidence and complexity of fistulas has increased substantially.[801,] Unfortunately, the use of a hydrogel injection system to inject synthetic polyethylene glycol hydrogel between the prostate and rectum prior to radiotherapy, which is designed to reduce the risk of rectal toxicity from radiation, can actually cause RUF if improperly injected.

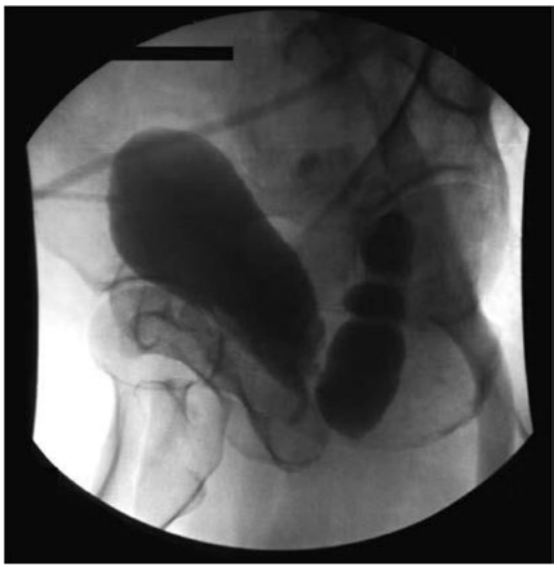


Figure 27. Cystogram demonstrates a rectourethral fistula that occurred after a laparoscopic radical prostatectomy.

Additional risk factors for postoperative RUF include locally advanced cancer, whereby adherence of the prostate to the rectum and the need for a wider surgical margin likely contributes to rectal injury, as well as prior ablative therapy, rectal surgery, or a history of bacterial prostatitis or transurethral resection of the prostate.[783,787,799,805,809,811,812,,] Interestingly, in the series reported by Thomas et al, diabetes, previous bladder surgery, and use of hormonal ablation were *not* risk factors predisposing to RUF formation.

In 1972, Smith and Veenema reported their 20-year experience with 160 patients undergoing radical retropubic prostatectomy (RRP) with an incidence of 15 rectal injuries. Only four fistulas developed in this group. Roberts et al published a series of 11,452 men who underwent open (RRP) or laparoscopic (LRP) radical prostatectomy. Rectal injury occurred in 18 men—12 in the RRP group (0.12%) and six in the LRP group (0.47%). When recognized intraoperatively and primarily repaired, rectourethral fistula was prevented in 87.5% of men. Primary repair performed with vascularized tissue interposition prevented rectourethral fistula development. In men with unrecognized rectal injury, the rectourethral fistula tended to persist and eventually required delayed surgical repair.[821] Thomas et al[819] reported that rectourethral fistulas developed in 13 of 2,447 patients (0.53%) after RP.

Noldus et al reported 23 (3.9%) rectal injuries during 589 RRP and cystoprostatectomy procedures. Eastham and Scardino summarized the incidence of rectal injury during RRP in 3834 patients with an average of 0.7% (range 0.2-2.9%). The incidence of RUF, as an immediate perioperative complication of open perineal prostate surgery, is 1.4 %.[823]

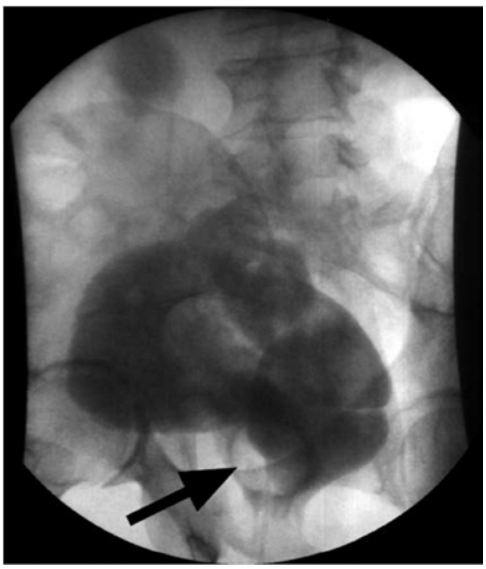


Figure 28. A. Cystogram demonstrates RUF caused by a TURP. Negative shadow from Foley catheter is seen in the bladder.

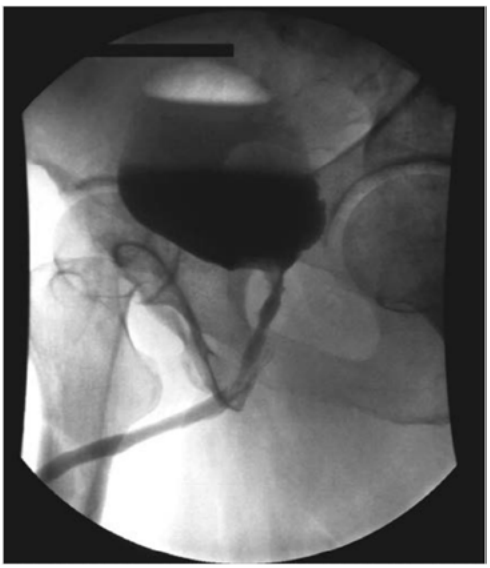


Figure 28. B. Retrograde urethrogram after transperineal closure of RUF.

With external beam XRT, brachytherapy, cryotherapy, and combination therapy, the risk of RUF is substantially higher than with RRP, generally ranging from 0.1-6%.

2.2.4.1. Salvage Radical Prostatectomy

RUF can result from unrecognized (or recognized but insufficiently repaired) injury during RRP. While the rate of rectal injury is quite low for patients undergoing primary RRP, generally in the range of 0-4%, it has been reported as high as 9% in patients undergoing prostate extirpation following radiation treatment, although there may be improvement in the complication rate more recently. Gotto et al[835] assessed data of 3,458 consecutive patients who underwent open radical prostatectomy and 98 who underwent open salvage radical prostatectomy from January 1999 to June 2007. The catheter was routinely left indwelling for 3 weeks after SP to allow healing of irradiated tissue. Postoperative cystography was done more often in patients with SP (36% vs 2%, *P*<0.001). The salvage group had a higher adjusted probability of medical and surgical complications, including urinary tract infection, bladder neck contracture, urinary retention, urinary fistula, abscess and rectal injury. There was a significant association between rectal injury and subsequent urinary fistula after SP but not after RP. In the SP group fistula developed in 2 of 9 men with (22%) vs. 2 of 89 without (2%) rectal injury (*P*=0.041). In the RP group fistula developed in 0 of 21 men with (0%) with vs 2 of 3,435 without (0.06%) rectal injury. There was also a significant association between persistent urine leak beyond 48 hours after surgery and subsequent fistula in the SP and RP groups. In the SP group fistula developed in 2 of 5 cases with (40%) vs. 2 of 93 without (2%) persistent leak (*P*=0.012). In the RP group fistula developed in 2 of 79 cases with (2%) vs. 0 of 3,379 without (0%) persistent leak (*P*<0.001).[835]

The potential for cure with salvage RP must be balanced against the risks of substantial potential toxicities. These risks are greater in the salvage RP setting than in the de novo setting because of radiation changes in the operative field that may cause fibrosis, merging of tissue planes used for dissection, and poorer wound healing.

2.2.4.2. Primary XRT

With primary XRT, RUF is a rare event, occurring at a rate of 0-0.6%. **[**Following primary brachytherapy, RUF is slightly more common than with external beam radiotherapy, ranging from 0.3-3% of cases, but is generally less than 1% in most series.[750,797,825,] However, with combined external beam radiotherapy and brachytherapy, the rate of RUF is substantially higher, generally around 3%.[785,810,]

2.2.4.3. Salvage XRT

It appears that with salvage brachytherapy–that is interstitial radiation treatment in the setting of disease recurrence following external beam radiotherapy, RUF incidence is approximately four times higher, up to 12% in one series. Chrouser et al[797] identified a total of 51 patients with a history of external beam radiation for prostate cancer that subsequently had a urinary fistula. Of 20 patients meeting inclusion criteria, 30% received external beam RT alone, 30% received brachytherapy and 40% had received combined external beam RT/brachytherapy. Most fistulas (80%) were from the rectum to the urinary tract with an average diameter of 3.2 cm. Of patients with rectal fistulas 81% had a history of rectal stricture, urethral stricture, rectal biopsy, rectal argon beam therapy or transurethral prostate resection after radiation. All patients with rectourethral fistulas who achieved symptomatic resolution required urinary and fecal diversion.

2.2.4.4. Cryotherapy

With *primary* cryotherapy, RUF is reported to occur at a rate of 0.5-2%.[831,] With *salvage* cryotherapy, the incidence is slightly higher, with recent reports showing RUF rates ranging from just less than 1% to as high as 3.3%.[277,800,] Badalament et al managed one patient (0.4%) with a urethrorectal fistula after cryoablation therapy for prostate cancer. Zippe reviewed preliminary results of prostate cryosurgery and reported a 2 to 5% incidence of RUF.[842] Porter et al[724] found a 2.5% rate of RUF in 210 patients after TRUS-guided prostate cryosurgery and no urethroperineal fistulae. Ismail et al reported the experience of using salvage targeted cryoablation of the prostate (TCAP) in 100 patients for the recurrence after radiotherapy. The mean follow-up was 33.5 months and RUF occurred in 1%.[851] A more recent series showed a substantially lower rate of fistulization decreased to 0.55% with improvements in patient selection and technical improvements.

Aminsharifi et al[852] recently noted a learning curve with reduced RUF from 1.2% to 0.55% over the last several years, suggesting better patient selection and technical improvement. Gleason score ≥ 7, and preoperative urinary incontinence were the key demographic, clinical, and pathologic features associated with RUF formation in this study.[852]

2.2.4.5. High Intensity Focused Ultrasound

High intensity focused ultrasound (HIFU) as primary treatment for prostate cancer is associated with a relatively low risk of RUF of 0.1%. Focal HIFU also has a low risk of <1%.

HIFU has recently gained popularity as a salvage treatment for disease recurrence following primary radiotherapy.[854] HIFU is associated with the highest rate of RUF among all the commonly used ablative treatments. Fistula rates are wide-ranging, reported to occur in 0-16% of cases.

In one older series of salvage HIFU following external beam radiation, RUF developed in 6% of patients. HIFU following combined external beam and interstitial radiation had a very high fistulization rate in one small series, with three of five patients (60%) developing a post treatment RUF.[824] There has also been a recent report of RUF associated with HIFU as a salvage technique for local disease recurrence after RRP in the non-radiated patient. Montorsi et al reported a RUF after transrectal prostatic hyperthermia (43°C) in patients with advanced prostatic cancer after multiple treatment sessions. The fistula was cured after a urethral catheter was left in place for one month.

2.3. Clinical Presentation of RUF

After radical prostatectomy, RUF manifests during the peri-operative period, with one large series reporting a mean of 14 days (range 7–49 days) from RRP until RUF diagnosis.[819] In contrast, following radiation or ablative therapy, RUF typically occurs much later. On average, fistulization becomes evident 4 months post-therapy. In one report, RUF occurred as late as 14 years after the last radiation treatment.[810,]

Whereas surgically-induced RUFs typically are small, often located in the bladder neck/trigonal region and generally can be closed primarily, radiation/ablation induced fistula are larger (>2 cm), tend to involve the prostatic urethra, and are fibrotic, therefore often requiring a combination of onlay grafting and interposition muscle flap for closure. Lacarriere et al noted that the use of radiotherapy had a major negative impact on the prognosis of the RUF patient. Multimodal therapy for high risk prostate cancer with radiation and ablative energy across the rectal wall induces microvascular injury

with resultant mucosal injury and ischemia. This in turn can lead to ulcerations, perforations and fistulization. The anterior rectal wall is less likely to heal well given the fibrotic, and generally fixed tissue that is characteristic following radiation.[797] Thus, these radiation and ablative therapy-induced fistulas tend to be associated with a larger rectal wall defect, and they are not uncommonly associated with urethral or rectal stricture and concomitant urinary or fecal incontinence.[807]

2.4. Evaluation of Rectourethral Fistula

RUF is often suspected based on the patient's history (fecaluria, abnormal urethral discharge, pneumaturia, leakage of urine from the rectum during micturition). Other common symptoms may include hematuria, recurrent uti (often with fever), and lower abdominal pain.[819,,] On digital rectal examination, the fistula can often be palpated on the anterior rectal wall. Direct vision with proctoscopy, and methodical cystourethroscopy is recommended as well. Retrograde urethrogram and voiding cystourethrogram can definitively make the diagnosis of RUF, as the radiopaque contrast agent placed into the bladder usually appears in the rectum on X-ray following voiding.[764] Radiographic imaging is useful for definitive diagnosis, as well as determining the size and location of the RUF, but direct visualization with cystourethroscopy and anoscopy/proctoscopy is important to rule out local cancer recurrence and to assess vascularity and the viability of the surrounding tissue. Sa et al evaluated the value of three-dimensional spiral computed tomography/cysto-urethrography (CTCUG) in diagnosing posterior urethral strictures associated with RUF. The accuracy in determining the RUF was higher with CTCUG (93%) than with conventional urethrography (71%).[868]

Rectal ulcers are extremely common before frank RUF development, and fistulization may be hastened or induced by biopsy.[810] Shakespeare et al reviewed the potential factors in fistula development and identified three cases (0.2%) of RUF among 1455 patients treated with prostate brachytherapy (BT), occurring at 19-27 months following BT. All these patients had BT monotherapy and had been investigated with endoscopy and low rectal biopsy. Marguet et al[810] described 6 cases of RUF in patients treated with BT plus external beam radiotherapy for localized prostate cancer and subsequent rectal biopsies or rectal surgery. Four patients underwent hyperbaric oxygen therapy, which failed. Three patients underwent fecal diversion with gracilis interposition flaps, and two underwent pelvic exenteration. *Thus, with the poor wound healing known to be associated with ablative and XRT, rectal biopsy for post-radiation proctitis or ulcers should be discouraged*.[815] While concern for colorectal carcinoma in patients with persistent bleeding and ulceration after radiation treatment is typically the indication for biopsy, it is the biopsy itself that may actually cause the RUF. The increased risk in rectal carcinoma following pelvic radiation does not manifest until 5–15 years later.[870,] Therefore, biopsy for radiation proctitis should be discouraged.

As there is a high rate of associated urethral and anal sphincter dysfunction, it is vital to assess for stricture and for continence. Cystourethroscopy can identify bladder neck contracture or urethral stricture. Assessment of sphincteric integrity is important for proper preoperative counselling, as repair of RUF will not restore continence in the setting of sphincteric insufficiency. Similarly, bladder compliance should also be evaluated in the radiated patient prior to surgical repair.

2.5. Therapy for RUF

2.5.1. Initial Management

Small fistulae may resolve spontaneously with urinary and/or fecal diversion. Therefore, an initial trial of conservative therapy is reasonable. Conservative therapy may involve urinary and or fecal diversion.

Selected patients with chronic fistulas who are poor surgical candidates may also be managed conservatively with antibiotics, pads and symptomatic care. Timing of repair is often individualized, mainly according to the etiology, delay in diagnosis, size of fistula, whether it is the first or subsequent repairs, and the general condition of patient.

Diversion of urine (suprapubic cystostomy) is generally recommended as well as correction of any urethral stricture distal to the fistula. Fecal diversion, with colostomy is used by some as a mandatory part of double diversion or selectively by others.[819] Gibbons stressed the need for a diverting colostomy for 3-4 months. In the multi-institutional series of 201 RUFs from Harris et al,[750] 35% of non-energy treated and 16.4% of the energy-treated patients did not have a bowel diversion.

Currently, colostomy is recommended in circumstances where antibiotics alone cannot control the inflammation and infection associated with the fistula or when the fistula involves radiated tissue. Low residue diet is also useful for healing. Suitable drainage (perineal and urethral splinting) is stressed.

2.5.2. Surgical Approaches

Surgical management for rectourinary fistulas remains a reconstructive challenge. Two-layer closure of the urethra and rectum with suture lines at right angles and with interposition of soft tissue (e.g., omentum, gracilis muscle, or scrotal flap) have been described. Surgical approaches include transabdominal, transvesical, transperineal, or posterior (transanal or transsphincteric).

There are only a few guidelines to direct the surgeon to the most successful and least morbid technique. Hechenbleikner et al[815] searched MEDLINE (PubMed, Ovid) and the Cochrane Library by using the term RUF. All studies were retrospective. Of the 569 records identified, 26 articles were included. Four hundred sixteen patients were identified, including 169 (40%) who had previous pelvic irradiation and/or ablation. Most patients (90%) underwent 1 of 4 categories of repair: transanal (5.9%), transabdominal (12.5%), transsphincteric (15.7%), and transperineal (65.9%). Tissue interposition flaps, predominantly gracilis muscle, were used in 72% of repairs. The fistula was successfully closed in 87.5%. Overall permanent fecal and/or urinary diversion rates were 10.6% and 8.3%. Most high-volume centers (>25 patients) performed transperineal repairs with tissue flaps in 100% of cases.

Rivera et al staged RUF as: stage I, low (less than 4 cm from anal verge and nonirradiated); stage II, high (more than 4 cm from anal verge and nonirradiated); stage III, small (less than 2 cm irradiated fistula); stage IV, large (more than 2 cm irradiated fistula); and stage V, large (ischial decubitus fistula). Diverting colostomy was performed for stages III to V 6 weeks before definitive therapy.

Some of the patients in addition to the RUF will also have urethral strictures that have to be managed. Reconstruction of both aspects to restore functional anatomy is possible with complex reconstructions.[829]

In 2018, Martini et al from Italy, published a novel classification of RUF following prostate cancer treatment that was used to guide management. This classification is broken down by stage and grade. The stage is mainly based on the size of the fistula (< or > 1.5 cm) and on involvement of the urethral sphincter; the grade and definition of complexity depend primarily on the etiology and surrounding tissue condition. Lastly, they recommended assigning recurrent fistulae into the grade complexity. The precise RUF size can be estimated by calculating the greatest diameters at computed tomography-urography, cystography, or by digital rectal examination (e.g., >1.5 cm when the tip of a finger passes easily through the opening). This fistula size subdivision relies on the fact that fistula smaller than 1.5 cm rarely causes evident fecaluria or sepsis and therefore unlikely requires fecal diversion before definite surgery. Grade 0 fistula are secondary “only” to surgical trauma, grade 1 category includes RUFs after radiation, grade 2 - men after salvage therapies such as salvage RP and prostate ablation following non-surgical management of localized PCa. According to this classification, stage 1 G0 fistulas can be treated with a minimally invasive approach with no tissue flap interposition and no fecal diversion.[881]

More recently Mishra et al published a meta-analysis of 7 studies with 490 patients in order to validate the Martini staging system. They found that receiving radiation/ablation increased the risk of permanent bowel diversion by 11.1 fold, eventual fistula recurrence by 9.1 fold, and post-op urinary incontinence by 2.6 fold. Similarly, compared to a Grade 0 fistula, a Grade I fistula increased the risk of permanent bowel diversion by 9.1 fold, fistula recurrence by 20 fold, and post-op UI by 2.7 fold. Since there were some valuable variables that were not captured by the staging system, they recommended development of a more comprehensive system.

The surgical approaches including the numbers of reported patients are listed in Table 5.[749,751,764,811,812,820,822,874,875,879,,,,,,,,,,,,,,,,,,,,,,,,,,,,,]

2.5.2.1. Perineal Approach

In 1926, Young[886] dissected the rectum away from sphincters, divided the fistula, closed the urethra, and mobilized the rectum further cephalad in such a fashion as to pull the affected rectum caudally out of the anus where it was then transected and discarded, suturing the proximal rectum to the anal skin. Subsequently Lewis,[887] in 1947, described suturing the levator muscle fibers together in the anterior midline when possible.

Goodwin et al[888] reported a series of 22 RUF approached perineally. They extensively mobilized the rectum posteriorly and the bladder anteriorly through wide perineal exposure allowing interposition of the levator ani muscles between the urinary tract and rectum. Singh et al[769] described the management of a delayed post-traumatic RUF repaired via transperineal access without rectal or sphincteric transgression. An example of a preoperative and postoperative urethrogram is in Figure 28.

Vanni et al[872] reported results in 74 patients using anterior transperineal approach with a muscle interposition flap (usually gracilis), and selective use of a buccal mucosal graft urethral patch onlay. At a mean follow-up of 20 months 100% of nonradiated rectourethral fistulas were closed with 1 procedure while 84% of radiated/ablation rectourethral fistulas were closed in a single stage. 31% of the patients with radiation/ablation RUFs required permanent fecal diversion.

Samplaski et al[811] reported transperineal repair with gracilis muscle interposition in 13 patients with complex RUFs of varying etiologies. One patient developed recurrence. They demonstrated low morbidity with high success rates regarding fistula repair.

Voelzke et al812 divided the fistula cohort of 23 patients into 2 groups, including postoperative and energy ablative fistulas, respectively. They recommended rectal sphincter preserving transperineal repair as a successful surgical method to repair postoperative and energy ablative rectourethral fistulas. An interposition muscle flap should be considered in the setting of energy ablative rectourethral fistulas to increase successful outcomes.

In the largest series to date, Harris et al[750] reported results in 201 patients after prostate cancer treatment in a multi-institutional retrospective study. All had a transperineal repair with or without concomitant transabdominal approach. In the energy ablation group (104 men) 84% had bowel diversions compared to 65% in the post-prostatectomy group (97 men). An interposition flap or graft (muscle or omentum) was placed in >90%. The ultimate success of repair

TABLE 5. Surgical Approaches to Rectourethral Fistulas

Approach	Author, Year	N
PERINEAL	Young, 1926.	11
	Lewis, 1947.	13
	Goodwin, 1958.	22
	Culp & Calhoon, 1964.	20
	Smith & Veenema, 1972.	4
	Youssef, 1999. (perineal dartos flap)	12
	Benchekroun, 1999.	11
	Ng, 2004. (buccal graft)	27
	Pratap, 2006.	8
	Vanni, 2010.	74
	Samplaski, 2011.	13
	Selph, 2015.	6
	Voelzke, 2013.	23
	Harris, 2017.	166
POSTERIOR – SAGITTAL	Kilpatrick & Thompson, 1962.	6
POSTERIOR – TRANSSPHINCTERIC	Stephenson, 1996.	15
	Kilpatrick & Mason, 1969.	7
	Culp & Calhoon, 1964.	20
	Fengler & Abcarian, 1997.	8
	Fournier, 1996.	1
	Bukowski, 1995.	7
	Dal Moro, 2006.	7
	Erickson, 2006.	1
	Lorente, 2011.	10
	Pera, 2008.	5
	Rouanne, 2011.	10
	Kyrklund, 2014.	34
	Forest, 2014.	17
	Alam, 2014.	18
	Pfalzgraf, 2014.	17
	Theveniaud, 2018.	16
	Van der Doelen, 2020.	28
TRANSANAL	Vose, 1949.	4
	Parks & Motson, 1983.	1
	Tiptaft, 1983.	3
	Noldus, 1997.	5
	Culkin, 2003.	5
COMBINED (posterior transsphincteric anterior rectal wall advancement)	al-Ali, 1997.	16
	Joshi, 2011.	5
	Keller, 2015.	30
ANTERIOR TRANSANORECTAL (ASTRA)	Geceleter, 1973.	19
	Venable, 1989.	1
	Zinman, 2003.	22
ENDOSCOPIC	Wilbert, 1996.	2
	Bardari, 2001.	1
	Pigalarga, 2011.	1
	Serra-Aracil, 2018.	8

in the ablation and prostatectomy groups was 87% and 99% with overall success of 92%.

Pratap et al[891] described a simultaneous perineal and abdominal approach in a series of 8 patients with traumatic perineal injuries who had both complex urethral disruptions and RUF. All patients had successful RUF closure on cystourethrography. Pfalzgraf et al[904] assessed fistula recurrence rate and health-related quality of life (HRQL) after repair in a retrospective study of 17 patients treated for RUF after RP between 1993 and 2008. Fistula closure was abdominal in 10 patients, perineal in five and combined abdominal and perineal in two, some with tissue interposition. Perineal or abdominal fistula repair yields excellent success rates and high patient satisfaction.

Selph et al[892] confirmed that patients who require placement of an AUS after a perineal RUF repair seem to fare just as well as patients who undergo primary AUS implantation with no increased rate of complications postoperatively.

2.5.2.2. Posterior Sagital Approach

Kraske in 1885 described a posterior midline incision extending to the left paramedian aspect of the coccyx and sacrum that involved partial removal of the sacrum in addition to coccygectomy. His method did not involve division of the sphincters, but rather sweeping the rectum laterally to ultimately facilitate resection and reanastomosis of a tumor-bearing rectal segment, thereby preserving fecal continence. In 1962, Kilpatrick and Thompson[893] used this approach when the rectum was completely mobilized circumferentially proximal and distal to the fistula. The RUF was then divided, sparing as much as possible on the urethral aspect. The rectal part of the fistula was excised and closed in two layers, and the urethra was repaired and stented with a catheter.

2.5.2.3. Posterior (Parascrococcygeal) Transsphincteric Approach

In 1969, Kilpatrick and Mason[895] updated this method and advocated a more radical method of dividing the rectal sphincters to give direct access to the RUF. The procedure (the York-Mason approach) is simpler than some complicated transabdominal or transperineal approaches to RUF (Figure 29).

It is still used because it allows direct visualization of the fistula via parasacrococcygeal (transsphincteric) incision especially to fistulae in the mid to lower rectum.[885] After the skin incision the mucocutaneous junction is marked with sutures and the internal sphincter is exposed. Division of the sphincter mechanism and posterior rectal wall allows exposure of the fistula. Each sphincter muscle is tagged with color-coded sutures. The next step of this procedure is the incision around fistula, followed by excision of the fistulous tract exposing the catheter in the prostatic urethra. The undermining of rectal wall allows sufficient mobilization.

After closure of the prostatic urethra, it is recommended that the full-thickness rectal wall flaps are close in a “vest over pants” technique (Figure 30). It is important to make sure that the suture lines do not overlie each other. The procedure is completed by suture of the rectal wall and approximation of the sphincter muscles. Fengler and Abcarian[885] reported healing of RUF in all of 8 patients with the York-Mason approach. Bukowski et al[751] managed 7 acquired recurrent RUF (3 after prostatectomy, 3 after trauma and 1 after perineal abscess) using York-Mason technique and a similar experience was described by Fournier et al[896] in the management of a case of the urethroprostato-rectal fistula after a gunshot wound.

Stephenson and Middleton[894] modified the York-Mason repair and reported their experience with posterior sagittal, transanal, transrectal repair of RUF in 15 patients. The transsphincteric, transanal surgical approach provides many advantages, including easy access and identification of the fistula tract, good surgical exposure, adequate resection back to well vascularized tissue, and access to several vascularized flaps for interposition between the repaired urinary and gastrointestinal tracts.

Culkin[907] reported preliminary experience with the transsphincteric, transanal surgical approach to correct acquired urethrorectal fistula in five men. Mean patient age was 56.6 years (range 37–72). The etiology was surgical (radical prostatectomy) in 3 cases, traumatic in 1 and idiopathic in 1. The time from the diagnosis of urethrorectal fistula to surgery was 4 weeks to 4 years. Five men underwent excision and closure of a urethrorectal fistula with diverting colostomy. In 4 men (80%) urinary continence subsequently returned with adequate sphincter tone, while in 1 (20%) with perineal trauma and active proctitis the fistula recurred 6 weeks after surgery.

Dal Moro et al[897] reviewed a 15-year experience using the York-Mason posterior sagittal transrectal approach to iatrogenic RUF in 7 patients. In one patient with Crohn’s disease the fistula recurred 11 years after the first surgery. The colostomy remained in place only in one patient with Crohn’s disease and in another with ulcerative rectocolitis.

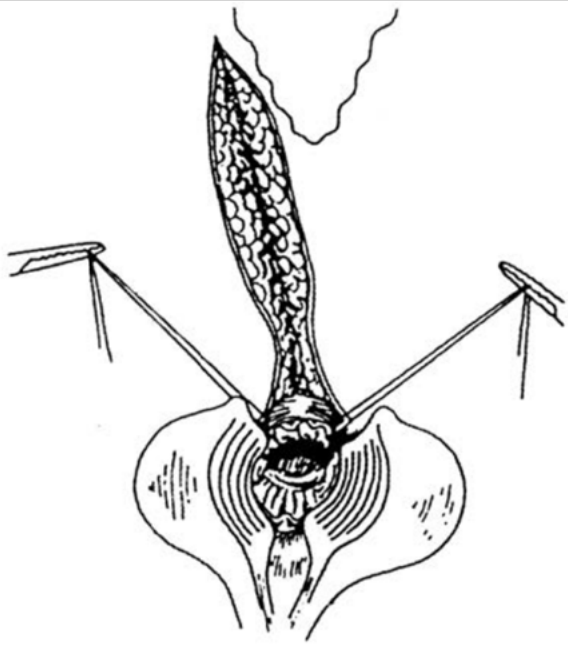


Figure 29. York-Mason approach to a rectourethral fistula via a parasacrococcygeal (transsphincteric) incision. Sutures are used to mark the sphincters. The speculum has been placed at the bottom of the incision and the anterior rectal wall is visible.

Erickson et al[875] reported a novel surgical technique used to repair a rectourethral fistula associated with two short-segment urethral strictures located in the anterior and posterior segments of the urethra in a patient with prior unsuccessful repairs. The anterior urethral stricture was reconstructed with a ventral onlay of buccal mucosa in the exaggerated lithotomy position. In a modified prone

position, the rectourethral fistula was repaired using the transrectal transsphincteric (York-Mason) technique and the posterior urethral stricture with a radial forearm fasciocutaneous free flap which was anastomosed to the inferior gluteal artery and vein. The coexistence of a rectourethral fistula and distal urethral stricture requires simultaneous repair, because the urethral pressure from the distal obstruction may compromise fistula closure.

Lorente et al[898] reported early successful closure in 10 patients with

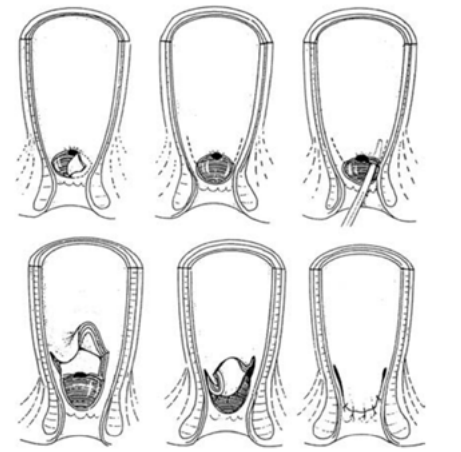


Figure 30. Rectourethral fistula repair. Full thickness rectal wall is mobilized to close in a "vest over pants" technique to close the fistula

the posterior transsphincteric York-Mason technique, with good recovery of urinary and fecal continence. Pera et al[899] reported on 5 patients successfully treated after RP with the York Mason technique. They reported minor morbidity and no impairment of continence.

Rouanne et al[900] reported 10 male patients with RUF due to radical prostatectomy who underwent York Mason repair between 1998 and 2009. All patients initially received both a urinary and a bowel diversion as the first step of the treatment. The second step consisted of a modification of the York Mason technique in which the approach began with a parasacrococcygeal incision extending from the coccyx to the anal verge. The mean time from surgery to York Mason repair was 15 (range, 4–42) months. All repairs were successful.

Kyrklund et al[901] aimed to define the long-term bowel functional outcomes following PSARP (posterior sagittal anorectoplasty) for RUF. They used validated Bowel Function Score (BFS) questionnaires mailed out to patients. Approximately one third of 34 respondents reported voluntary bowel movements (VBMs) and complete continence and 24% were reliant on anterograde continence enema (ACE) washouts, and 1 patient had a colostomy. Their results suggest that in the long-term, functional symptoms remain highly prevalent among patients treated for RUF with PSARP. However, the majority can be expected to achieve social continence.

Forest et al[902] retrospectively analyzed the data of 17 patients treated surgically for RUF with the York Mason technique between 2000 and 2012. All patients had a bowel diversion before surgery. They observed four recurrences of RUF (23.5%).

Van der Doelen et al reported on 28 patients who underwent 33 York-Mason procedures with concomitant graciloplasty in 4 primary and 2 secondary repairs. Success rates were 89% in and 50% in nonirradiated (18 men) and irradiated (10 men) respectively. Graciloplasty increased success rate in irradiated cases. No fecal incontinence was seen

Alam et al[903] from India prospectively reviewed the records of all the patients who developed RUF. A total of 18 patients were included and in all cases faecal and urinary diversion were done preoperatively. In 8 patients repair of fistula was done through the perineal approach where excision of the fistulous tract with anastomotic urethroplasty and repair of rectal wound was performed. Out of these 8 patients tunica vaginalis flap was applied in 3 and dartos pedicle flap in 5 cases; in the remaining 6 patients transrectal York-Mason repair was done. No patient developed urinary or faecal incontinence. Transrectal York-Mason repair is easier to do with less morbidity and complication while perineal approach with graft interposition may be done in cases where anastomotic urethroplasty is needed along with fistula repair.

2.5.2.4. Transanal Approach

Parks and Motson[906] popularized the addition of a full thickness local flap of anterior rectal wall as an adjunct to fistula repair through the intact anal canal (Figure 30 and Figure 31).

They modified the transanal technique by denuding the rectal mucosa lateral and distal to the fistula, and mobilized the rectal wall away from Denonvilliers´ fascia proximal to the fistula for four centimeters. Tiptaft et al[884] also used a special anal ring retractor for this surgery (Figure 32)

With the Latzko procedure the RUF is closed in three layers with absorbable suture. A transurethral catheter is placed for 3 weeks. Noldus et al[822] reported 23 patients (3.9%) with rectal injury during 589 RP and cystoprostatectomies. Of these 23 patients, 12 developed a RUF. Seven fistulas closed spontaneously with prolonged catheter drainage. The remaining 5 fistulas were all successfully closed with the transanal Latzko procedure.

Al-Ali et al[764] treated 30 men with RUF caused by war wounds. He used the method of posterior transsphincteric anterior rectal wall advancement as the treatment of choice. Double diversion (end sigmoid colostomy and suprapubic cystostomy) for one month was performed in all patients. Double diversion alone resulted in 'spontaneous' RUF healing in 47% of patients but 53% required reconstruction. Early repair was recommended for large fibrous fistulas. Undiversion was done after two months when the urethra and anorectal canals were normal.

Joshi et al[908] successfully used a rectal advancement flap in five patients with RUF.

Keller et al[874] introduced an algorithm-based treatment approach for RUF. Selective fecal diversion is possible, and the majority of patients who require definitive intervention can be treated with a transanal or transperineal (endorectal, dartos, or gracilis) approach. Only six patients (20%) required permanent urinary diversion or drainage catheters, but long-term urinary dysfunction is frequent. Healing rate was 90% and recurrence rate 0%.

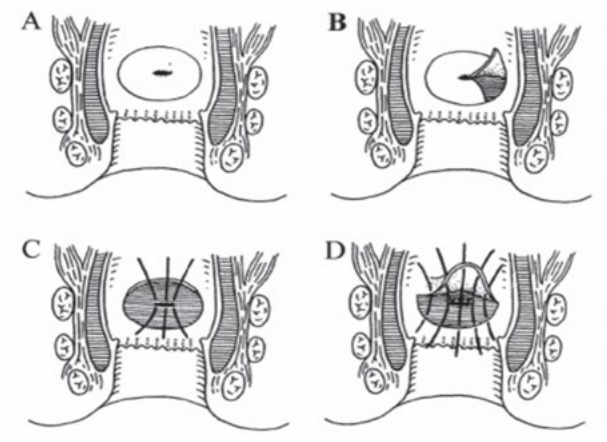


Figure 31. A. Elliptical incision of rectal mucosa around the fistula. B. Denudation of the rectal mucosa. C. Fistula closed with absorbable suture. D. Rectal mucosal flap sutured with absorbable suture.

2.5.2.5. Anterior Transsphincteric, Transanal Surgical Approach (ASTRA)

In 1973, Gecelter[909] performed a midline perineal incision to gain access to the urinary tract after placing the patient in exaggerated lithotomy position. The anal sphincter was incised anteriorly, tag sutures carefully placed, and the rectal incision was carried to the fistulous tract, which was excised and repaired in multiple layers with transposition of tissue as available. Castillo et al reviewed their first 110 consecutive laparoscopic extraperitoneal radical prostatectomies and reported 3 RUF. Only one was cured with conservative management. The other 2 patients were repaired by ASTRA.

2.5.2.6. Endoscopic Approaches

Wilbert et al[911] reported two patients with RUF who were repaired endoscopically transanally. The patients were positioned prone and the rectoscope mounted to the operating table was inserted into the rectum. The fistula was visualized and the opening excised to the level of the perirectal tissues with cautery. The rectal wall was mobilized full thickness with scissors and closed primarily in two layers with a microscope. The patient was then placed in lithotomy position and the urethral side of the fistula was coagulated and injected with fibrin.

Bardari et al[912] used cyanoacrylic biological glue to close one prostato-perineal fistula complicating an abdominoperineal resection of rectum and one persistent neobladder-ileal fistula. The biologic sealant was administrated endoscopically through an open-end 6F ureteral catheter. The fistulas were successfully treated. Quinlan et al presented the case of an iatrogenic fistula in a 71-year-old man

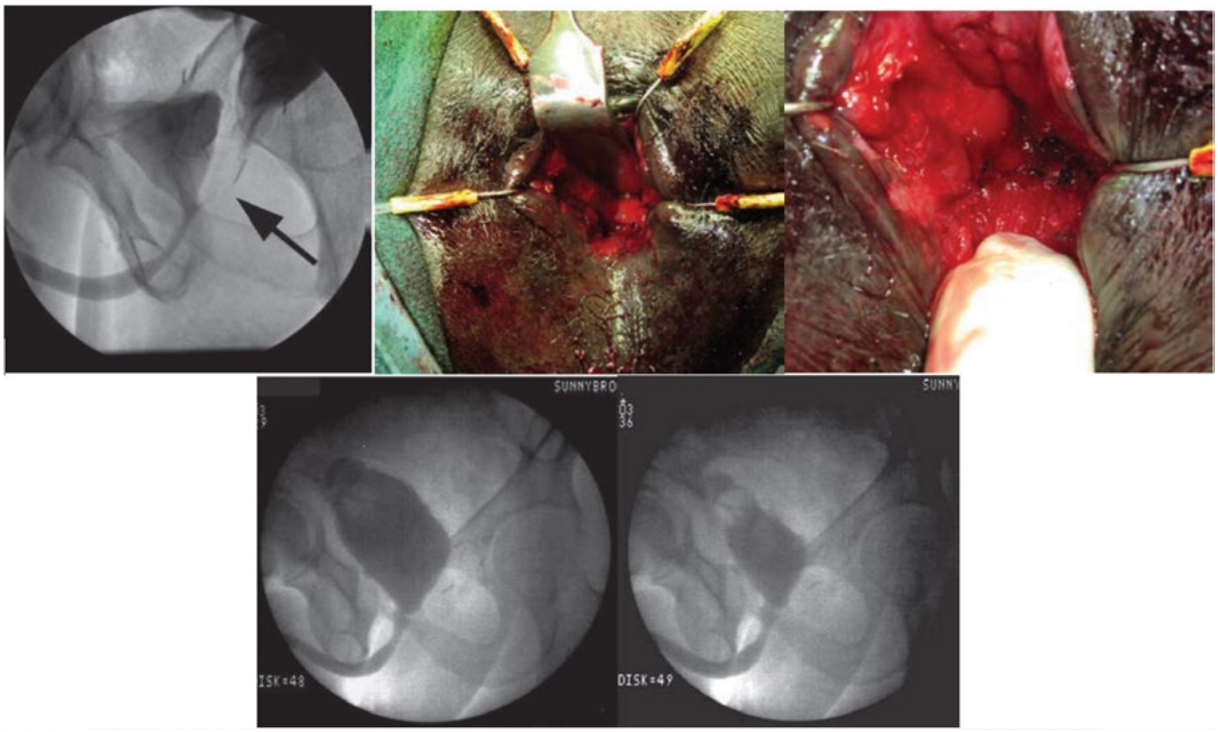


Figure 32. A. Retrograde urethrogram of a 55-year-old man who underwent a radical prostatectomy. He complained of fecaluria and urine per rectum. This shows urethral contrast in the rectum through a rectourethral fistula (Black arrow). B. Intraoperative photograph of transanal rectourethral fistula repair. The anus is held open by the ring retractor to permit direct access to the fistula. C. Intraoperative view of the rectal mucosal sutures in the rectourethral fistula repair. D. Retrograde urethrogram 3 months after transanal rectourethral fistula repair. There is no contrast entering the rectum from the urethra. The patient's suprapubic tube was removed and his colostomy was reversed

treated by a transanal endoscopic microsurgical (TEM) approach, without recourse to a stoma. Bochove-Overgaauw et al reported successful repair of 1 of 2 RUF with transanal endoscopic microsurgery (TEM): the RUF occurred after laparoscopic radical prostatectomy. Pigalarga et al[913] described a case of successful repair of iatrogenic RUF through a multidisciplinary approach consisting of cystoscopy, urethral stent placement, colonoscopy, and transanal endoscopic microsurgery assisted rectal advancement flap.

2.5.2.7. Other Modifications

Youssef et al[889] successfully treated 12 male patients who presented with RUF from 1990 to 1997 using the perineal subcutaneous dartos flap procedure. The RUF resulted from crush pelvic injury in 6 cases, gunshot wounds in 2, and post prostatectomy in 4. The fistula was associated with a urethral stricture in 4 cases. A perineal approach was used and combined with a transsymphyseal approach in the 4 patients with posterior urethral stricture. They interposed a subcutaneous dartos flap as a tissue flap between the repaired rectum and urethra. No leakage or perineal collection developed and there was no fistula recurrence. Follow-up ranged from 9 to 42 months. This technique of a perineal subcutaneous dartos flap may fulfill the principles for successful repair of RUF. Varma et al also concluded that dartos muscle interposition is a straightforward technique that can result in successful fistula repair, but should not be used in immune-compromised patients or after XRT.

Felipetto et al[772] used human fibrin sealant (Tissucol) to close a prostato-cutaneous fistula (as a complication of pseudomonas prostatitis). Venkatesh and Ramanujam prospectively studied the efficacy of autologous fibrin glue for closure of recurrent anorectal fistulas. Overall success rate was 60% however patients with acquired immunodeficiency syndrome who had fistulas associated with the urinary tract failed to respond. Verriello et al used fibrin sealant (Quixil) to inject it into the fistula tract and a rectal mucosal flap was used to close the internal opening. The fistula healed in a few weeks, and the patient remained symptom free after 1 year of follow-up. Chirica et al reported their experience with coloanal sleeve anastomosis (Soave procedure) as a salvage procedure for complex rectourinary fistulas after radical prostatectomy or following anterior resection for rectal cancer after radiochemotherapy. All eight patients had a temporary ileostomy, which was successfully reversed in 7. Lesser et al reported a case of radiation and salvage cryoablation induced RUF after treatment of prostate cancer which was successfully repaired with a combined endorectal advancement flap with an Alloderm graft.

Muhlmann et al compared techniques of rectal mucosal advancement flaps (RMAF) and fistula plugs (FP) used to manage complex anal fistulas. The results of treatment of complex anal fistulas are disappointing. The choice of operation of either a RMAF or a FP did not alter the poor healing rates of about one third of patients in each group.

Gonzalez-Contreras et al treated the RUF after radical prostatectomy with interposition of the gracilis muscle. Eight weeks after surgery and with colostomy closed, no evidence of recurrence was detected.

Chen et al gained a high success rate in the treatment of complex rectovaginal fistulas and RUF by the technique of the gracilis muscle transposition and postoperative salvage wound irrigation-suction.

Yo et al also treated the recurrent RUF in a man after anoplasty for anorectal malformation during early infancy.They used a gracilis muscle flap approximately 30 cm long which was harvested from the left thigh, brought into the deepest part between the separated rectum and urethra through a subcutaneous tunnel and afixed there.

Iwamoto et al introduced a successful novel operative technique of a RUF with a pedicled vastus lateralis musculofascial flap. A first attempt failed to close the fistula utilizing the transanal rectal flap advancement technique.

Solomon et al described a new perineal approach using the medial aspect of the puborectalis muscles as a double-breasted rotational interposition flap to repair the RUF.

Ganio et al achieved the closure of the RUF in all 11 patients by the repair of using a bulbocavernosus muscle graft.

Lee et al presented a novel minimally invasive procedure: robotic-assisted laparoscopic segmental resection with rectoanal anastomosis for the management of difficult RUFs.

2.6. Summary

A review of recent literature shows an increasing number of papers describing UCF or RCFtreatment. The vast majority of available studies are retrospective cases and case series (level 3 evidence). There are many causes of these fistulas described in the literature but there is a paucity of valid epidemiologic data about the incidence of UCF and RUF. The aim of the surgical approach is the closure of all types of fistulas. While spontaneous closure and success with a one-stage procedure has been reported, most cases to date involve 3 stages (double diversion, closure technique, and then undiversion).

Only a few urologists and general surgeons have gained wide experience in the management of UCF or RUF, and the management of these difficult conditions should remain in the hands of experts working in tertiary referral centres. Furthermore, with increasing use of energy ablation as well as salvage surgery for prostate cancer the resultant complex fistulae frequently require a multimodal approach. No single procedure has yet proved to be best or universally applicable. Conservative treatment is generally ineffective in the management of large RUF. Surgical intervention offers symptomatic relief and improved quality of life in most patients. Regardless of complexity, rectourethral fistulas have an initial closure rate approaching 90% when the transperineal approach is used. Permanent fecal and/or urinary diversion may be a last resort in patients with damaged fecal and urinary systems, especially associated with energy treatment for cancer.

All reports are still only retrospective case series **(Level of evidence 3; grade of recommendation C).**

VII. SUMMARY OF RECOMMENDATIONS

1. EVALUATION AND RECOMMENDATIONS

- Prior to surgery a basic patient evaluation should consist of history and physical examination, urinalysis and postvoid residual urine (Level of evidence 1-2: grade of recommendation A).

- A voiding diary is helpful to assess urinary frequency functional capacity and total urine output (Level of evidence 1-2: grade of recommendation B).
- Pad tests may be useful in certain circumstances, and pad use is a reasonable surrogate to a formal pad test (Level of evidence 1-2: grade of recommendation B).
- Blood testing (BUN, creatinine, glucose) is recommended if compromised renal function is suspected or if polyuria or poor urinary concentrating ability (in the absence of diuretics) is documented.
- Additional testing with cystoscopy and appropriate imaging of the urinary tract may be helpful in guiding therapy—this depends to a large degree on the type of incontinence and presumed etiology (Level of evidence 2-3: grade of recommendation B).
- Prior to surgical intervention for stress urinary incontinence, cystourethroscopy should be performed to assess for urethral and bladder pathology that may affect outcomes of surgery. Residual external sphincter function can also be assessed (Committee Opinion).
- The committee felt that multichannel urodynamics may be useful prior to invasive treatment for incontinence—this depends to a large degree on the type of incontinence and presumed etiology. (Level of evidence 3: grade of recommendation C).

2. INCONTINENCE POST-PROSTATECTOMY FOR BPO AND POST-RADICAL PROSTATECTOMY FOR PROSTATE CANCER

- After a period of conservative management, which may be from 6 to 12 months the following should be considered (Level of evidence 3-4; grade of recommendation C):
- The artificial sphincter is the preferred treatment for properly selected men who have moderate to severe stress incontinence after radical prostatectomy as the AUS has the longest record of safety and efficacy. The AUS has been reported extensively for men with moderate to severe incontinence. This recommendation relates exclusively to the AMS 800 as newer devices do not have a similar evidence base or experience (Level of evidence 2-3; grade of recommendation A)
- Male slings are an acceptable surgical approach with several-year follow-up data supporting their safety and efficacy in men with mild to moderate degrees of PPI. They are associated with a low rate of urinary retention, infection, urethral erosion, and urethral atrophy. Adjustable slings appear to have similar efficacy rates compared to nonadjustable slings, but have a higher reoperation rate, typically for readjustment. (Level of evidence 3; grade of recommendation C)
- The Master trial showed that if surgery is needed, both AUS and sling result in improved leakage and high satisfaction, despite most men not being completely dry. However, most other published results indicate that men with moderate to severe incontinence undergoing implantation of an artificial urinary sphincter have better outcomes than those who undergo sling placement. (Level of evidence 2; grade of recommendation A). In the Master trial male slings had more overall complications, AUS complications were generally more significant when they did occur.
- Injectable agents, even with repeated application, have a low success rate and should only be used when more effective treatments are not possible. (Level of evidence 3-4; grade of recommendation C)
- Adjustable balloons have also been reported, but have a higher complication rate than do the AUS and male sling. (Level of evidence 3; grade of recommendation D [no recommendation possible])

3. INCONTINENCE FOLLOWING EXTERNAL BEAM RADIATION FOR PROSTATE CANCER

- The artificial sphincter is most widely used, but radiation may be a risk factor for an increase in complications. (Level of evidence 3; grade of recommendation B).
- Slings generally have a lower success rate in radiated patients compared to those who have not had radiation. (Level of evidence 3; grade of recommendation C).
- Adjustable balloons have not been successful in the setting of radiation. (Level of evidence 3; grade of recommendation D).

4. INCONTINENCE FOLLOWING PELVIC TRAUMA

- The artificial sphincter is the most widely reported treatment for stress incontinence (Level of evidence 3; grade of recommendation C).

5. REFRACTORY URGENCY INCONTINENCE AND DETRUSOR OVERACTIVITY

- BTx-A bladder injection is a minimally invasive treatment with a high level of efficacy (Level of evidence 1-2; grade of recommendation B). Reported outcomes in male patients are limited compared to reports in female patients.
- Neuromodulation is a treatment option with a high level of efficacy, but reported outcomes in male patients are limited compared to reports in female patients. (Level of evidence 3; grade of recommendation C).
- Augmentation cystoplasty may also be indicated in select patients and is associated with a high level of success in improving urine storage but may be associated with troublesome complications. (Level of evidence 3; grade of recommendation C).
- Urinary diversion is an option for males with severe, complicated problems who fail all other less invasive options. (Level of evidence 3; grade of recommendation C).

6. URETHROCUTANEOUS FISTULA AND RECTOURETRAL FISTUAL

(Level of evidence 3; grade of recommendation C)

- Etiologic factors causing acquired urethrocutaneous or rectourethral fistulae are demonstrated by clinical, endoscopic and imaging studies.
- Similar diagnostic maneuvers are applied to rectourethral fistulae.
- In cases that do not close spontaneously with or without temporary urinary and/or fecal diversion, surgical reconstruction may be carried out.
- Surgical reconstruction may be applied in the majority of cases.
- Most repairs are now carried out after urinary and fecal diversion.
- Various techniques are available for closure and can be done in collaboration with colorectal surgeons.

7. MANAGEMENT OF AUS COMPLICATIONS

(Level of evidence 3; grade of recommendation C).

- Incontinence may result from alteration in bladder function, urethral atrophy, cuff erosion or mechanical malfunction of the device.
- Reported therapeutic options for recurrent urinary incontinence due to urethral atrophy include: change of the pressure regulating balloon for a newer one or one generating a higher pressure; repositioning of the cuff proximally or distally; downsizing the cuff (most common approach); increasing the amount of fluid in the system; transcorporal cuff, and second-cuff implantation.
- Infection and/or erosion of components usually require surgical removal of all or part of the prosthesis (standard of care).
- Compared to primary urethral repair techniques, a Foley catheter placement alone may represent suboptimal management following severe cuff erosions due to increased risk of urethral complications. (Level of evidence 3, grade of recommendation C)
- A treatment algorithm is presented to aid in management and in follow-up of patients.

8. NEW TECHNOLOGIES

- Tissue engineering has not been widely reported in males apart from isolated reports of preliminary studies.
- A number of new artificial sphincter devices and slings are being evaluated. Currently, the number of patients implanted and studies with reported outcomes are relatively limited.

9. FUTURE RESEARCH DIRECTIONS

- New technologies, bulking agents, sling materials, prosthetic devices (including integration of electronic components to the artificial urinary sphincter), neuromodulation devices and stem-cell based treatments should continue to be evaluated.
- Accuracy in reporting of early research results is mandatory.
- Mechanisms of post-prostatectomy incontinence and device effects need further research.

10. CLINICAL TRIAL RECOMMENDATION

- Further randomized trials (AUS and slings; other devices).
- Standardized workup and outcome measures including QoL.
- Evaluation of the role of urodynamics in the workup.
- Complete reporting of complications and outcomes especially those for slings.
- Standardized definitions of cure/improved/unchanged/worse.
- Reporting of procedures to salvage failures.
- Long-term results (>2 years).

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COMMITTEE 11

SURGERY FOR URINARY INCONTINENCE IN WOMEN

Chair:
Moore, Kate (Australia)

Members
Athanasiou, Stavros (Greece)
Chen, Zhuoran (Australia)
Gomelsky, Alexander (United States)
Gomes, Cristiano (Brazil)
Harding, Christopher (United Kingdom)
Peyronnet, Benoit (France)
Rovner, Eric (United States)
Serati, Maurizio (Italy)
Smith, Ariana (United States)
Tomoe, Hikaru (Japan)

COMMITTEE 11

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ABBREVIATIONS

AC	Augmentation Cystoplasty
ACT	Adjustable Continence Therapy
AE	Adverse Event
aPVS	Autologous Pubovaginal Sling
ARF	Autologous Rectus Fascia
ASC	Adult Stem Cells
AUASS	American Urological Association Symptom Score
AUS	Artificial Urinary Sphincter
BMI	Body Mass Index
BN	Bladder Neck
BTX-A	OnabotulinumtoxinA
CI	Confidence Interval
CISC	Clean Intermittent Self Catheterisation
CST	Cough Stress Test
CT	Computed Tomography
DO	Detrusor Overactivity
EL	Evidence Level
ES	Electrical Stimulation
FDA	Food and Drug Administration
FSFI	Female Sexual Function Index
GSI	Genuine Stress Incontinence
GRA	Global Response Assessment
IIQ	Incontinence Impact Questionnaire
IIT	Intention to Treat
IPG	Implantable Pulse Generator
I-QoL	Incontinence-Quality of Life Questionnaire
IQR	Interquartile Range
ISC	Intermittent Self Catheterization
ISD	Intrinsic Sphincter Deficiency
KHQ	Kings Health Questionnaire
LPP	Leak Point Pressure
LUTS	Lower Urinary Tract Symptoms
MDSC	Mesoderm Derived Stem Cells
MMK	Marshall Marchetti Krantz
MRI	Magnetic Resonance Imaging
MUCP	Maximal Urethral Closure Pressure
MUI	Mixed Urinary Incontinence
MUS	Midurethral Sling
NASHA-dx	Non-Animal Stabilized Hyaluronic Ac-Id/ Dextranomer
NBCi	Nocturnal Bladder Capacity Index
OAB	Overactive Bladder
OABSS	Overactive Bladder Symptom Score
OR	Odds Ratio
PAHG	Polyacrylamide Hydrogel
PDMS	Polydimethylsiloxane Elastomer
POP	Pelvic Organ Prolapse
PTFE	Polytetrafluoroethylene
PVDF	Polyvinylidene Fluoride
PVS	Pubovaginal Sling
PFMT	Pelvic Floor Muscle Training
PGII	Patient Global Impression of Improvement
PNE	Peripheral Nerve Evaluation
PP	Per Protocol
PRO	Patient Reported Outcomes
PTNS	Percutaneous Tibial Nerve Stimulation
RCT	Randomized Controlled Trial
RFA	Radio Frequency Ablation
RP	Retropubic
RR	Relative Risk
QoL	Quality of Life
SIMS	Single Incision Mini-Sling
SMT	Standard Medical Therapy
SNS	Sacral Nerve Stimulation
SPARC	Supra Pubic Arc Sling
SS	Sample Size
SUI	Stress Urinary Incontinence
TO	Transobturator
TOT	Transobturator Tape
TVT	Tension Free Vaginal Tape
TVT-O	Tension Free Vaginal Tape-Obturator
UD	Urethral Diverticula
UDI	Urogenital Distress Inventory
UF	Urgency Frequency
UI	Urinary Incontinence
UITN	Urinary Incontinence Treatment Network
UR	Urinary Retention
USI	Urinary Stress Incontinence
UTI	Urinary Tract Infection
UUI	Urgency Urinary Incontinence
VAS	Visual Analog Scale
VDM-PDMS	Vinyldimethyl-Terminated Polydime-Thylsiloxane Polymer
VLPP	Valsalva Leak Point Pressure
WHO	World Health Organization

INTRODUCTION

In accordance with the last (2017) IC-6I report, our topic is defined as surgery for Non-Neurogenic Incontinence in women, because surgery for Neurogenic Incontinence is considered by Committee Ten. Thus, this Chapter evaluates procedures for urodynamic stress incontinence (USI), “open” surgery for refractory non-neurogenic detrusor overactivity, and surgery for mixed incontinence. The precise urodynamic diagnosis for these conditions is used in preference to the symptom complexes of Stress Urinary Incontinence and Urgency Urinary Incontinence, although the Committee recognises that not all clinicians routinely perform urodynamic tests prior to incontinence surgery in all countries.

Intravesical injection of Botulinum Toxin is allocated to the chapter on Pharmacological Treatment of Urinary Incontinence. Surgery for refractory detrusor overactivity has undergone major changes in the last 20 years with the advent of Sacral Nerve Stimulation: although evaluation of the economic implications of the procedure continues in Chapter 22 (Economics of Incontinence), surgical procedures for detrusor overactivity are considered in the second half of this chapter.

Most continence clinicians, including urogynaecologists, urologists, physiotherapists and nurse continence advisors, have a compelling interest in the topic of surgery for USI, a condition which affects up to 60% of incontinent women. Thus, critical comment about this matter is considered to be the backbone of this Chapter. The subject has undergone a series of radical changes since the first ICI report in 1997. For example, Gerry Jarvis and his Committee included a section on Bladder Neck Buttresse / Kelly plication sutures, which had been common practice for 20 years. However objective data were very limited. By this stage the colposuspension had become the first line procedure for female stress incontinence, arising from quite robust long-term outcome studies. The risks of de novo detrusor overactivity and incomplete emptying were noteworthy after the colposuspension, not to mention the need for a Pfannenstiel incision. The first report also briefly described the Aldridge abdominovaginal sling, in which strips of the rectus abdominus fascia are incised from the abdominal plane and brought to lie underneath

the urethra with midline vaginal sutures. Complications from this procedure were substantial.

Hence, in parallel, interest developed in a variety of "needle suspension" techniques, Stamey, Raz, Gittes or Peyrera sling, which did not require a full Pfannenstiel incision. The second ICI (2002) report indicated that these procedures had a substantial risk of failure, as the paraurethral sutures tended to "cut out" over time. In parallel with the development of needle suspension techniques, the colposuspension was modified in order to perform the procedure laparoscopically (albeit only two non-absorbable or absorbable sutures were applied to Cooper's ligament, rather than the three sutures employed in the open procedure). At that stage, the laparoscopic colposuspension appeared to be slightly less effective than the open procedure in longer term studies. In that report, the new concept of "paravaginal repair" was mentioned but long-term objective outcome studies were not available.

The use of autologous tissue and synthetic materials for the pubovaginal sling was also discussed in the second report. The authors made several pertinent remarks, namely that synthetic materials were associated with a risk of erosions (up to 16%) and sinus formation, as well as urethral erosion up to 5%, and a risk of sling revision or removal, ranging from 2% to 35%.

The second ICI report (2002), also gave a detailed list of 18 studies regarding the use of Bulking Agents for USI, which generally included only subjective outcomes. Confounding variables, such as whether the urethra was "fixed" or "hypermobile" were seldom considered. "Success" judged as more than 50% improvement, ranged from a low of 4%, up to 83%, and the duration of surveillance could not be stated uniformly in the Table.

At the end of the second ICI report, Tony Smith and his Committee made almost "prophetic" conclusions, which deserve to be reproduced:

"The medical press is still publishing case series of surgical procedures for stress incontinence that are scientifically flawed in many areas. This does not serve to inform and may mislead, often presenting an over-optimistic view of the outcome. A minimum data set of information should be included in the assessment of any surgical procedure. Such a data set should include the following domains:

1. Anatomical/ physiological-structured physical examination (POPQ) and urodynamics
2. Symptoms (Validated questionnaire)
3. Urine loss (pad test)
4. Quality of Life (Validated questionnaire)
5. Full documentation of all confounding variables
6. Economic costs"

These comments published in 2002 have still not been widely adopted for the evaluation of success of continence procedures.

Discussion about the value of the bladder neck buttress (BNB), the Marshall Marchetti Kransk (MMK) procedure, the paravaginal repair and the needle suspension continued during the Third Report (2005), but by the Fourth Report (2009), the following conclusions were reached:

- Anterior colporrhaphy (BNB) should not be used in the management of SUI alone [Grade A].
- The MMK procedure is not recommended for the treatment of SUI [Grade A]
- Endoscopic… bladder neck needle suspension procedures… are not recommended for the treatment of SUI. [Grade A]
- Paravaginal defect repair is not recommended for the treatment of SUI alone [Grade A]

In keeping with these Grade A Recommendations, studies employing these operations as a comparator may be cited in the text, but will not be analysed or discussed further in this Chapter.

The field of surgery for female stress urinary incontinence was radically altered by the introduction of the retropubic polypropylene mid urethral sling (eg Tension Free Vaginal Tape (TVT), which was widely adopted after the publication of robust 3 year outcome data in 1999. At long last, a highly successful operation (92% dry rate on pad test) was available that did not require a Pfannenstiel incision, nor a full general anaesthetic as for a laparoscopic procedure. Further simplification of the procedure, to avoid the retropubic space and the small risk of bladder perforation, came with the introduction of trans-obturator tape (TOT). Although small longitudinal series and randomised controlled trials with minimum of 2 year follow up have been well constructed and carefully published regarding both the TVT and the TOT, national long- term "mesh registries" were employed in very few countries in the 1990's, so that the risks of the symptoms and signs of 'foreign body mesh rejection' could not be accurately detected.

Unfortunately, since the last ICI report in 2016, there has been a large international controversy surrounding vaginal polypropylene mesh. The relatively robust MUS procedure has been grouped together in the same "basket" as the larger sheets of polypropylene mesh with four projectile arms, which are used for women with vaginal prolapse and have significantly greater risks.

The present chapter will update information about the subjective and objective efficacy and safety of currently employed surgical techniques for incontinence in women, with a focus upon the events of the last four years. Previous ICI chapters included a vast array of often short-term data about all of the relevant procedures, however in this chapter **we will focus upon studies that include objective outcome measures of success (as recommended by the Committee in 2002) for these procedures, and include complication rates.**

SEARCH STRATEGIES

As in prior editions, material collected for this chapter was based on electronic searches of Medline, EMBASE, Cinhai, Cochrane Database of Systematic Reviews and the NICE website (www.nice.org.uk). Review papers were separately searched for additional references not identified by initial database search. Individual papers were then selected from these searches for inclusion where appropriate. Search terms included; Urinary incontinence: stress, mixed, urge. Surgical procedures: minimally invasive, urogenital, gynaecologic, urologic, urinary tract, urethra, vagina, bladder, colposuspension, urethrosuspension, vesicourethral or urethrovesical, colpourethrosuspension, Burch, obturator, surgical mesh, sling, bladder, surgical or synthetic, or biological or autologous; tape; urethra, suburethra, midurethra, transurethral, pubovesical; PVS, suprapubic; pubovaginal, implant; Prostheses: injections; bulking agents, Contigen; collagen; Macro-plastique, silicones; micropar-

ticulate; hyaluronic acid; carbon particles; biocompatible materials; urinary sphincter, artificial.

In contrast to previous ICI Chapters, the Committee members agreed that publications which do not provide both objective (either pad test, valid cough stress test or urodynamic testing) and subjective (validated Quality of Life questionnaire) outcomes, preferably at a minimum of two years, may be cited in the text but not discussed in detail. Publications which discuss confounding variables that affect success, and reports that clearly document complications in a systematic way, will be emphasised. Related procedures such as urethral diverticula, new techniques, will not require such stringent long term outcomes.

EVALUATION PRIOR TO SURGERY

In keeping with Committee 13, (Surgical Treatment of Urinary Incontinence in Men) this Committee now includes our recommendations for evaluation prior to surgery, and includes comments about variations in certain countries. In keeping with the Algorithm regarding the initial assessment of urinary incontinence in women published by the last ICI report (page 2568 – 2571), a standardised history and physical examination is the cornerstone of preoperative evaluation.

The history should consider precipitating events (childbirth, menopause, weight gain, surgery or trauma) that may have led to the incontinence. History of confounding variables such as bowel dysfunction, neurological conditions (back surgery, stroke, etc) or untreated chronic cough, that may be associated with pelvic floor weakness should be noted. Previous difficult bowel resection with prolonged postoperative recovery may suggest disruption of the pelvic parasympathetic plexus with subsequent atypical bladder dysfunction. Childhood bedwetting or daywetting that is associated with a poor prognosis in detrusor overactivity should be noted. Symptoms suggesting sleep apnoea should be considered as a confounding variable in patients with detrusor overactivity and nocturia. A psychiatric history associated with use of psychotrophic medications should be noted, as these may have anticholinergic properties that can promote bladder atonia during the postoperative Trial of Void. The use of Lithium medication may be associated with a risk of permanent polydipsia and gross overconsumption of fluid, which may also promote bladder atony. Any prior conservative treatments, successful or not, should be documented. Disruption of sexual function or leakage during intercourse should be noted, as well as a history of sexual abuse that may be associated with levator muscle spasm. Medications that may promote incontinence, such as diuretics, alpha blockers should be noted, as well history of narrow angle glaucoma that precludes anticholingergic therapy. Joint hypermobility, Sjogren's syndrome and other connective tissue disorders should be noted.

A history of ataxic gait, tremor, visual disturbance, previous stroke, Multiple Sclerosis, persistent swallowing dysfunction, peripheral neuropathy or weakness, in conjunction with severe urinary and/or faecal incontinence, should prompt careful neurological assessment.

"Complicated" incontinence should be noted i.e. those with prior UI surgery, neurological conditions, elevated PVR, bladder pain or haematuria, recurrent infections, suspected or proven voiding problems, symptomatic pelvic organ prolapse, or previous pelvic irradiation, radical pelvic surgery for malignancy, or symptoms suggesting fistula. Eradication of recurrent bacterial cystitis should be considered in women with refractory detrusor overactivity prior to invasive surgical therapies, and use of topical oestriol cream or vaginal oestradiol pessaries should be considered to prevent bacterial cystitis or to reverse genitourinary symptoms of menopause (GSM).

Women with previous incontinence surgery should be considered as a separate entity, both in terms of clinical management, and in terms of statistical analysis in research studies. This concept will be emphasised in the present Chapter.

The three main groups of incontinence not complicated by the above factors should be identified, i.e. women with stress incontinence on physical activity, women with urgency, frequency with or without urgency incontinence (overactive bladder), and women with mixed urgency and stress incontinence.

The level and type of pad usage should be determined, i.e. pantyliner, continence pads, adult diapers, and the degree of bother of the incontinence in daily life, e.g. curtailment of physical activity or reduction of fluid intake to avoid incontinence. If a woman does not use any form of protection against incontinence, nor employ any change of lifestyle to avoid incontinence, then the value of surgery for incontinence needs to be carefully considered and balanced against the known risk of complications.

Documentation of severity of leakage on a pad test is recommended, and is also an important Objective Outcome Measure. This may comprise a 24 hour home pad test, a 1 hour office test, or other tests described by Committee 13 (Surgery for Incontinence in Men). The cough-stress test is also a suitable Outcome Measure, so long as the bladder volume is standardised, at least > 200 ml, (most common is >300 ml**), before and after** the intervention. The Bladder Diary is also an important Patient Report tool that should be assessed prior to surgery, to exclude over-consumption of fluid, or large bladder volumes typical of an atonic bladder, or under-consumption of fluid typical of untreated detrusor overactivity; it is also a valid Outcome Measure. (See Chapter 5A from the Sixth Report, Initial Assessment of Urinary Incontinence).

Physical examination should begin with an evaluation of the patient's general mental status, and ability to understand the risks/benefits/limitations/convalescence/etc of surgical intervention in order to gain informed consent. In the current climate of our ageing population, possible dementia should be noted in the surgical candidate, and further evaluated by her general practitioner or a geriatrician if warranted.

Measurement of height and weight, to derive Body Mass Index is important, as obesity remains a confounding variable in regard to surgical outcome and should be included in prospective trials of any surgical procedure. Severe arthritis of the hands, or significant visual impairment, may preclude clean intermittent self-catheterisation if postoperative voiding dysfunction occurs. Previous injuries that involve the sacrum or sacral plexus at S3 should be noted in candidates for sacral nerve stimulation.

Cardiovascular and respiratory disease must be considered if the patient is a candidate for a laparoscopic colposuspension with the need for prolonged Trendelberg position.

Abdominal examination is essential: large ovarian tumours, ascites, or large fibroids may precipitate incontinence. However removal of

the abdominal mass does not always resolve the incontinence, which must be discussed with the patient. Surgical scarring of the abdomen is important in patients considered for autologous sling procedures, as harvesting of a graft from the rectus fascia may not be feasible.

Leakage during coughing with a comfortably full bladder should be noted. Vaginal atrophy in the postmenopausal woman should be treated with topical oestriol cream to enhance tissue quality and wound healing. Specific examination to exclude prolapse is essential if the patient is a candidate for continence surgery. Assessment of ability to contract the pelvic floor muscle should be performed, particularly in mild to moderate incontinence, since pelvic floor muscle training is highly effective in these cases and may obviate the need for surgery (See Chapter 12, Adult Conservative Management).

A brief neuro-urological examination (perineal sensation, anal tone) should be performed in any female with neurological symptoms. Ataxia of the gait, postural hypotension, nystagmus, tremor, or obvious focal peripheral weakness should prompt specialist neurological evaluation.

In keeping with previous ICI guidelines, all women should be offered conservative therapy prior to any surgical intervention and should be given a patient decision making aid regarding what is available /feasible for them.

I. SURGERY FOR STRESS URINARY INCONTINENCE (SUI)

In the last two ICI chapters on Surgery for Female Incontinence, operations for stress incontinence have been analysed on a procedure-by-procedure basis, as if to employ the notion that any patient with stress incontinence might undergo any one of these procedures. In the current climate, “mesh operations” for incontinence have received much negative comment, for example the synthetic retropubic mid-urethral sling versus the transobturator mid-urethral sling versus various sling-incision “mini-slings”. Therefore, it seems timely to analyse each procedure partly according to its value as a primary procedure (for “uncomplicated SUI), in which urethral function may well be normal, versus its use as a remedy for the previously failed continence procedure or “complicated” incontinence, wherein urethral function is more likely to be abnormal (i.e. partially denervated, fibrosed, with low urethral closure pressure or low Valsalva leak point pressure, and be no longer hypermobile). Then procedures involving only autologous materials can be analysed separately, as no “mesh” is involved in such cases.

As per the Introduction, the Burch colposuspension had become a first line surgical procedure in the first ICI Report of 1997 (a move away from the Kelly Plication procedure). However, the autologous pubovaginal sling has also been employed as a first-line procedure in some case series/ RCTs.

1. TRADITIONAL PUBOVAGINAL SLING

The term “traditional” sling procedure is used here, in line with the terminology used in the latest Cochrane review (1). This is done mainly to distinguish open sling procedures typically placed at the region of the bladder neck from the newer, minimally-invasive mid-urethral sling (MUS) procedures. Sling procedures were first reported in 1907, using gracilis muscle wrapped around the urethra (2). Further historical perspectives are considered in previous ICI chapters. The modern autologous pubovaginal sling exists mainly due to the work of Aldridge in the 1940’s and McGuire and Blaivas in the latter part of the twentieth century (3-5).

In the first modern publication of this procedure (4), 52 patients with poor urethral function (i.e. a urethral pressure of less than 10cm), of whom 47 had undergone a previous operation for stress incontinence, and 29 (56%) had coexistant detrusor overactivity, were operated upon. The procedure entailed harvesting a 12 cm strip of rectus abdominus and external oblique fascia , then a median incision was made in the anterior vaginal wall, the vaginal mucosa was reflected laterally off the posterior urethra and bladder neck , a tunnel was established by blunt and sharp dissection on either

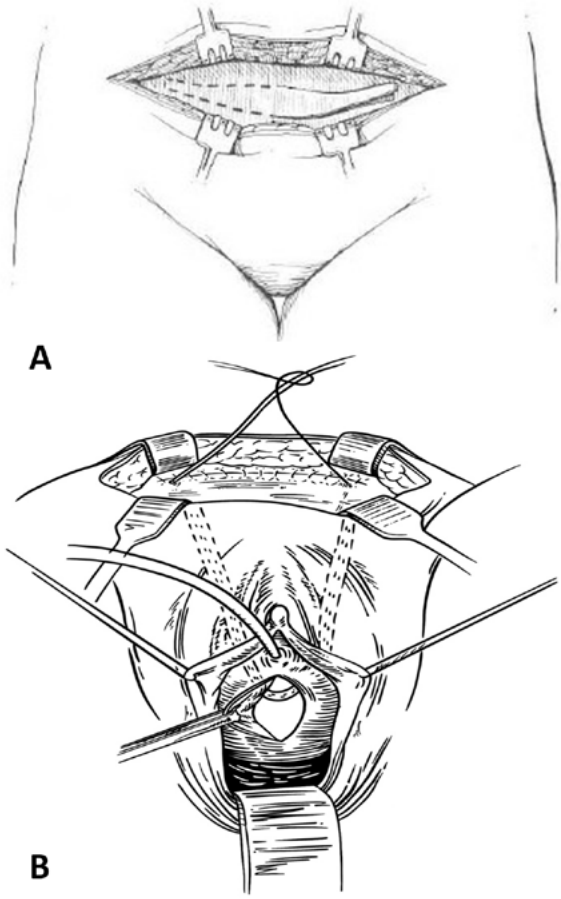

Figure 1: A. Traditional pubovaginal sling; length of autologous sling ranging from 12cm to 20cm. Published with permission from Te Linde’s Operative Gynecology, Ninth Edition Eds Rock JA, Jones HW, pub. Lippincott Williams and Wilkins Philadelphia Pennsylvania.

B. Autologous sling passes from suburethral vagina, through the urogenital diaphragm, into the rectus abdominus sheath. Drawn by artist Bailey Connor.

side of the bladder neck, so that the autologous fascia could be brought through from the vagina up into the retropubic space, and tied across the top of the rectus abdominus sheath (See Figure 1).

At a mean follow-up of 2.3 years, stress incontinence was cured on urodynamics by operation alone in 41 (80%) of cases, and coupled with anticholinergic medication in a further 6 (11%) of cases. McGuire clearly recognised that this somewhat invasive procedure was designed for those with previous failed continence operations. This technique was then reported in several standard textbooks, for example Te Linde's Operative Gynecology (6). However, when writing the chapter on pubovaginal sling for Campbell's Urology in 2002, McGuire altered the sling length to 9 cm, but stated that both ends need to lie in the retropubic space via full dissection of the urogenital diaphragm (7).

McGuire's group published a further review of 247 consecutive women having a PVS in 2000 (8). In the introduction the authors noted that "a 2% - 12% incidence of urinary retention (greater than 4 weeks) is 80% more common after PVS compared with other anti-incontinence procedures" (9). The outcome (8) was assessed by a postal UDI questionnaire. Chart review was performed at mean of 51 months (range 22-68 months). The cure rate on UDI questionnaire was 91% in those with a normal abdominal leak point pressure and hypermobile urethra, versus 84% in those with a low ALPP (88% success overall). The subset of patients with preoperative urge incontinence had a failure rate of 26%, with 5% of all patients self-catheterising for one month and 2% needing urethrolysis to restore normal voiding

As described in the previous ICI chapter, numerous biological or synthetic grafts were also employed as slings. Many synthetic grafts e.g. polyethylene, PTFE, Marlex, Gortex, were commonly accompanied by extrusion, erosion or sinus formation, and *most are no longer included in this chapter*.

The latest Cochrane review compared traditional slings with 10 other treatments including drugs or other types of surgery (colposuspension, mid-urethral slings, bladder neck needle suspension, mini-slings) (1). The review included 34 randomised or quasi-randomised controlled trials (RCTs) involving 3244 women with urodynamic stress incontinence or symptoms of stress or mixed urinary incontinence, in which at least one trial arm involves traditional sling procedures. Many trials were small and used different outcome measures. As a result, the quality of evidence for most outcomes was judged to be low or very low (Level 2-3) and most of the conclusions about traditional slings were uncertain.

The National Institute for Health and Care Excellence (NICE) committee (2019) agreed that women should be offered a choice between colposuspension, retropubic mid-urethral mesh slings and autologous rectus fascial slings, as evidence showed that there were no important differences in the short- and medium-term effectiveness. However, they emphasised that there is substantial uncertainty about the long-term complications for each procedure, and that women should be made aware of this when choosing a procedure (10). The recent AUA guideline for Surgical Treatment of Female Stress Urinary Incontinence (11) also indicates that such patients can be offered any of these procedures, in line with patient's bother, expectations, and individual risk/ benefit profile. The recent EUA guidelines (12) also indicate that any of these procedures may be offered, but that the autologous PVS has a greater risk of voiding difficulty/ CISC (RR 1.46 RR).

1.1. Traditional Pubovaginal Sling (PVS) vs. Colposuspension

The latest Cochrane review (1) systematically evaluated eight trials comparing slings with open colposuspension. Two trials involved an autologous pubovaginal sling (13, 14). Three trials used materials no longer in use; a lyodura sling (15), the Zoedler sling made of Teflon (16), and Gortex mesh (17). Only two of these trials reported follow-up for longer than five years (14, 17). Although not stated by the Cochrane reviewers, the autologous PVS used by Demirci et al (13) was only 6cm long, which is actually a "Sling-on-a-String", to be considered in Section 1.2 below.

Although dura mater slings are not currently in use, Enzelsberger (1996) performed a quasi-randomised RCT of this material versus modified open colposuspension (only two retropubic non-absorbable sutures) in 72 women with recurrent SUI after at least one previous anterior repair (15). The results remain of interest. At a minimum follow-up of 32 months, the combined objective and subjective cure rates (no symptomatic stress leak and negative stress cough test at 300mL) were 92% after dura mater sling, versus 86% after colposuspension. Significantly more women in the sling group developed postoperative voiding difficulty or urinary retention (29% vs 11%), mean duration of SPC was 15days versus 7days. More women in the colposuspension group developed a postoperative rectocoele (13%). De novo urgency occurred in 16% vs 8% **[EL=1/2]**. Therefore, the authors concluded that pubovaginal slings "***should only be used in patients with… recurrent stress incontinence, or those with a low urethral closure pressure***".

Three trials compared PVS with open colposuspension. Bai *et al* (18) randomised 92 women to either pubovaginal sling, colposuspension, or TVT. Patients with detrusor instability or ISD were excluded. Cure was defined as no complaint of stress incontinence and a negative stress test at 300ml. Pubovaginal sling was significantly superior to colposuspension at 12 months (92.8% cure vs. 87.8%), versus TVT, 87%. Demirci and Yucel (13) actually employed "Sling on a String" [see section 1.2 below]

Finally, the Urinary Incontinence Treatment Network conducted the Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr) (14). This RCT measured the efficacy of <u>any</u> form of pubovaginal sling (minimum sling length of 8cm but full retropubic dissection), versus <u>any</u> colposuspension (2 or 3 sutures), in patients with stress predominant UI: detrusor overactivity was <u>not</u> <u>excluded</u>. Urethral function was only assessed by hypermobility on exam (no MUCP or ULPP). Previous continence surgery had been performed in 14% of cases: these were equally randomised. Hence the PVS, which is often used for women with failed incontinence surgery, was compared to the colposuspension, which is often considered first-line. Subset analysis of primary versus "re-do" surgery was not done.

Overall, 655 women were randomised, 79% of them (265:255) were available for 24-month outcomes. PVS was significantly superior to colposuspension both in cure of SUI (66% vs. 49%) and overall incontinence cure (47% vs. 38%) at 24 months. The low success rates are explained by the stringent "composite" criteria used to define success, including no self-reported symptoms of SUI, less than 15g pad weight in 24 hours, no leakage on a 3-day diary, a negative cough stress test, and no retreatment for incontinence. Although highly effective for SUI, the PVS was accompanied by higher rates of urge incontinence (27% vs 20%, P = 0.04), voiding dysfunction (14% vs. 2%, p<0.001), and need for surgical revision to improve voiding, when compared with colposuspension **[EL=1].** The same group assessed complications from the SISTEr trial in a separate paper (19). Women undergoing PVS had a higher percentage of

postoperative UTIs in the first six weeks (p<0.01), and a higher incidence of voiding and storage symptoms. **[EL=1]**

The same group presented their long-term results (20). Women who completed the SISTEr trial were asked to join in a long-term study for 5 years (Brubaker et al, 2012). Continence was again strictly defined, as no leakage on a three-day voiding diary and no self- reported stress leak (telephone or mail) AND no stress incontinence surgical re-treatment. Incontinent participants were more likely to enroll in the follow-up than continent patients (85.5% vs. 52.2%), regardless of surgical group (p<0.0001). Continence rates were lower in the Burch group than in the PVS group (p=0.002) at 5 years: 24.1% (95% CI 18.5% to 29.7%) compared to 30.8% (24.7% to 36.9%), respectively. Satisfaction at 5 years was higher in women undergoing a sling (83% vs. 73%, p=0.04). [EL=1]

Overall, regarding all 8 studies, the latest Cochrane review (1) concluded that the traditional PVS probably leads to more continent women in the medium term (1-5 years) (69% vs 59% after colposuspension: OR 1.70, 95% CI 1.22 to 2.37). This result was reached when both the urodynamic and symptom diagnosis were combined in the analysis. However, the data from four trials comparing slings to open colposuspension in women with urodynamic SUI (urethral pressures/ leak pressures not analysed), showed no significant difference in cure rate within a year after treatment (OR 2.70, 95% CI 0.69 to 10.55; n = 147). Data beyond five years were provided by two trials (14, 17), suggesting that women were more likely to be continent long term after PVS than after open colposuspension (OR 1.55, 95% CI 1.06 to 2.27; n = 190). Pooled data from 5 trials **showed significantly more voiding dysfunction after sling (14% vs. 2%, p<0.001, RR 6.08**; 95% CI 3.10 to 11.95,) (19) **[EL=1].**

1.2. "Sling on a String" vs. Conventional Pubovaginal Sling

The previous paragraphs, comparing autologous pubovaginal rectus fascial sling, with other procedures such as Burch colposuspension or Modified Colposuspension, have revealed considerable variation in the length of the autologous sling that is harvested from the anterior wall, ranging from 8cm to 13cm. However, McGuire wrote that the harvested graft should be 13cm or 12 cm in length (4), so that the strips of the graft proceed through the urogenital diaphragm into the retropubic space, prior to the Nylon sutures being tied across the rectus fascia. The shorter "String on a Sling" is anchored only by the sutures attached to the smaller graft (thus less dissection of the urogenital diaphragm would be needed).

In 2001, Demirci and Yucel (13) alternated 46 women with primary USI, no Detrusor Instability and a normal VLPP, to a Sling on a String (5-6cm strip of fascia, delayed absorbable sutures) versus a modified Burch colposuspension (two delayed absorbable sutures each side). "Cure" was defined as "symptom-free patients" at 12 months. "Sling on a string" had similar "cure" to colposuspension at 12 months (94% vs. 88%). (**EL = 2**]

In 2007, urologists from Wales (21) hypothesised that the shorter "Sling on a String" procedure might be equally efficacious but require less dissection of the retropubic space with attendant morbidity, and might be a valid alternative to the TVT mesh operation. The "standard pubovaginal sling" used by these authors was **20cm long** x 1.5cm wide, whereas the "Sling on a String" was **8cm long**. In their RCT of 165 women with proven USI but no DO, cure was assessed by UDI and IIQ scores, one hour pad test, and a satisfaction score, along with the need for CISC or re-operation at 12 months. Prior continence surgery occurred in 30% of the "long sling" and 30% of the "short sling" women (which mainly comprised anterior vaginal repair). UPP and VLPP were not assessed. Success was evaluated at medium term (3.5years) and long term (6.5years), by UDI and IIQ questionnaire.

The QoL Questionnaires (21) showed no significant difference between the two procedures at any time point; in the short term the Sling on a String was slightly better, but long term the larger sling appeared better. Mean pad test data at 12 months was clearly no different between groups. "Voiding difficulty" occurred in 23% of "long sling" vs. 20% of "short sling". Re-admission within 3 months occurred more often in the traditional sling group (24% vs. 11%; p=0.03). However, further continence surgery was more common in the Sling on a String group (13% vs. 5%; p=0.016) (21).

The same senior author performed a later RCT which compared the porcine dermis pubovaginal sling vs. "Sling on a String", and also vs. tension-free vaginal tape (TVT) (22). Women recruited had primary SUI. Main outcome was patient-reported improvement rates at 6 months and 1 year. At 1year, porcine dermis slings had significantly lower dry rates (22%) as compared to TVT (55%) and PVS

Table 1A: RCTs of Autologous Pubovaginal Sling versus Colposuspension (Previous RCTs versus MMK and Stamey are discussed in previous ICI Chapters)

Author, Year, Ref	Sling	Versus	N/N (n1/ n2)	F/U (mth)	Cure; effect size	EL	Comments
Enzelsberger, 1996 (15)	Dura Mater	Colpo	72/72 (36:36)	32-48	92% vs. 86% (s)	2	All patients had recurrent SUI after failed incontinence surgery; no S.S. calculation; analysis not clear if ITT
Bai, 2005 (18)	PVS	Burch or TVT	28:33:21	6-12	92.8% vs. 90.9% (s+o), p-ns; 92.8% vs. 87.8% (s+o), p-sig	2	No S.S. calculation; minimal details about randomisation; some disparities between text and tables
Albo, 2007 (14) Chai, 2009 (19)	Any PVS	Any Colpo	520/655 (326:329)	24	SUI cure: 47% vs. 38% (s+o); p-sig Overall cure: 66% vs. 49% (s+ o); p-sig	1	79% outcome assessment at 24m (265:255); voiding/storage symptoms higher in PVS group
Brubaker, 2012 (20)	Any PVS	Any Colpo	357/482 (183:174)	60	Overall cure: 30.8% vs 24.1% (s+o) p-sig	1	Participants enrolled in long term study more likely to be incontinent (85.5%) VERSUS (52.2%), irrespective of assigned surgical group (p<0.0001).

Table 1B: RCTs of Sling on a String

Author, Year, Ref	Sling	Versus	N/N (n1/ n2)	F/U (mth)	Cure; effect size	EL	Comments
Demirci, 2001 (13)	Sling on a String	Modified Colpo (2 sutures)	34/46 (17:17)	12	94% vs. 88% (0); RR 2.0; 95%CI 0.20, 20.04	2	Quasi RCT by alternation; no S.S. calculation; Colpo sutures were delayed absorbable.
Guerrero, 2007 (21)	Sling on a String	"Long String"	165/168 (81:84)	42 Range (12-78m)	81% vs. 78% per protocol	2	RCT but no method; S.S. fulfilled; ITT analysed
Guerrero, 2010 (22)	Sling on a String	TVT and Pelvicol Sling	189/201 (79:72:50)	12	Dry rate: 48% Sling on String, 55% TVT	1	S.S. done; Recruitment could not be completed (TVT increasingly popular).
Khan, 2015 (23) (FU from Guerrero, 2010)	Sling on a String	TVT (Pelvicol deleted)	162/201 (61:38)	Median 10 years (R =6-12)	Dry rate: 73% TVT, 75% sling; p=0.036	1	Postal questionnaires and telephone conversations: BFLUTS and EQ-5D

slings (48%). Long term follow-up was via questionnaires (23). The porcine dermis arm was suspended following interim analysis, and Porcine slings are no longer considered.

1.3. Pubovaginal Sling vs Other Slings

The latest Cochrane review (1) identified 9 trials comparing various types of sling operation, including materials such as porcine dermis, lyophilised dura mater, along with fascia lata, vaginal wall, autologous dermis, and rectus fascia. The results could not be pooled due to clinical heterogeneity and because different materials or types of traditional slings were used.

Eight non-randomised studies compared the outcomes of autologous and allograft slings or xenograft material (porcine dermis). All were retrospective reviews, and all studies were considered to be of poor quality, and are not considered in this chapter.

In a quasi-RCT of pubovaginal sling versus a polypropylene mesh sling (24) in 50 women (median follow-up 2 years), the PVS was **20cm x 2cm**, the polypropylene mesh sling was 30cm x 2cm. Preoperative detrusor overactivity and previous surgery was not recorded. Cure and satisfaction rates were similar, delayed voiding and wound pain occurred more often in the PVS sling group. Similar results were obtained by Maher *et al* (25), in a non-randomised study; Considerable detail about these studies is given in the ICI- 6, and are not considered further.

1.4. Traditional Sling vs Retropubic MUS

In the last Chapter in ICI-6 there were 17 trials that compared traditional PVS and MUS operations. But only 3 RCTs provided long-term outcomes of these studies ((26, 27), see Table 2,and (22), see Table 1B "Sling on a String"). Most of these previously discussed studies did not provide objective outcomes, or were not randomised trials, and two compared synthetic sling material (Porcine dermis and Prolene), which are no longer included (see previous chapter for detail).

Six RCTs compared Autologous pubovaginal sling with TVT. However, Bai et al (18) is discussed in Table 1A. Studies by Wadie et al 2005 / 2010 (26, 27), Kondo et al 2006 (28) are in Table 2; Amaro 2009 (29) had little objective data.

Trabuco et al (2009) performed a retrospective cohort study of 242 women, who underwent a 10cm long autologous PVS (n = 79)

Table 2: Traditional Sling vs Retropubic P MUS

Author, Year, Ref	RCT	Sling	Versus	N/N (n1/ n2)	F/U (mths)	Cure; effect size	EL	Comments
Wadie, 2005 (26)	Yes	PVS	TVT	53/53 (25:28)	6m	92% vs. 92.9% (o-1 week); p=ns	2	No ss calculation; may be underpowered; cure determined at first F/U visit because of results of interim analysis; UDI-6, IIQ-7 significantly decreased at 24m
Wadie, 2010 (27)				63/75 (39:24)	24m (median 54m)	93.7% vs. 95.2% (s+o); p=ns		
Kondo, 2006 (28)	Yes	PVS	TVT	60/63 (29:31)	24m	66.7% vs. 82.6% (s); p=ns 47.6% vs. 69.6% (o); p=ns	2	Subjects for analysis reduced to 21 in ARF group & 23 in TVT group about randomisation; subjective cure (IIQ) similar
Trabuco, 2009 (30)	No	PVS	TVT (Uretx)	79/163	43m/32m	52% vs. 66% (s+o); p=0.11 Adjusted risk; p=0.04		"50% of PVS had ISD and 92% of TVT had ISD. Outcome = questionnaire + no repeat surgery."
Mock, 2015 (31)	No	"Sling on a String"	Top-down MUS	91/110	13.8m	75.8% vs. 80.9% (o+s); p=ns		Patients allowed to choose which procedure (after FDA report)

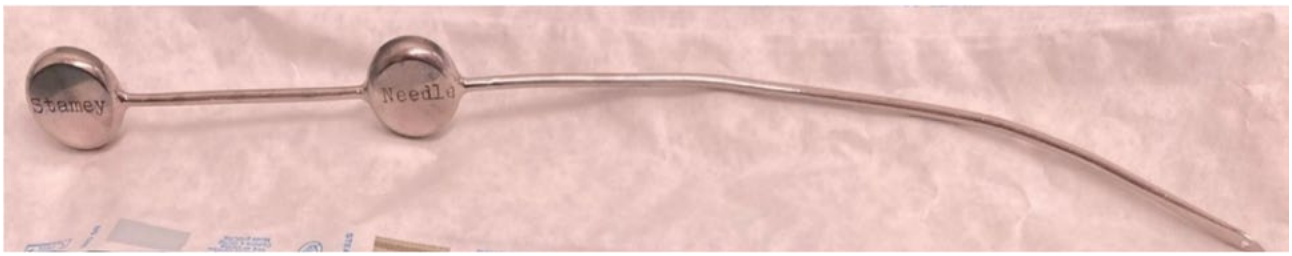

Figure 2: Stamey Needle (courtesy of St George Hospital)

or midurethral sling (n = 163) (30). Women having PVS revealed pre-operative ISD in 51%, whereas women having MUS revealed ISD in 29% (P < 0.001). Those with PVS were more likely to report any leakage of urine (P = 0.04, RR 1.6), and **were 13 times more likely to require urethrolysis (for incomplete emptying)** (P < 0.001) than patients with MUS. Patient satisfaction was lower in the PVS group compared with the MUS group (P = 0.01). [EL=3]

In 2015, Mock et al performed a non randomised prospective study of PVS versus 'top down' MUS (31). However, in the last ICI chapter it was not identified that this PVS was in fact a "sling on a string" (8 cm long, ***with the sling positioned retropubically using a Stamey needle***), shown in Figure 2. The study was interesting because, since the negative findings from the FDA re polypropylene mesh, the authors had decided to give 201 women the option between a 'sling on a string; and a 'top-down' MUS. All had no previous continence surgery; of whom 91 women (45%) chose the short autologous sling and 110 chose MUS (55%). Cure was defined as a negative supine cough stress test at 300 ml with no symptoms of stress incontinence on SEAPI score (32) ((Note that SEAPI score is validated Stothers 2004, see Appendix A). At a median follow-up of 13.8 months, the cure rate in the Sling on a String group (75.8%) was not significantly different from that in the MUS group (80.9%).

De novo urge incontinence appeared in 16.7% of the PVS group and 33.3% of the MUS group (not significant). Complications were similar between the groups (4.4% in Sling on a String vs 2.7% in MUS) (31). [EL=2] Prolonged urinary retention occured in a median of 8% (4-15) and 3% (2-4) after PVS and MUS respectively. The authors commented that 'Although our MUS retention data are consistent with published reports, the PVS group was lower. … **This single-surgeon series is from a fellowship-trained urologist practicing at a high-volume referral centre, and most contemporary series have shown a trend between lower retention rates with increasing surgeon experience."**

1.5. Traditional Sling vs Trans Obturator MUS

As regards autologous PVS versus the trans obturator tape, two RCTs compared a traditional PVS to a Trans Obturator MUS (Safyre-t). Silva-Filho et al (2006) had only 20 patients with short term data (33), but showed that pad weight at 6 months was 39g for PVS versus 8.4g after TOMUS. The RCT by Tcherniakovsky et al (2009) did not define "cure", had only 41 patients, followed up at only 12 months (34). [**EL=2**]

A retrospective study by Jeon et al (2008) of 253 women compared traditional PVS sling versus TVT, versus the TO MUS (35). Complications were not significantly different between groups. At 2 years, the cure rates on cough stress at 300 ml for the traditional sling, TVT, and TO MUS groups were significantly different (87.3% vs. 86.7% vs. 34.9%, respectively; p<0.0001). Cox proportional hazard regression revealed that the risk of failure in women having TVT was not significantly different compared with PVS, but in those who received TOT, the risk of failure was **4.6 times higher** (P= 0.0001). The 7-year cumulative cure rates of traditional sling and TVT groups were 59.1% and 55.1%, respectively. **[EL=2/3].**

1.5.1. Overview of Traditional Slings versus all Mid Urethral Slings

The 2011 Cochrane database (36) analysed 12 trials that compared traditional PVS with any MUS operation. All these studies are considered in this chapter. In summary, postoperative incontinence was reported by 31.6% of women in the traditional PVS and 25.3% of those in the MUS groups, which was not statistically significant (RR 1.23; 95% CI 0.91 to 1.66). Improvement after a year was addressed by two trials ((22) and(37)) which only involved questionaires, and included porcine dermal sling); responses were not significantly different between the two types of sling (RR 1.30; 95% CI 0.57 to 2.94).

As regards complications, bladder perforations occurred more commonly after MUS, but this did not reach statistical significance (RR 0.62; 95% CI 0.34 to 1.11). Three trials showed less de novo urgency *symptoms* after MUS (RR 3.13; 95% CI 0.96 to 10.24), not significant due to wide confidence interval, but 3 other trials showed significantly less de novo DO after MUS operations (RR 3.21; 95% CI 1.29 to 8.03).

Five trials showed that more women had postoperative voiding dysfunction after PVS than after MUS (RR 1.60; 95% CI 0.94 to 2.71) but this did not quite reach statistical significance. More women in the traditional sling group required release of sling (9% versus 2%), reported in two trials (RR 3.67; 95% CI 0.95 to 14.22 not significant).

Summary

Since ICI-6, no new studies have emerged on traditional slings, however the Cochrane met-analysis was updated in 2020 (1). Pubovaginal sling (AFS, autologous fascial sling) is the most widely evaluated biological sling and is an effective and durable treatment for SUI. [EL=1].

In comparison to other procedures: *PVS are as effective as MUS in the short term [EL=1] however operating time and LOS are significantly shorter with MUS.*

PVS is modestly more effective than colposuspension at mid-long term (EL= 1/2) albeit with a higher rate of postoperative voiding dysfunction.

The current data indicate that the "traditional" autologous Pubovaginal Sling (length of graft 13 – 20 cm with full para-ure-

thral dissection) is the gold standard for correction of incontinence, when compared by RCT to other procedures. However, this operation was initially designed for women with previous failed incontinence procedures, for which it is clearly effective. Because several studies show that it does have a higher risk of voiding dysfunction/ CISC/ UTI, and postoperative detrusor overactivity (DO), this procedure is likely to best serve the needs of incontinent women when performed in high-volume centres that focus upon women with recurrent incontinence, and is less appropriate as a primary procedure, unless surgeons are highly experienced in this procedure.

The less invasive "Sling on a String" (smaller Pfannenstiel incision, 5-6 cm length of autologous graft, less need for full vaginal dissection) may become more widely used in the future, because some women are becoming increasingly concerned about the small risks of mesh erosion after polypropylene mid-urethral slings. Preliminary studies indicate that 'sling on a string' has a similar cure rate at 12 months to the traditional sling, but prospective studies or RCTs with objective outcomes and longer term follow up of complications are necessary.

Recommendations

Traditional autologous fascial sling (PVS) is recommended as an effective treatment for female stress urinary incontinence, which has longevity for both primary and repeat surgery. [Grade A]

Research

Further long-term objective and subjective outcome data should be collected for the less invasive "Sling on a String", particularly in relation to the likelihood of voiding dysfunction/ CISC and de novo DO.

2. COLPOSUSPENSION

2.1. Open Colposuspension

The open Burch colposuspension was first described in 1961 (38). While performing a MMK procedure (39), the surgeon found that the sutures placed in the retropubic periosteum continually pulled out, so that the author used the iliopectineal (Cooper's) ligament as an alternative point of fixation for three sutures on either side of the midline, which were displayed by placing two fingers in the vagina. In the 45 cases of USI reported (of whom only four had previous continence operations), there were no failures in the short term. Burch went on to perform 143 cases over nine years, of which two were failures at six months (40). In discussion, Burch had aimed to find an operation that was more effective than the Bladder Neck Buttresse/Kelly plication, but which conferred less risk than the Aldridge sling.

Before considering randomised trials of the colposuspension efficacy, studies that report the medium and long term objective outcomes of the procedure, which have not been summarized in recent ICI chapters, are briefly reviewed. In 1979, an open colposuspension procedure comprising four bilateral Dexon sutures placed both proximal and distal to the bladder neck was performed by Stanton and Cardozo in 180 women (41). Subjective and objective outcomes (stress leak symptoms, leakage on cough stress test, and Urilos pad test) were reported; overall at 2years, patients were dry on symptoms in 79%, on stress test in 93%, and Urilos test in 86%. The 2 year cure rate in women with no previous incontinence surgery was 87.5% versus 84% in previously operated women.

In 1990, Erikson *et al* (42) evaluated 86 women who underwent modified colposuspension (two Ethibond sutures) at 5 years. "Cure" was defined quite strictly, as a dry symptom-free patient with negative cough stress test at 300ml and a positive urethral closure pressure. Cure occurred in 67% of patients (but in 71% of those with no pre-operative "motor urge incontinence"). Previous failed anterior repair did not affect success. Enterocoele occurred in 10%. Neither of these studies (41, 42) focused on post-operative voiding dysfunction.

In 1993, a follow-up study of 100 Swedish women undergoing colposuspension with four Dexon sutures bilaterally, were evaluated at 8-12years (43). "Cure" was defined as symptom-free patients, dry on all occasions, with a negative cough stress test at 300ml. Only three patients had a low MUCP. The cure rate was 90.3%. In 1994, a postal questionnaire was sent to 236 Swedish women after colposuspension, of whom 232 replied, at a median of 6years (range 2-10years) (44). Of these, 63% were completely cured. Previous incontinence surgery had been done in 16 patients, of whom only 33% were cured. Posterior vaginal wall prolapse needing surgery occurred in 15%.

Poor Outcome After Previous Failed Continence Surgery: 1n 1995, the longest objective follow-up was published (45). Of 366 women who had a modified colposuspension, 109 underwent a clinical exam and pad test at 10-20yrs (mean 14 years). The other 257 had died (10%), moved (28%), or didn't reply. Cure was defined as no stress leak on exam or pad test. Stress leak was seen on pad test in 20%, but another 11 patients (10%) had needed a repeat continence operation, so objective cure was 70%. Previous continence surgery (mainly anterior repair) had occurred in 29% of women. The cure rate in primary procedures (79%) was significantly better than in recurrent cases (61%; p=0.02).

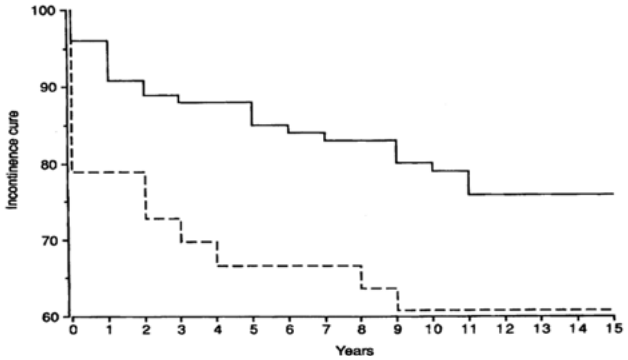

Figure 3: Survival analysis of objective incontinence cure comparing patients with primary and secondary operations. The curves are significantly different (Log rank test, P = 0.02). Solid line=primary surgery; dotted line=secondary surgery (Reproduced with permission from Alcalay, et al 1995) (45)

Four other long-term studies (follow-up at 4.2-8 years) gave absolutely no objective data.

A Cochrane review of open colposuspension versus "sling procedures" was published in 2012 (46), which included the retropubic MUS in the overall analysis (see Section 3.1.4). Findings related to the colposuspension versus PVS revealed a nearly 40% lesser

risk of developing voiding difficulties after open colposuspension as compared to sling procedures (RR 0.41; 95% CI 0.26 to 0.67). Women had a higher risk of developing new or recurrent prolapse when undergoing open colposuspension compared to sling procedures (RR 1.85; 95% CI 1.25 to 2.75). See section 3.1.4 for more detail.

2.1.1. Open Burch Colposuspension: Long Term Studies

There have been no new published randomised trials with long-term data since ICI-6. In the recent (Lapitan et al 2017) Cochrane review (47) a subgroup analysis comparing traditional PVS and open colposuspension showed better effectiveness with traditional PVS in the medium and long term (RR 1.35; 95% CI 1.11 to 1.64 from one to five years follow up, RR 1.19; 95% CI 1.03 to 1.37). Unfortunately, none of the Cochrane analyses (Forest plots) segregated the data as to whether the two operations were being performed for primary stress incontinence or for failed continence surgery.

In summary, previous systematic reviews supported by the Cochrane meta-analysis (47), indicate that the combined results show open colposuspension to have comparable subjective and objective out- comes to both traditional sling procedures and to the newer minimally invasive midurethral sling procedures; EL=1].

Recommendations

Open Burch PVS colposuspension can be recommended as an effective treatment for primary stress urinary incontinence, which has longevity. [Grade A]. It was not designed as a treatment for recurrent stress incontinence, therefore it is not recommended as a salvage procedure.

2.2. Laparoscopic Colposuspension

Laparoscopic colposuspension was introduced by Vancaillie and Schuessler in 1991 (48), as an alternative technique to open colposuspension with the advantages of reduced wound pain, a shorter length of hospitalisation, and a more expedient return to activity while avoiding the morbidity associated with the open colposuspension such as voiding dysfunction and de novo detrusor overacitivity

2.2.1. Laparoscopic versus Open Colposuspension (Table 3)

The 2019 Cochrane review of laparoscopic colposuspension (49) was published since the last ICI -6 chapter, but the Committee was disappointed to find that there have been no new trials comparing these procedures, and no further long term follow up studies of the previously included papers.

The 2019 Cochrane review includes details of 26 RCTs that include laparoscopic colposuspension (49). Of these, thirteen compared laparoscopic with open colposuspension, nine compared laparoscopic colposuspension with midurethral vaginal tapes. Unfortunately, this 2019 review also included four studies that compared variations in the surgical techniques, mainly laparoscopic colposuspension using mesh to elevate the bladder neck, but with staples attaching the mesh to the ileopectineal ligament. These studies feature throughout the Forest plots in the summary analyses. Because such procedures are no longer employed, it is necessary to look carefully at the subset analyses, which calculate the relative risk of cure solely for the traditional lap colpo, using sutures.

As regards short term follow-up from 6 – 18 months, there were 6 studies of traditional lap colpo that showed *subjective* cure, thus RR 1.04 (95% CI 0.99 – 1.08), which tended to favour the lap colpo (p = 0.09) but 8 studies of *objective* outcome using pad test or cough stress test showed cure RR 0.97 (95% CI 0.89-1.06 which favoured the open colposuspension (p=0.05,).

For subjective cure in the mid-term, at 18m–5years, only one study existed (50), which showed equivalence (RR 1.0, 95% CI 0.81d-1.25). For objective cure at 18m–5yrs, only two studies occurred (50, 51), which slightly favoured open cases (RR 0.82, 95% 0.41-1.63), but p = 0.58.

Table 3: Randomised controlled trials: Level 1 & 2 evidence relating to Laparoscopic Colposuspension.

Author, Year, Ref	Lap Colpo	Versus	N/N (n1:n2)	F/U	Cure; effect size	EL	Comments
Su, 1997 (50)	Lap Colpo	Open colpo	92/92 (46:46)	6m	80% vs. 95&: p= 0.044(o)	2	Part preference, part randomised: sample size calculation req'd 152.
Ustun, 2005 (53)	Lap Colpo	Open colpo	52/52 (26:26)	3-24m	81% vs. 81%; p=ns	2	Many concurrent procedures - varied between groups
Kitchener, 2006 (50)	Lap Colpo	Open colpo	242/291	2y	80 vs.70% (o)	1	5 had no op., & 12 changed op, after randomis'n. Objective data on 83
Carey, 2006 (54)	Lap Colpo	Open colpo	164/200 (766:88)	3-5y	72% vs. 78%, p=0.22 (o at 6m); 69% vs. 80%, p= 0.38 (s at 2y)	2	Telephone interview at 3-5y; results similar to 24 m
Ankardal 2005 (55)	Lap Colpo	Open colp	75/ 49	12m	91% vs 92% obj, p =ns Dry on 24 h pad test	1	Third arm = lap colp mesh, not considered here
Cheon 2003 (56)	Lap Colpo	Open Colpo	47: 43 RCT	12m	85% vs 86% subj	1	Pad weight: 29 to 3.6 gm versus 36 to 4.4 gm
Fathy 2001 (57)	Lap colpo	Open Colpo	74 total RCT	18 m	87.9% vs 85%, success not defined in abstract	1	Full paper not avail on line
Summit 2000 (58)	Lap Coplo	Open Colpo	"28:34 RCT"	12m	93% vs 88%, success not define in abstract	1	Full paper not avail on line

For objective cure after 5 years, there were only 2 small studies (both only scientific abstracts not fully published (51) and Morris 2001 (abstract no longer available)) which favoured the open procedure (RR 0.89, 95% CI 0.29 – 2.8, but p = 0.84), with no studies of subjective cure in the long term. In Table 3 below, references re single suture procedures and "mesh colposuspensions" are now deleted.

Note that in the ESTER study, which analysed Surface Under the Cumulative Ranking (SUCRA), the number of women cured by open colposuspension was 76.7%, versus 48.9% for the laparoscopic procedure (see full discussion at end of Surgery for Stress Incontinence section, Imamura et al (52)).

2.2.2. Complications of Laparoscopic Colposuspension

In the most recent Cochrane review (49), the traditional lap. colposuspension has a 3.8% risk of bladder perforation needing formal suturing, versus 1.5% for open cases (RR 2.1., 95% CI 0.97-4.77). The traditional lap colpo has 9.9% rate of de novo detrusor overactivity (on urodynamic study)) versus 7.5% for the open case (RR 1.29, 95% 0.72-2.3m effect size p = 0.40). The rate of voiding dysfunction was 9.25% versus 10.8 % respectively (RR 0.81, 95% CI 0.5 – 1.31, effect size p = 0.38).

Longer operating times are a significant disadvantage of the laparoscopic approach; however, women have reported significantly less pain (51, 59, 60), shorter hospital admissions, faster recoveries and quicker return to normal activities (50, 56, 61).

In summary, the data for comparison of laparoscopic versus open colposuspension remains dissapointingly limited, both in the medium term and the long term. This lack of evidence needs to be corrected, as the laparoscopic colposuspension is likely to become increasingly attractive to women in countries where the polyprolene mesh mid urethral slings are no longer available, or to women who are fearful of the risks of mesh implantation for urinary incontinence.

2.2.3. Laparoscopic Colposuspension vs. Midurethral Sling Procedures

For a more extensive discussion, see Section 3.1.4 (Retropubic MUS versus Colposuspension)

In the 2019 Cochrane review of laparoscopic colposuspension (Freites et al), nine trials have compared laparoscopic colposuspension with mid-urethral slings: there was no statistically significant difference in subjective cure rates within 18 months (RR 1.01, 95%CI 0.88 to 1.16) [EL=1].

The 2019 review did not provide data about objective cure for the Lap Colpo versus MUS comparison. However, the 2017 Cochrane review (47) did comment that the definition of objective cure varied widely between studies, yet overall the objective cure rate was higher for mid-urethral slings than laparoscopic colposuspension (RR 0.92, 95%CI 0.85 to 0.99) [EL=1].

Although laparoscopic colposuspension is regarded as a less invasive operation than the open colposuspension, the mid-urethra tape procedures had even more significantly shorter operating time (<0.001), hospital stay (<0.001) and time for resuming normal activity (<0.01-0.001) as compared to the laparoscopic colposuspension. As regards Adverse Events, the risk of de novo detrusor overactivity (in women undergoing urodynamics at 18 months) was RR 0.80 (0.34 to 1.88) favouring the lap colpo. As regards voiding dysfunction, the RR was 1.06 (0.47 to 2.41).

2.2.4. Different Techniques of Laparoscopic Colposuspension

Different aspects of the laparoscopic technique have been compared including one vs. two sutures (62), sutures vs. mesh (58, 61, 63) and transperitoneal vs. extraperitoneal approach to laparoscopy (58). Two sutures on either side of the bladder neck resulted in higher subjective (RR 1.37, 95% CI 1.14 to 1.64) and objective (RR 1.42, 95%CI 1.14 to 1.77) cure rates as compared to one (64), and single-suture colposuspension is not further discussed [EL=2].

2.2.5. Longevity of Laparoscopic Colposuspension

In 2009, Barr et al retrospectively compared 52 women who had undergone an open colposuspension 10 years previously, with 139 women who had had laparoscopic colposuspension in Manchester, using the BFLUTS questionnaire by telephone (65). Approximately 20% of patients in both groups had undergone previous continence surgery. At least two Ethibond sutures were placed bilaterally. Cure was defined as no urinary leakage in the last six months. Loss to follow-up occurred in 31% of laparoscopic and 40% of open cases (further details not provided). Subjective cure rates were 48% of laparoscopic cases at 12.8 years, versus 32% of open cases at 14.7 years (duration of follow-up significantly different; p<0.001).

The Cochrane Review concluded that the available evidence suggests that laparoscopic colposuspension may be as effective as open colposuspension 18 months postoperatively. However, the authors indicated that the place of laparoscopic colposuspension in clinical practice could not be clearly defined without further long-term results.

It should also be noted that much of the published research in this area is from individuals with enthusiasm and skill in laparoscopic surgery; their results should not necessarily be seen as being generalisable to the urogynecological/urological community at large. The NICE guidance states that laparoscopic colposuspension is not recommended as a routine procedure for the treatment of SUI, but that the procedure should be performed only by an experienced laparoscopic surgeon working in a multidisciplinary team with expertise in the assessment and treatment of SUI.

Summary

Laparoscopic colposuspension shows comparable subjective outcome to open colposuspension in the short term but objective outcome favours the open procedure up to medium term; longer term out- comes are unknown [EL=2]. Objective cure data at 18 m -5 years are inadequate.

Recommendations

Laparoscopic colposuspension can only be recommended for the surgical treatment of SUI in women by surgeons with appropriate training and expertise. (Grade C)

Women should be advised about the limited evidence available about the long-term durability of laparoscopic colposuspension, and the inferior outcomes compared to open colposuspension, and compared to classical or short Pubovaginal Sling. (Grade C)

Research

Objective Cure data for the laparoscopic colposuspension at 18 m – 5 years should be obtained.

3. MIDURETHRAL SLING (MUS)

3.1. Retropubic MUS

The tension-free vaginal tape (TVT) procedure for treatment of female urodynamic stress incontinence was first introduced by Ulmsten et al. in 1996 (66). The development of the TVT operation was an attempt to support the middle portion of the urethra, instead of restoring anatomy and correcting urethral hypermobility at the bladder neck. The idea of supporting the "mid-urethra" was derived from several research projects conducted during the last thirty years. The work of Zacharin in 1968 and DeLancey in 1994 had already shown that the pubourethral ligaments inserted at the mid-urethra and that the urogenital diaphragm also was closer to the middle portion of the urethra than the bladder neck (67, 68). The most densely innervated portion of the urethra is well known to be the middle part, and Huisman in 1983 (69) showed in histological studies that the mid-urethra had the most abundant vascularization. Additionally, Westby et al. (in 1982) showed in radiographic studies how the urine stream was interrupted at the mid-urethra on holding in continent women (70) and Asmussen *et al.* (1983) showed that the maximal urethral closure pressure was situated at the midurethra (71). It became apparent that focusing on the mid-urethra might achieve improvement in the performance of continence surgery. Retropubic MUS is shown in **Figure 4**.

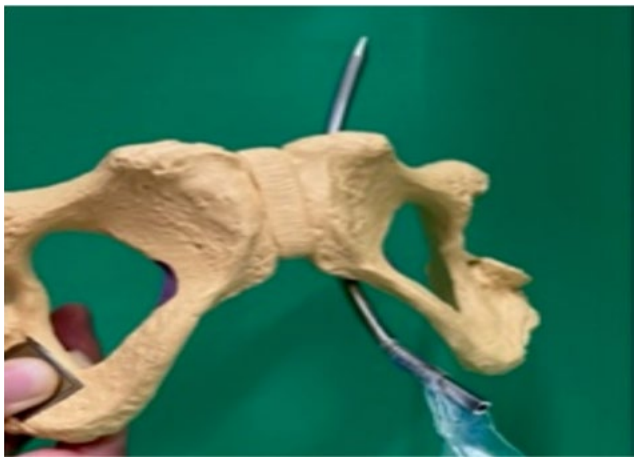

Figure 4: Retropubic mid-urethral sling (MUS) [Tensions free Vaginal Tape, TVT]

Prospective observational cohort studies revealed that placing a macroporous, monofilament polypropylene tape at the mid urethra resulted in cure rates between 80-90 % in primary cases of SUI (see references [(66, 72, 73) from ICI-6)], in recurrent cases (74), and in mixed incontinence cases (75). Retrospective case review found that repeat MUS had a 62% subjective cure rate compared to 86% in those undergoing primary MUS placement (p<0.001) at a mean follow up of 50 months (76). Preoperative intrinsic sphincter deficiency was more common among women undergoing repeat MUS compared to primary MUS. Repeat MUS was more successful using a retropubic than a transobturator approach (77). While general complication rates were similar, deno urgency and UUI were more frequent in those undergoing repeat MUS (30% vs. 14% and 22% vs. 5%, p<0.001; respectively).

Since those initial reports of success, several groups have reported long-term outcomes exceeding 5 years (78-82) and 10 years after a retropubic MUS procedure (83, 84). In 2017, 13-year follow-up data (85) on 55 of the original 63 participants found an objective cure rate of 90.9% and a subjective cure rate of 85.5%. More recently, 17-year follow-up data on 56 of the original 61 participants found an objective cure rate of 83.9% and a subjective cure rate of 78.6% (86). The cure rates for TVT are durable over the long-term with a small decline in both objective and subjective cure rates over time.

Since the last ICI review, the literature regarding the TVT and other RP MUS procedures has expanded rapidly. The number of RCTs and large cohort studies now available significantly exceeds the previous review, and there has been a recent Cochrane review in 2020 (1). Unless otherwise mentioned, only fully published studies have been included herein.

3.1.1. Retropubic MUS vs. No Treatment

No recent trial has compared RP MUS with no treatment.

3.1.2. Retropubic MUS vs. Pelvic Floor Muscle Training (PFMT)

Pelvic floor muscle training (PFMT) with or without biofeedback is an effective treatment for urodynamic stress incontinence. Labrie *et al*. (2013) published a multicentre RCT of MUS (n=215) versus pelvic floor physiotherapy (n=202) which favoured the retropubic MUS (87). Although the authors pointed out in their introduction that severe incontinence is associated with a poor physiotherapy outcome, nevertheless the randomised subjects all had moderate to severe incontinence. Women who were unable to contact their pelvic muscle were not necessarily provided with electrostimulation.

3.1.3. Retropubic MUS vs. Bulking Agents See Section 4.6

3.1.4. Retropubic MUS vs. Open Colposuspension (See also section 2.23)

A Cochrane systematic review was published from 2012, comparing open colposuspension and sling procedures (46), fully discussed in ICI-6**.** Twenty-two trials compared suburethral slings (traditional slings or trans-vaginal tape or Trans Obturator tape) and open colposuspension, involving a total of 2343 women (slings procedures n=1254, vs. open colposuspension n=1089). The authors acknowledged the variability of the data due to the different types of sling operations performed. There were non-significant differences in long-term patient reported cure rate (RR 1.11; 95%CI 0.97 to 1.27) and in objective cure rate (RR 0.70; 95%CI 0.30 to 1.64). For details, see ICI-6 but important trials are shown in Table4A.

In 2018, Trabuco et al (89) reported 2-year results of their open colposuspension vs. retropubic MUS at the time of sacrocolpopexy trial. They found retropubic MUS produced significantly higher rates of stress specific continence at 1 and 2 years (70% vs 45%, p=0.006). There was no difference in voiding dysfunction, urgency incontinence, antimuscarinic medication use or patient satisfaction.

In 2021, Karmakar et al. (95) published a 13 year follow up of a matched cohort involving 1,344 women (336 Burch colposuspension, 1008 retropubic MUS) with urodynamic SUI, without ISD.

Table 4A: Studies of Retropubic MUS versus Open Colposuspension (OC) with objective outcomes.

Author, Year, Ref	RP MUS	Vs. Open Colpo	N/N	F/U (mth)	S.S.	# Lost to F/U	% Cure	Sig. Diff.	LE	Notes
Ward, 2002* (90)	TVT	OC		6	Yes RCT	N/A	66/ 57 (o)	No	1	24hr pad test
Ward, 2004* (91)				24		19/26	63/ 51 (o)	No	1	24hr pad test
Ward, 2008* (92)				60		103/120	81/ 90 (o), 91/ 90 (s)	No	1/2	>50% lost to F/U
Liapis, 2002* (93)	TVT	OC	36/35	24	No RCT	N/A	84/ 86 (o)	No	2	1hr pad test
Wang, 2003* (94)	TVT	OC	49/49	22	No RCT	N/A	82/ 76 (o), 92/ 93 (s)	No	2	1hr pad test
Bai, 2005* (18)	TVT	OC	31/33	12	No	0/0	87/ 87.4 (s)	No	2	See table 1A

83% of the colposuspension group reported no SUI at 13 years vs. 85% of the retropubic MUS group (p=0.038). Validated questionnaires, eg Patient Global Impression of Improvement, were similar between groups, with no difference in reoperation rates, de novo overactive bladder, or voiding difficulty. Subsequent prolapse surgery was greater in the colposuspension group (3.3% vs. 1.1%, p=0.01).

3.1.5. Retropubic (RP) MUS vs. Laparoscopic Colposuspension

Since ICI-6, the Cochrane review (49) included 4 trials comparing laparoscopic colposuspension to TVT and found little difference in subjective cure between groups; however, certainty of the results was limited by the low-quality evidence. (See Table 4B). Only two trials gave objective results.

Paraiso *et al.* (98) performed postoperative urodynamic studies in 32 laparoscopic Burch colposuspension and 31 TVT patients, which showed a 18.8% rate of USI at one year in the laparoscopic Burch group, versus 3.2% in the TVT (p=0.056). At long-term follow-up of the same study, median 65 months (range 12-88 months), Jelovsek *et al.* (99) confirmed bothersome SUI symptoms in 11 and 8%, respectively (P = 0.26). [EL=2]

The conclusions of studies comparing retropubic MUS with laparoscopic colposuspension may be limited due to underpowering.

Dean *et al.* performed a systematic review of laparoscopic colposuspension (n=264) and TVT (n=290) which included 7 trials (101). The subjective cure rate between laparoscopic colposuspension and TVT was no different within 18 months (RR 1.12, 95%CI 0.98 to 1.29). However, objective cure rate was significantly higher for TVT (RR 1.16, 95%CI 1.07 to 1.25). There were no significant differences between perioperative complications, de novo DO, voiding dysfunction, procedural costs and QoL scores. The authors confirmed that the TVT procedure was quicker to perform, with a shorter hospital stay. **[EL=1/2**]. A systematic review by Fusco et al. in 2017 (102) evaluated open and laparoscopic colposuspensions together with all types of Slings and found superiority of the MUS over the Burch colposuspension. The ESTER study found that retropubic MUS had a cumulative cure (SUCRA) of 89.1%, versus lap colposuspension of 48.9% (61).

3.1.6. Standard Retropubic MUS (TVT) vs. Other Modified Retropubic MUS

There have been several modifications of the standard procedure with use of different tape materials. The 2017 Cochrane Systematic Review (103) on MUS found that retropubic bottom to top approaches were more effective than retropubic top to bottom for subjective cure (RR 1.10, 95% CI 1.01 to 1.19; 3 trials, moderate quality evidence).

Table 4B: Retropubic MUS versus Laparoscopic Colposuspension

Author, Year, Ref	RP MUS	Vs.	N/N (n1:n2)	F/U	Cure; effect size	LE	Comments
Persson, 2002 (96)	TVT	Lap Colpo	28/32	12m	89/87 (o) 57/52 (s)	1	Cost analysis
Cheon, 2003 (56)	TVT	Lap Colpo	68/79 (31:370	12m	87% vs.89% RR 0.98: 95% CI 0.82, 1.16	2	270 approached: 79 randomised. Study designed to examine costs.
Ustun, 2003 (97)	TVT	Lap Colpo	23/23	12 m Range 12-24	82.6% vs 82.6%	1	3 conversions to open in the lap group
Paraiso, 2004 (98)	TVT	Lap Colpo	71/72 (35:36)	Median 18m Range 12-43m	97% vs 81% (o), 43% vs 52% (s)	2	S.S. 130; recruitment stopped early because of slow recruitment. 63 (88) FU at 1y; 33(46%) at 2y
Jelovsek, 2008 (99)				Median 65m Range 12-88m			
Tong, 2008 (100)	TVT	Lap Colpo	67/30	9m (±10m)	99.5 vs 86.5 (s)	2	Matched cohort. No objective outcome. Paper = non English

Studies comparing TVT with "top-down" Supra Pubic Sling are no longer discussed in this Chapter, as the SPARC procedure is no longer available.

In 2019, Marschke et al. (104) reported on 303 women, 152 randomised to TVT Exact® and 151 to RetroArc®. Objective cure was similar between groups but subjective cure favoured TVT Exact® (76.1% vs. 54.3%, p=0.002). Voiding difficulty was lower in the TVT Exact® group.

3.1.6.1. Retropubic MUS in ISD, Obesity, and Previous Failed Continence Surgery

In 2019, Kim et al. (105) reviewed 28 studies (n=2,607) comparing safety and efficacy of TVT and TOT in select groups (e.g., patients with *obesity, ISD*, prolapse, *and recurrent SUI*). At a mean follow-up of 26.9 months, they found superiority of the TVT over the TOT for objective outcomes overall and in each sub-group. The TVT was superior on subjective outcomes over the TOT overall, and in patients with ISD and recurrent SUI. There was no significant difference in complications between groups.

Barco-Castillo (2020) analysed 3 RCTs of *obese* (BMI>30) women (n = 316) and non-obese women (n = 566) undergoing TVT, TOT, or "anti-incontinence surgery (106). Objective success was defined as pad test < 1 gm, negative cough stress test or no USI on urodynamics. Risk of objective failure was significantly increased in obese women (RR 1.62, 95% CI 1.26- 2.07), similar to the risk of subjective failure (RR 1.69, 95% CI 1.32 – 2.16). This analysis included a report by Brennand et al (2015), which was then further followed up in 2017 showing similar results (107).

Laterza et al (108) performed a secondary analysis of a TVT vs TVT-O RCT demonstrating that higher age and higher BMI was associated with greater objective failure at 5 years in both groups.

3.1.6.2. Risk of Voiding Dysfunction/ Need to Cut Tape After Retropubic MUS

Adverse events after mesh midurethral slings are not uncommon. In the Trial of Midurethral Slings (TOMUS, 2011), Brubaker et al (109) found that voiding dysfunction requiring surgery occurred in 9 participants (3%; all in TVT group) and 16 participants (3.4%) experienced voiding dysfunction (10 in TVT group, 6 in TOT group).

Laurikainen et al performed 5 years follow-up (110) from their RCT comparing TVT to TVT-O, revealing that 4.6% of the TVT group and 5.7% of TVT-O group had post void residual (PVR) volumes >100 ml.

3.1.6.3. Risk of Mesh Extrusion, Mesh Pain After Retropubic MUS

The TOMUS trial by Brubaker et al (2011) reported 4.7% of women experienced a mesh "complication" following TVT surgery at 2 years of follow up (109).

In 2021, MacCraith et al (111) performed a systematic review of synthetic mesh erosion and chronic pain, which contained 13 studies regarding mid-urethral slings, additional to the TOMUS trial. In their summary table, the risk of mesh erosion varied extremely widely, from 0.22% to 17.99%, but the overall risk was 1.9%. The duration of followup for these studies varied from 12 months to 84 months. The mean duration from surgery to onset of mesh erosion was 357 days +/- 183 days. A subset analysis of erosion after TVT versus TOT showed that the risk was slightly higher after TVT (1.43% versus 1.23% after TOT) which was not significant (p = 0.8). The risk of chronic pain for all mid-urethral slings was 0.6%, with a mean duration of onset at 428 +/- 238 days (no subset analysis for TVT versus TOT).

3.1.6.4. Sexual function after MUS

A recent systematic review performed in 2020 (112) to look at the impact of MUS on sexual function revealed 22 trials utilising validated questionnaires. Sexual function scores significantly improved following MUS, with sustained improvement at 24 months post-op. Sexual desire, arousal, orgasm, lubrication, satisfaction, and dyspareunia all significantly improved postoperatively (all p < 0.05). A significant reduction in coital incontinence (risk ratio 5.78; 95% CI 3.16-10.58; P<.00001) was observed.

3.1.7. RP MUS vs. Single-Incision Mini-Slings (SIMS)

Single-incision mini-slings (SIMS) were introduced as an attempt to decrease complications associated with retropubic and transobturator slings. These procedures theoretically require minimal anesthesia and may be performed under local anesthestic (Figure 5). A Cochrane Review in 2017 (113) evaluated 31 trials (*n* = 3290) comparing single incision slings to retropubic MUS. Several trials included the mini-sling TVT-Secur which is no longer on the market. The meta-analysis reported significantly more patients had ongoing incontinence after surgery in the SIMS group (41% vs. 26%; RR 2.08, 95% CI 1.04-4.14). The meta-analysis concluded that TVT-Secur was considerably inferior to MUS for treatment of stress incontinence and not enough evidence is available on alternative SIMS to allow reliable comparisons.

Figure 5: Single Incision Sling (courtesy K H Moore)

In 2018, Melendez-Munoz et al (114) compared TVT Abbrevo™ to MiniArc™ in 183 women by RCT. The TVT Abbrevo was designed to evoke less groin pain. The subjective cure for MiniArc at 12 months was 73.6%, the objective cure (negative cough stress test with a "comfortably full bladder") was 90.5%, versus subjective/ objective cure of 76.9% and 96% for the TVT Abbrevo (difference not significant). All groin pain resolved by 5 weeks. The MiniArc has been withdrawn from the market. In 2020, Braga et al (115) published 3 year open prospective data for the TVT Abbrevo in 41 women, with 90% subjectively cured and 92.5% cured on a cough stress test at 400 ml, with de novo OAB in 15%.

3.1.8. Comparison Studies of the Retropubic MUS vs. Trans-obturator MUS

Because much of the literature on the trans obturator (TO) MUS comprises various comparisons with the retropubic MUS (eg RCT or Cohort study) these comparisons are considered here. Studies that only feature the TO MUS are discussed in the next section

A notable complication of the retropubic MUS procedures has been inadvertent puncture of the bladder or urethra and, on rare occasions, intra-abdominal viscera or neurovascular structures. The bladder is most commonly punctured; rates vary from 0.8% to 21% in different studies (116). Two systematic national registries on the rates of complications associated with the TVT operation have been published, one from Finland including the first 1455 operations performed nation-wide (117) and one from Austria including 2795 operations (118). The rates of bladder perforation were 3.8% and 2.7%, respectively.

In an effort to minimise the incidence of bladder injuries, Delorme in 2001 introduced a modified tape procedure in which the tape was brought to support the mid-urethra from the groin through the obturator foramina to enter the vagina, bilaterally ('outside-in', most commonly called TOT or 'Monarc') (119). **See Figure 6.**

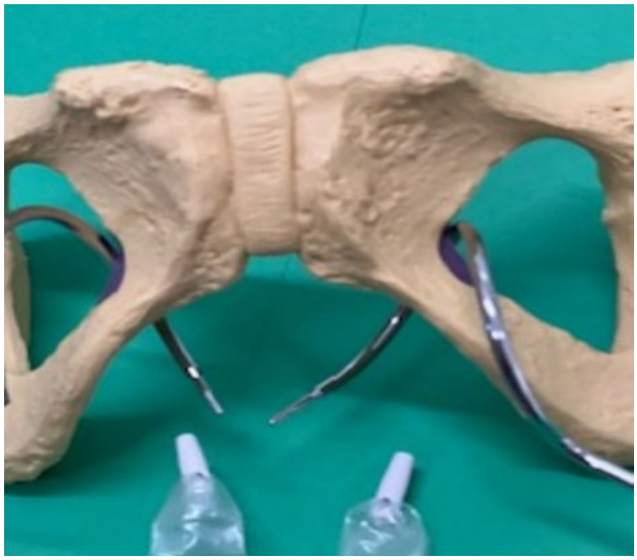

Figure 6: Trans-obturator Outside–In Tape (Monarc) (Courtesy KH Moore)

De Leval further modified the outside-in TO MUS procedure to be an 'inside-out' procedure, now called the tension-free vaginal tape-obturator (TVT-O) (120). These terms are used in future commentary.

As per ICI-5, probably the largest RCT comparing retropubic MUS with TO MUS was published by Richter et al (2010) (121). This was a multicentre equivalence trial of 597 women (94% completion) with objective and subjective outcomes at 12 months. Objective success was strictly defined, as negative cough stress test, negative 24 hour pad test and no retreatment for stress incontinence. The objective success rates met the criterion for equivalence (80.8% for TVT versus 77.7% in TOT group) but the subjective success rates did not meet the criterion (62.2% versus 55.8%). Voiding dysfunction requiring further surgery was greater in the retropubic group (2.7% versus 0%, p=0.004) but the rate of neurological symptoms e.g. 'leg pain" were higher in the TO group (4.0% versus 9.4%, p=0.01 **[EL=1]**

The comparison between the Retropubic and TO MUS procedures has been the subject of numerous publications. ICI-6 reported the results of two Cochrane systematic reviews (122, 123), and one review from EAU (124). The first two reviews by Ogah and Novara showed no difference for subjective cure between procedures, but objective cure rate was significantly higher for the retropubic route (122, 124).

In the most recent 3rd Cochrane review [Ford et al 2017], of TO MUS and retropubic MUS (103), fifty-five trials with a total of 8652 women were included (sample size range n= 20 to 597). The meta-analysis reported non-significant differences in subjective cure rate at 12 months (RR 0.98, 95%CI 0.96 to 1.00) Long-term subjective cure was also similar between groups (RR 0.95, 95%CI 0.80 to 1.12, slightly favouring the retropubic approach). Long term objective cure (RR 0.97, 95% CI 0.9-1.06) was similar. In terms of complications/ adverse events, TO MUS are characterized by lower risk of voiding dysfunction, vascular/visceral injury, operative blood loss and length of stay. On the other hand, TO MUS are clearly associated with a higher risk of groin pain (see section 3.1.8.1 below), and repeat anti-incontinence surgery may be more frequent in TO MUS versus retropubic MUS (103). The following Table 4C includes studies of currently available MUS at least 12 months' objective data.

An important RCT (132) of TVT versus Monarc (TOT) in women with a low MUCP (intrinsic sphincteric deficiency) was performed in 164 women, with an adequate sample size, showing a markedly reduced cure rate for the Monarc in ISD (objective cure 55% versus 79% at 6 months; p=0.004). Most studies of MUS do not evaluate the MUCP as a confounding variable. Long term results of this study were presented in 2019 [(77), see Table 4C) with similar results.

In Albo 2012 (143) the TOMUS trial participants (253 TVT and 263 TOT) were followed at 2 years. Objective (negative stress test, negative pad test and no re-treatment for SUI) and subjective (no self-report of stress leakage, no leakage on 3-day bladder diary and no re-treatment for SUI) success was analysed. The predetermined equivalence margin was 12%.

At 2 years, the subjective (55.7% versus 48.3%, 95%CI for difference of 7.4%: -0.7, 15.5%) and the objective cure rates (77.3 versus 72.3%, 95%CI for difference of 5.1%: -2.0, 12.1%) were similar. Neither objective nor subjective success rates met the prespecified criteria for equivalence. Occurrence of mesh exposure (retropubic 4.4% vs transobturator 2.7%, p =0.26) were not significantly different. The retropubic mid urethral sling group had higher rates of voiding dysfunction requiring surgery (3.0% vs 0%, p = 0.002)), whereas the transobturator group had more neurological symptoms (9.7% vs 5.4%, p = 0.045). The 2 year data showed widening difference in benefit for TVT / TOT, favouring the TVT.

Bohlin 2015 (144) gathered postoperative (8 weeks and 1 year) data from the Swedish National Register for Gynecological Surgery of all MUS procedures (retropubic MUS, n=4,539; TO MUS, n =1, 769) performed over 6 years; multiple logistic regression analyses were performed between the outcome variables. Cure was defined on questionnaire as no leak, or leak < 3 times per month. and BMI and smoking, presented as adjusted odds ratios (adjOR) with 95%CI; Subjective 1-year cure rate was 88.3% with RPMUS and 85.2% with the TO technique (p=0.002). Lower cure rate was seen in women with a BMI >30 (0.49; 95%CI 0.33–0.73), in diabetics

Table 4C: Retropubic MUS versus TO MUS, with medium term objective outcomes (at ≥12 m – 5 ys).

Author, Year, Ref	RP MUS	Vs.	N/N	F/U	S.S.	# Lost to F/U	% Cure	Sig. Diff.	LE	Notes
Laurikainen, 2007 (125), Rinne, 2008 (126), Palva, 2010 (127)	TVT	TVT-O	136/131	2m	Yes	0/0	98.5/95.4 (o)	No	1	ITT analysis not significantly different
				12m		2/0	95.5/93.1 (o), 90/93 (s)			
				36m		5/5	94.6/89.5 (o)			
Zhu, 2007 (128)	TVT	TVT-O	28/27	22m	No	0/0	92.6/92.9 (s)	No	2	All had concomitant prolapse surgery
Araco, 2008 (129)	TVT	TVT-O	120/120	12m	Yes	12/20	100/66 (o) (severe SUI)	0.001	1	Favours TVT for severe SUI
							100/100 (o) (mild SUI)	No		
Barber, 2008 (130)	TVT	Monarc	88/82	18.2m	Yes	2/6	58.8/62.3 (s)	*	1	Monarc not inferior to TVT; p=0.006*
Long, 2008 (131)	TVT	TVT-O	53/29	36m, 14m	No	0/0	92.5/79.3 (s), 94.3/86.2 (o)	No	3/4	
Schierlitz, 2008 (132)	TVT	Monarc	82/82	6m	Yes	15/11	79/55 (o)	0.004	1	Favours TVT; all women with ISD
Longterm 2019 (77)			76/60	12yrs	Yes	6/22	71.6/47 (s)	<0.001		Repeat Op= 1% of TVT, 24.4% of Monarc; RR 19 (95%CI 3-139)
Gungorduk, 2009 (133)	TVT	Safyre-t	180/120	12m	No	0/0	93.9/82.5 (s+o)	0.0002	3	Favours TVT
				48m		-	78.3/52.5 (s+o)	0.0001		
Karateke, 2009 (134)	TVT	TVT-O	81/83	12-16m	Yes	2/1	88.9/86.7 (s+o)	No	1	
Ross, 2009 (135)	TVT	Obtryx	105/94	12m	Yes	18/10	77/81 (o)	No	1	TO MUS palpable in 80% (vs. 27% TVT)
Wang, 2009 (136), Wang, 2011 (137)	TVT	TVT-O	160/155	6m	No	6/9	93.5/91.1 (o)	No	1/2	
				12m		45/37	89.6/89.8 (o)			
				24m		82/68	87.2/86.2 (o)			
				36m		125/125	82.9/83.3 (o)			
Castillo-Pino, 2010 (138)	TVT	Safyre-t	55/49	12m	No	0/0	74.5/77.6 (o)	No	3	
				24m			81.8/83.7 (s+o)			
Deffieux, 2010 (139) (Deffieux, 2007 (81)	TVT	TVT-O	75/74	6m	Yes	3/3	88/91 (s+o)	No	1	
				12m		6/5	89/88 (s+o)			
				24m		8/9	83/83 (s+o)			
Duckett, 2010 (140)	TVT	TO MUS	34/34	6m, 12m	No	0/0	0% vs 29% had repeat surgery)	Yes	3	Not RCT;outcome = number needing repeat surgery
George, 2010 (141)	TVT	Uretex-TO	76/73	24m	No	0/0	97.3/94.5 (s+o)	No	3	
Richter, 2010 (121)	TVT	TVT-O/ Monarc	298/299	12m	Yes	17/15	80.8/77.7 (o), 62.2/55.8 (s)	No	1	Per protocol analysis. Large study

Author, Year, Ref	RP MUS	Vs.	N/N	F/U	S.S.	# Lost to F/U	% Cure	Sig. Diff.	LE	Notes
Teo, 2011 (142)	TVT	TVT-O	66/61	12m	Yes	25/32	80.5/86.2 (o), 85.4/89.7 (s)	No	1	trial stopped early (leg pain with TVT-O)
Albo 2012 (143)	TVT	TOT	253/263	24m	yes	81/597	77.3% 72.3%	no	1	Large study
Bohlin, 2015 (144)	RP MUS	TO MUS	4539/ 1769	12m	No		88.3/85.2	0.002	3	Large study , Swedish database
Palos 2018 (145)	TVT	Monarc	45/47	12m	yes	9	100/93 (o) 92/90 (s)	No	1	ITT results failed the non-inferiority test

(0.50; 95%CI 0.35–0.74) and women aged>80 years (0.18; 95%CI 0.06–0.51).

Palos et al in 2018 (145) compared retropubic sling to TOT at 12 months (*n*=81) and found objective cure rates (on cough stress test) of 100% with retropubic MUS and 93% with TOT (p=0.03). Subjective cure rates were 92% for the retropubic sling and 90% for the TOT (p=0.02). On intention to treat analysis, TOT was found to be inferior to the retropubic sling. The retropubic MUS was associated with higher rates of voiding difficulty only in the first 7 days (37.5% vs 9.7%, p=0.007).

3.1.8.1. Complications After Retropubic Versus Trans Obturator Mus

The rate of vaginal extrusion was slightly higher following TO MUS in the review by Navara (2010) possibly due to the use of ObTape which was removed from the market due to high risk of erosion/ extrusion (124). However, the Cochrane review by Ogah et al (2009) showed no significant difference (122).

In these two early reviews, the retropubic MUS showed no significant difference from the TO MUS in the need for repeat incontinence surgery, postoperative DO, de novo urge incontinence (122, 124). There was a significantly higher occurrence of groin pain (**12%**) in women with a TO approach, versus a higher incidence of suprapubic pain in women with a retropubic sling (**1.7%).** However, postoperative voiding dysfunction occurred significantly less frequently in the TO route group (4% versus 7%, RR 0.63, 95%CI 0.44 to 0.89) in one of these reviews (122).

As expected, bladder perforation was less common after TO MUS compared with retropubic MUS (RR 0.13, 95%CI 0.08 to 0.20), as was major vascular/visceral injury (RR 0.33 95%CI 0.19 to 0.55). Mean operating time was lower (RR -7.54 95%CI -9.31 to -5.77); many surgeons do not perform mandatory cystoscopy after TO MUS. Postoperative voiding dysfunction was less frequent following TO MUS (RR 0.53, 95%CI 0.43 to 0.65). Postoperative de novo urge incontinence was no different between groups (RR 0.98, 95%CI 0.82 to 1.17). Groin pain was much higher in the TO MUS group (**RR 4.12**, 95% CI 2.71 to 6.27) whereas suprapubic pain was lower (RR 0.29, 95% CI 0.11 to 0.78). There was no difference in vaginal tape erosion/ exposure/ extrusion (RR 1.13, 95%CI 0.78 to 1.65) or bladder or urethral erosion (RR 0.34, 95%CI 0.01 to 8.13) between the two groups.

Repeat incontinence surgery in the long term was highly significantly more likely with the TO approach as compared to retropubic MUS (**RR 8.79**, 95%CI 3.36 to 23.00).

A subsequent systematic review (Maggiori et al 2017) including 11 RCTs and 5 non-RCTs (146) found that TVT and TOT had similar long-term objective and subjective cure rates with no significant difference in complications. Later that year Fusco et al (2017) published their meta-analysis, revealing that patients treated with TVT had higher subjective (OR: 0.83, p=0.03) and objective (OR: 0.82, p=0.01) cure rates than those treated with TOT but with higher risk of intraoperative bladder or vaginal perforation, hematoma, UTI and voiding symptoms (102). However, the morbidity of intra-operative bladder perforation with the TVT trocar (diameter 1.2 cm) is small, usually requiring overnight catheterization.

3.1.8.2. Effect of Obesity Upon Results

A study (147) on 760 women who had TVT showed that the overall cure rate in women of normal weight was 81.2% compared with 52.1% in the very obese (BMI >35).

In 2010, Stav et al performed a retrospective review of 950 retropubic MUS (TVT) and 270 TO MUS (mostly TVTO/ Monarc, to seek features that predicted failure (62). At mean follow-up of 50± 24 months (range, 12–114), the subjective cure rate (on UDI by telephone) was 84.7%. Multivariate analysis revealed that BMI >25 was the most significant risk for failure (OR, 2.9, $p < 0.001$). The next highest risk factors for failure were urodynamic mixed incontinence (OR, 2.4) and previous continence surgery (OR, 2.2) both $p < 0.001$, followed by intrinsic sphincter deficiency (OR, 1.9, $p = 0.01$).

Jeong 2014 (148) was a retrospective study at 36+ months; when dividing women by the route of approach, the success rates in the TO approach became worse with increasing BMI (P=0.037), while success in the retropubic approach did not differ according to the BMI groups (P=0.06). On multivariate logistic regression, only preoperative MUI (clinically-defined) was a risk factor for failure in all patients.

The Brennand 2015 study (107) is subset of original RCT by Ross 2009 (135). TO and retropubic MUS were grouped together in this analysis. The probability of objective cure remained significantly higher for non-obese women than obese women (85.6% versus 67.8%, (p=0.018, RR 1.26, 95%CI 1.04–1.52). Surgery type was not significantly associated with cure (p=0.492, RR 0.95, 95%CI 0.83–1.10). Brennand 2017 (149) followed these women for 5 years and found obese women continued to experience lower rates of cure.

In 2016, Pereira et al (150) compared TVTO outcomes in women with BMI at < 30 and > 30 at 4 years, however almost half of the retrospective participants had mixed incontinence and the drop-out rate was nearly 40% in both groups. Success rates (on cough

stress test) declined over 4 years from 98 % to 96% in non-obese, versus 95.1% to 90% in the obese.

In 2018, Laterza et al (108) performed a secondary analysis with respect to obesity of a RCT at 5 years, including TVT and TVT-O RCT together (the Austrian Study Group). At 5 years a positive cough stress test was seen in 56/277 (20%) women. The probability to have a positive stress test at 5 years significantly increased with higher BMI (p = 0.01) (I.e. a high BMI (>35) had a failure rate of 30% versus failure rate of 10% for BMI of 25)

Barco-Castillo (2020) analysed 3 RCTs of obese (BMI>30) women (n = 316) and non-obese women (n = 566) undergoing TVT, TOT, or "anti-incontinence surgery (106). Objective success was defined as pad test < 1 gm, negative cough stress test or no USI on urodynamics. The risk of objective failure was significantly increased in obese women (rr 1.62, 95% CI 1.26- 2.07), which was similar to the risk of subjective failure (RR 1.69, 95% CI 1.32 – 2.16).

Summary

Retropubic MUS has demonstrated equal or superior efficacy compared to other procedures for female SUI (LE=1/2).

Retropubic MUS is at least as effective as open colposuspension in the short and medium term, and may be superior to laparoscopic colposuspension although most studies are small/ underpowered (EL=1/2). The rate of complications of retropubic MUS and colposuspension are similar. However, the rates of specific complications (e.g. bladder perforation, need for subsequent POP surgery, etc.) differ between the procedures. Retropubic MUS is associated with a shorter operative time and hospital stay. (EL=1/2)

Overall, retropubic MUS and TO MUS procedures perform equally at a short-term follow-up of 6 to 12 months. (EL= 1/2). At longer term follow up, repeat incontinence surgery is highly significantly more likely with the TO approach as compared to retropubic MUS (**RR 8.79)** The overall rate of vaginal MUS erosion is no different between these techniques. (EL=1/2)

The rate of bladder puncture, postoperative voiding dysfunction, and haematoma formation lower after the TO approach versus the retropubic MUS approach. Groin pain is more common with the TO approach **(RR 4.12**). [EL=1/2]. However, bladder puncture by the small trocar involved seldom requires more than overnight catheterization, and haematoma formation is generally managed conservatively, whilst cure of groin pain often requires substantial surgical exploration to remove mesh from the groin.

Recommendations

Retropubic MUS is recommended as an effective and durable treatment for stress urinary incontinence. [Grade A]

For both the retropubic and trans obturator procedure, substantial evidence from retrospectively analysed RCTs now indicates that obese patients have a poorer outcome than non- obese patients [Grade B].,

Although the risks of bladder perforation and haematoma are significantly higher for the retropubic approach, substantial evidence from systematic reviews indicates that the risk of groin pain and reoperation for incontinence is significantly higher for the trans-obturator approach. [Grade A]

3.2. Trans Obturator Tape Long Term Results

As explained in Section 3.1.8 (Comparison of Retropubic versus Transobturator MUS), Delorme modified the TVT to minimise the incidence and morbidity of bladder and urethral injuries. The polypropylene mesh tape was brought from inside the thigh through the obturator foramen to support the mid-urethra (119).

De Leval further modified this "outside-in TO MUS" procedure to be an "inside-out" procedure, now called the tension-free vaginal tape-obturator (TVT-O™; Gynecare (120), made of Amid type I polypropylene mesh, with less risk of mesh adverse events (151). The "outside-in" and "inside-out" techniques are important categories for consideration of outcomes, but are not always described.

In 2017, a systematic review with meta-analysis (146) exclusively regarding long-term (>5 years) outcomes of MUS was published, comparing the retropubic vs transobturator approach. The definition of "cure" varied widely, ranging from negative cough stress test to "no self-reported stress incontinence". The authors concluded that both TVT and TOT are associated with similar long-term objective (OR: 0.87 [95% CI: 0.49-1.53], p = 0.62) and subjective (OR: 0.84 [95% CI: 0.46-1.55], p = 0.58) cure rates. Similarly, no significant difference was observed between TTOT-OI and TVT-O) in objective (OR: 3.03 [95% CI: 0.97-9.51], p = 0.06) and subjective (OR: 1.85 [95% CI: 0.40-8.48], p = 0.43) cure rates. This study also shows that there was no significant difference in complication rates for all comparisons: TVT versus TOT (OR: 0.83 [95% CI: 0.54-1.28], p = 0.40), TOT-OI versus TVT-O (OR: 0.77 [95% CI: 0.17-3.46], p = 0.73) (146).

Other long term outcome studies with duration of 48 months to 10 years have emerged (see Table 5) (150, 152-160)]. This table only lists studies that reported objective outcomes, only using standardized tools such as a pad test or at least a cough stress test under standard conditions. With regard to subjective outcomes, we preferred to consider the studies that used the bladder diary.

In Costantini 2016 (158), a Kaplan–Meier survival curve showed that the continence rate decreased for up to 25 months after surgery, with stabilisation thereafter for the TVT group while continuing to drop in the TO MUS group. **Figure 7.** Patients in both groups were highly satisfied at long-term follow-up

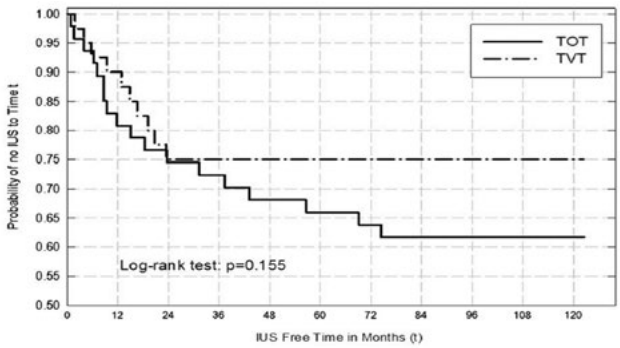

Figure 7: Free survival times from UI subdivided according to surgical techniques, reproduced from Costantini et al 2016 with permission

Laurikainen 2014 (110) is a 60-month update of Palva *et al*. (127), showing no differences between groups (TVT and TVT-O). In Kenton 2015 (161), a per protocol analysis at 5 years showed retropubic MUS success rate was 7.9% greater than TO MUS (95%CI -1.4 to 17.2), and did not meet the pre-specified criteria for equivalence. (The 95% CI included 0%, indicating non-significant results).

Ross 2016 (162) followed 176 women for 5 years; serious adverse events and tape effectiveness did not differ between groups. However, palpable (non-exposed) TOT occured in 48.5% vs. 22.4% in TVT; p=0.001. Tammaa et al in 2018 (163) compared TVT to TOT at 5 year follow up and found subjective and objective cure rates were stable and similar between groups.

Offiah et al 2021 (164) reported results of a multicentre RCT comparing retropubic and transobturator MUS at a mean follow up of 12.8 years (via postal questionnaire). Data was available on 110 of the 180 original participants. While at 1 year there was no significant difference between groups, at 12.8 years they found TVT to be superior to TOT for subjective SUI cure (41.8% vs 21.8%, p=0.045). This represented a significant decline in efficacy since 1 year, particularly for the TOT. There were no differences in severe groin or vaginal pain, or complications between groups.

The data (Table 5) appear to confirm that objective cure rates and subjective satisfaction are generally greater than 80% at ten or more years after the procedure. The reported rates on extrusions, exposures and other mesh-related complications are < 5%, with except for the study by Costantini et al that reported 15% of cases of extrusions (158).

3.2.1. Mesh Related Extrusions and complications

After the warning issued by the US Food and Drug Administration in April 2019, which ordered the manufacturers of surgical mesh intended for transvaginal repair of pelvic organ prolapse to stop selling all devices, the use of mesh intended for treatment of SUI has also been widely questioned, especially transobturator mesh midurethral slings. The Scottish government suspended all mesh surgery in 2014 then halted its use in 2018, which was followed by a national “pause” in England and Ireland, pending further evidence (Imamura et al, 2019 [61]).

Table 5: Long-term Outcomes of TO MUS with objective outcome measures

Author	MUS	N	RCT	F/U	# Lost To F/U	% Obj. Cure	% Subj. Cure	AEs / Comments
Liapis, 2010 (152)	TVT-O	74		48-52m	6	82.40%	81%	9 UTI, 13 ↑PVR, 2 extrusion, 13 leg pain
	TVT-O+AC	41	Yes			80.50%	76%	
Heinonen, 2013 (153)	Out in TO MUS	139	No	6.5y mean	52	89%	83%	-
Chun, 2014 (154)	Out in TO MUS	129	Yes	7.1y median	-	87.10%		-
	TVT-O	86				66.70%		
Yonguc, 2014 (155, 165)	Out in TO MUS1	126	No	61.2m (55-82)	12	87.30%	65.9% (higher for SUI vs. MUI)	1 UTI, 5 groin pain, 2 extrusion, 2 retention
Laurikainen, 2014 (110)	TVT TVT-O	136/ 132	Yes	60+ m	5/9	84.7/86.2	94.2/91.7	Neg 24 hr pad test + neg cough stress test
Toz, 2015 (156)	Safyre (out in)	153	No	96m	-	77.60%	77.60%	-
Kenton, 2015 (161)	RP MUS	TO MUS	298/ 299	60m	7/6		51.3/43.4	P = significant Success = no repeat surgery and no leak
Ross, 2016 (162)	TVT TVT-O	93/83	Yes	60m	8/9	75.7/86.4	90.1/96.3	P = not significant
Lo, 2016 (157)	Monarc (out in)	56	No	80.3m (78-83)	4	89.30%	87.50%	No AEs
Costantini, 2016 (158)	TVT TVT-O	40/47	Yes	100 m	4/4	87.5/70.2	59.6/75.0	7 extrusions (14.9%)
Serati, 2017 (159)	TVT-O	168	No	120 m	8	92%	97%	14% OAB de novo; 1% persistent groin pain
Tammaa, 2019 (163)	TVT TVT-O	161/ 170	Yes	60m		83.3/ 75.5	Not available	No
Serati, 2020 (160)	TVT-O	157	No	156 m	11	92%	95%	2.5% mesh extrusions 15.6% OAB de novo 1% persistent groin pain

MUS: midurethral sling; N: number; F/U: follow-up; AEs: AEs; TO MUS: transobturator midurethral sling; m: months; y=years; med: median; VLPP: valsalva leak point pressure; UTI: urinary tract infection; PVR: post-void residual; MUI: mixed urinary incontinence; SUI: stress urinary incontinence; KHQ: King’s Health Ques-tionnaire; BMI: body-mass index.

The recent NICE guidelines (10) on management of female incontinence no longer recommends transobturator slings for first line therapy for SUI. One reason for this statement is that TO-MUS presented a higher rate of mesh exposure than Retropubic-MUS (OR, 3.25, 95% CI, 1.02-10.36), as reported in the ESTER systematic review (166). However, the distinction between the terms "extrusion" and "exposure" are not very clear in the few studies that assessed these outcomes, whereas the rate of tape/mesh erosion or extrusion are similar for both procedures (OR, 1.10, 95% CI, 0.70-1.70).

Morling et al. (2017) (167), in a large cohort study of 13,133 women undergoing a first, single incontinence procedure with mesh in Scotland, showed that compared with non-mesh open surgery (colposuspension), mesh procedures had a lower risk of immediate complications (adjusted relative risk [aRR] 0·44 [95% CI, 0·36-0·55]) and of subsequent prolapse surgery (adjusted incidence rate ratio 0.30 [0.24-0.39]), and a similar risk of further incontinence surgery (0.90 [0.73-1.11]) and later complications (1.12 [0.98-1.27]).

Also, Gurol-Urganci et al (2018) (151) published a retrospective cohort study from England of 95,057 women (60,194 women underwent retropubic insertion and 34,863 underwent transobturator insertion). Using actual raw data from the Hospital Episode Statistics, they examined long-term mesh removal and reoperation rates in all women who had a first midurethral mesh sling insertion for SUI. The rate of midurethral mesh sling removal overall was 3.3% (95% CI, 3.2-3.4) at 9 years. When separating MUS from TOT, the 9-year removal risk after transobturator insertion (2.7% [95% CI, 2.4-2.9]) was lower than the risk after retropubic insertion (3.6% [95% CI, 3.5-3.8]. The raw data did not capture the cause of the mesh removal (eg voiding dysfunction versus groin pain), nor could the data distinguish between partial or complete mesh removal. The overall rate of reoperation for stress incontinence was 4.5% (95% CI, 4.3-4.7) at 9 years (no subset analysis).

Serati et al, in their 13yr follow up study (160), found four cases of sling exposure (2.5%), but all appeared between the 10-year point (159) and the 13-year follow-up. It seems that there is a border-line significant increase ($P = .05$) of the incidence of sling exposure over 10 years after the sling.

3.2.2. Groin pain

Post-operative groin pain is one of the most debated issues about TO MUS. The original work by De Leval described 16% of patients developing immediate postoperative pain. This was treated with simple analgesics and abated within 2 days and always by 1 month (120). A review by the same group in 2009 showed a low incidence of persistent groin pain/discomfort after the TVT-O procedure (168). Unfortunately, the vast majority of available data are regarding the immediate postoperative period, and few reports on the medium- and long-term persistence of groin pain exist.

It is evident that groin pain is more frequent after transobturator MUS than retropubic MUS [6.3% vs. 1.3%; OR: 3.80]. The short-term rate reported is about 1-5% (166). In an RCT comparing TVT with TVT-O, a pain score was significantly higher in the TVT-O group in the initial postoperative period, but not at 24 months (139). In the longest available follow-up study, Serati el al (160) reported a low rate of persistent groin pain (<1%), 13 years after the surgical procedure [EL=3].

Several case reports presented different possible managements of persistent groin pain after TO MUS (169-171). Persistent pain may be due to adductor muscle strain, osteitis pubis, obturator/groin abscess, structural adhesions, and inflammation, edema or nerve entrapment of the anterior branch of the obturator nerve (172). A review article on this topic (173) concluded that pain after TOT suburethral sling is a relatively uncommon occurrence requiring specialist intervention. Up to 1% of patients will require removal of some or all of their tape owing to pain. Long-term support with the involvement of a pain management team may be required.

3.2.3. Outcomes in elderly patients

A RCT evaluating risk factors for failure of TVT vs TO MUS (TVT-O) found that age is an independent risk factor (OR: 1.7 per decade) for the recurrence of SUI symptoms at one year of follow-up (174). Another prospective evaluation of 655 women at 2 years follow-up showed that older age is associated with a higher risk of objective and subjective recurrence or persistence of SUI (175). However, a cohort study published by Serati et al (2013) (176) revealed quite different results. The authors enrolled 181 women undergoing TVT-O surgery and found that women over 70 had similar outcomes to women under 70 in terms of cure rates (92.5% vs 88.3%, p = 0.40), voiding dysfunction, vaginal erosion and groin pain, at a median follow-up of 24 months (176).

A systematic review of the efficacy of treatments of UI in older patients confirmed that TO MUS are associated with the same subjective and objective outcomes in patients ≥ 65 years vs women < 65 years (177).

3.2.4. Learning curve

In 2011, Ito et al. (178) investigated data regarding a learning curve for the transobturator sling procedures, but have only shown that this learning curve for this technique is shorter than for retropubic slings. Four years later, Serati et al. (179) assessed several outcomes of TO MUS potentially influenced by the experience of the surgeon. They found that postoperative pain levels decreased with the increase in the level of expertise (pain levels: 1-day: from 6.6 (±3.3) to 4.3 (±3.1); 95%CI: -0.01603 to 0.001235, p=0.04; 2-day: from 5.6 (±4.1) to 3.6 (±3.7); 95%CI: -0.02092 to -0.002497, p=0.01; 12-month: from 0.1 (±0.7) to 0 (±0); 95%CI: -0.001814 to 0.05019, p=0.07). The change in ICIQ-sf (from 12 (±8.7) to 14 (±6.0); p=0.04) improved over the time. Therefore, they concluded that a higher experience of the surgeon could significantly improve the subjective cure rate and could reduce postoperative groin pain.

More recently, a study (180) that evaluated the number of procedures required for an untrained resident surgeon to learn TVT-O procedures showed that ten procedures were needed to improve outcomes. There appears to be a learning curve for TO MUS, in particular to minimise postoperative pain; however, this period appears to be shorter than for retropubic MUS. Previous studies of the incidence of groin pain have not considered the level of experience of the surgeon.

3.2.5. TO "Inside-Out" Approach vs. "Outside-In" Approach

Nine trials in the Cochrane review (Ford et al 2017 (103)) compared the inside-out approach with the outside-in approach (82, 123, 181-186). Median sample sizes were 110 (range 74 to 341). Median follow-up was 12 months (range 3-36 months). In terms of subjective and objective efficacy, the Cochrane review concluded that, when comparing transobturator techniques of a medial-to-lateral versus a lateral-to-medial insertion, there is insufficient evidence to support the use of one approach over the other. There was moderate quality evidence that voiding dysfunction was more frequent

in the medial-to-lateral group (RR 1.74, 95% CI 1.06 to 2.88; 8 trials, 1121 women), but vaginal perforation was less frequent in the medial-to-lateral route (RR 0.25, 95% CI 0.12 to 0.53; 3 trials, 541 women).

A systematic review and meta-analysis of inside-out vs. outside-in TO tapes summarised five RCTs and three cohort studies (187). As in the Cochrane Review, there was no significant difference in short-term subjective cure/improvement. In 2019, Serdinšek et al. (188) published the first 10-yr follow up of their randomised trial comparing the two different approaches of TO MUS. The authors did not find any statistically significant difference in terms of **objective cure rate, subjective satisfaction**, sexual function, complication rate. The only significant difference in terms of **complications** reported both in the Cochrane review and in the recent metanalysis published by Fusco et al. is the risk of vaginal perforation that is lower in the inside-to-out TO MUS (102).

Three trials in the Cochrane Review evaluated post-operative **sexual function** following inside-out and outside-in TO MUS (185, 189, 190). There was a significant improvement in PISQ-12 scores following surgery, but no significant difference between the two groups at follow-up

3.2.6. Overview of All Surgeries for Stress Incontinence In Women (excluding Bulking Agents): The ESTER Study

In 2019, Imamura et al conducted the largest meta-analysis of surgical procedures to date, comprising 175 studies of which 147 were listed in Cochrane reviews and 28 from additional studies (52). Bulking agents were excluded as no trials were found that compared this with other surgical interventions. Using sophisticated WinBUGS software, they estimated the ranking probabilities of the different surgical treatments for cure and improvement using the surface under the cumulative ranking curves (SUCRA), which gives probabilities of each intervention being ranked the best (ie, having the highest proportion of women cured or improved)." Note that "cure" was defined by patient subjective response or pad tests, but cough stress test and bladder diaries were not used. These analyses are shown in Figure 8, and have been discussed in previous sections where relevant.

Overall Summary and Recommendations Re Mid Urethral Slings: Retropubic versus Trans Obturator Procedures

The retropubic mid urethral sling is a robust procedure which is equivalent or superior to the open colpuspension in short term and long-term studies (without the increased risk of rectocoele and enterocoele), and which confers a lower risk of voiding dysfunction and de novo detrusor overactivity. Short term and mid-term studies show that the retropubic sling has superior success

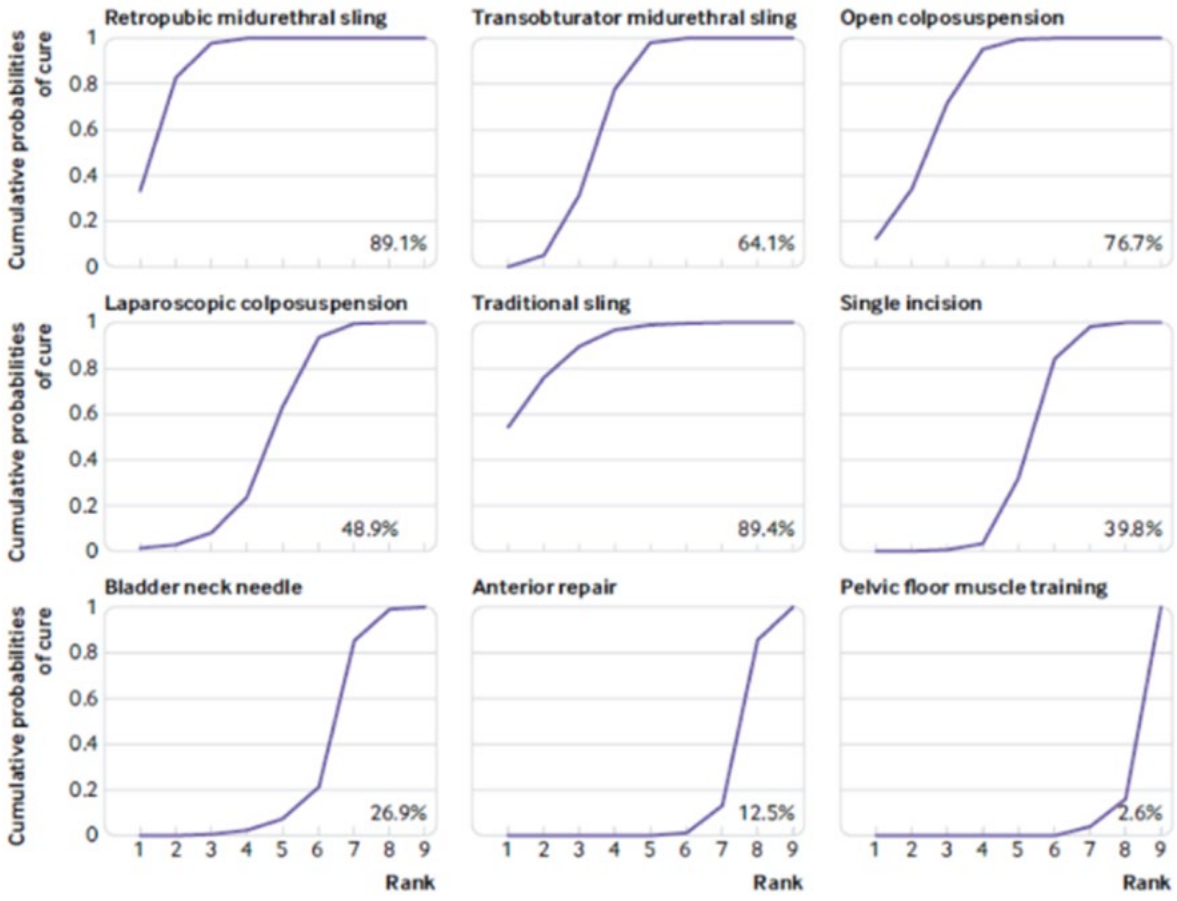

Figure 8: Surface under cumulative ranking curves (SUCRA) for number of women showing improvement of urinary incontinence symptoms (Reproduced with permission from Imamura et al, 2019 (52)

rates to the laparoscopic colposuspension. The comparison of trans obturator tape with these two procedures has received little attention.

As regards adverse events, several meta-analyses have demonstrated a significantly higher risk of thigh/groin pain with TOT compared with TVT. This applies particularly for the inside-out technique (3.1% TOT vs 15.7% TVT-O) where the trocar is directed more laterally in this critical area thus getting much closer to the nerve stem. More serious complications in this area include myositis, fascitis, and abscess formation. The 2017 Cochrane review of TVT versus TOT (103) found a significantly higher risk of groin pain after the trans obturator procedures (RR 4.12, 95% CI 2.71 – 6.27). [EL = 1/2]

Analysis of data regarding the risk of groin pain is difficult because these data are not systematically reported in all studies. Mesh exposure versus extrusion not always accurately reported, and may not be observed in short duration studies eg 12 – 18 months Note that complete removal of a retropubic MUS can be performed by a combined vaginal and laparoscopic procedure, but complete removal of a trans obturator MUS requires vaginal surgery as well as substantial groin incisions bilaterally.

As regards re-operation rates, in the medium term, more women required repeat continence surgery in the TOT group RR 21.89 (95% CI 4.36–109.8), with a similar trend in long term studies RR 8.97 (95% CI 3.36-23.00).

Research: Further longer term data regarding risks of groin pain, need for groin dissection to entirely remove trans-obturator tapes, and risks of repeat continence surgery after the trans-obturator approach are needed.

4. URETHRAL BULKING AGENTS

Stress continence is reliant on effective coaptation of the urethra during increases in intra-abdominal pressure. If the “water-tight seal” is inadequate, SUI results. Urethral bulking agents are designed to address defective coaptation and may be injected either trans-urethrally or peri-urethrally in a retrograde fashion, using either direct cystoscopic, ultrasonographic, or implacer-guided device implantation. The procedure may be performed under local, regional, or general anesthesia. Device implantation optimally occurs in the mid-to-proximal urethra (see Figure 9), and the need for possible reinjection at some point should be explained. Clinical trials have defined specific injection protocols (usually three injections); however, the optimal injection technique has yet to be standardised.

Many clinicians feel that injection of urethral bulking agents is generally more successful in the presence of a non-mobile urethra, which provides a fixed background against which the agent can sit firmly. As regards Intrinsic Sphincter Deficiency, in the 1990’s, a group from London published a 7 year follow-up study of 37 women, in which Cox regression analysis showed that low MUCP (<20cm) was significantly correlated with failure of collagen injections (p = 0.034) (191). However, many studies do not analyse their data in terms of urethral mobility or MUCP. Also, at least half of the publications do not indicate the percentage of patients who had received repeat injections at the time of outcome assessment.

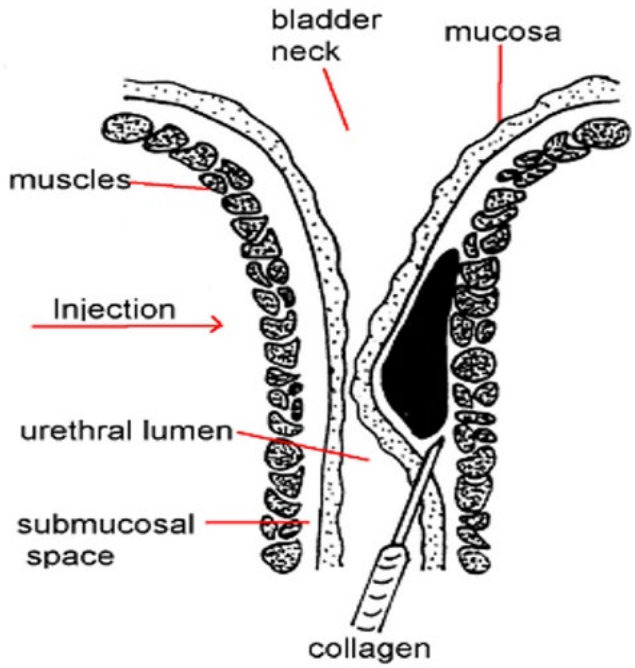

Figure 9: Trans urethral injection of bulking agent (collagen was the typical agent initially).(Courtesy of Alfred Yu , Medical illustration Dept, St George Hospital)

The duration of effectiveness of bulking agents is often quite high for 9-12 months but tends to fall off over time. The conclusions from ICI-6 were that multiple injections are required for optimal outcomes and that no single bulking agent, location, or method of injection was superior to another. This section emphasises new developments since ICI-6 and highlights long-term studies with objective outcomes.

4.1. Available Agents

Due to manufacturing cessation (delayed skin reactions, arthralgia, (192)), bovine collagen (Contigen®) was obsolete at the time of ICI-5, not included in this chapter except for comparison with other agents. Limited data were published regarding **stabilised hyaluronic acid/dextranomer** (NASHA-dx; Zuidex®), but the latest Cochrane Review (192) noted that women treated with NASHA-dx had significantly higher rates of injection site complications compared to bovine collagen (16% vs. 0%, respectively; RR 37.78, 95% CI 2.34 to 610) and this product was withdrawn from the U.S. market (192) but is available for vesicoureteric reflux. Similarly, the 2017 Cochrane review noted that evidence of particle migration has stopped the clinical use of **Polytetrafluoroethylene** (Polytef paste).

a) **Carbon coated zirconium beads** (Durasphere®), available USA, Europe, Australia (Hoe 2021, 214)

b) **Calcium hydroxyl apatite** (Coaptite®), available in USA and Turkey

c) **Polydimethylsiloxane elastomer** (PDMS; Macroplastique®), UK, Europe, Australasia, USA

d) Polyacrylamide hydrogel (PAHG; Bulkamid®). UK, Europe, North America, Australasia

e) Urolastic (Urogyn) consists of **vinyldimethyl terminated PDMS, tetrapropoxysilane cross-linking agent, platinum vinyltetramethyl siloxane complex catalyst, and titanium dioxide radiopacifying agent**.

4.2. Outcomes of Recent Studies

- Before reading this section, a few comments about the Outcome Measures employed in these studies of bulking agents may enhance understanding. This topic is particularly relevant because many patients are expressing increasing interest in such agents, in their effort to avoid polypropylene mesh Mid Urethral Slings (e.g.which are not available in the UK).

- The Stamey Grade is often reported as a measure of overall cure, but it comprises 4 simple questions about degree of leakage and is actually a subjective outcome. The PGII has 4 levels of response (cured, improved, no change, worse) but unfortunately 'cured' and 'improved' are often combined. The cough stress test needs to be performed at a standardised volume (commonly 300 ml) for it to be considered a valid objective measure, which is often not specified. The results of a pad test should ideally be reported as raw data, thus a 50% reduction in pad test weight is not a standard outcome measure.

4.2.1. Cohort Studies

4.2.2. Carbon-Coated Zirconium Beads;' DURASPHERE

There have been no novel studies of periurethral carbon-coated zirconium beads since ICI-6.

4.2.3. Calcium Hydroxyl Apatite; COAPTITE

There have been no novel studies of calcium hydroxyl apatite since ICI-6.

4.2.4. Polydimethylsiloxane Elastomer (PDMS) MACROPLASTIQUE

Outcomes of studies of Macroplastique by Ghoniem et al. (2009, 2010, 2013) are fully described in ICI-6 (193-195), including a RCT comparing PDMS vs. bovine collagen (194), in which mean pad test weight was 24 g at baseline and 4 gm at 12 months. A systematic review by Ghoniem and Miller of literature from 1990 to 2010 (195) showed cured/dry rates on Stamey grade were 43%, 37%, and 36% at <6, 6-18, and >18 months, respectively. Higher reinjection rates were associated with improved long-term SUI outcomes.

A prospective database of women undergoing Macroplastique/PDMS injections at University of Texas has yielded two recent manuscripts. Rosenfeld et al (2016) evaluated PDMS in 3 groups of women: Naive (Group I), Prior Anti-Incontinence Surgery (Group II), and combined Prior Bulking Agent and Anti-Incontinence Surgery (Group III) (196). The title of this paper stated that all participants had ISD but this entity was not defined. "Success" was defined as sufficient improvement after one injection that no retreatment for SUI was needed at last follow-up. In 59 women at a mean follow up of 9 months,the success rate was 83% for Group I, 70% for group II, and 69% for Group III (p=0.54).

Carroll et al. evaluated the aforementioned cohort at a median follow-up of 20 months (range: 6-71), and defined success after the last Macroplastique injection as a UDI-6 Question 3 score of 0 (dry) or 1, and no reoperation for SUI (with no objective outcomes) (197). From 2011-2017, in 106 of the original 142 women, success rate was 41% for Group I, 40% for Group II, and 65% for Group III (p = 0.22. The completely dry rate was highest in those with the most "fixed" urethra, Group III at 29%, compared to 4% for Group I and 15% for Group II (p = 0.05).

Serati et al (2019) reported on 85 women at 3-year follow-up after Macroplastique injection (198). The subjective (via PGI-I, ICIQ-SF) and objective (via cough test during urodynamics) cure rates were 49% and 47%, respectively. A history of radical pelvic surgery and a "low surgeon's skill" were significantly associated with failure.

Montera et al (2018) prospectively studied 47 women who had occult stress incontinence on a 300 ml cough stress test when the bladder was replaced into the vagina (despite no symptoms of USI in daily life), in whom Macroplastique was injected at the time of prolapse repair (199). Patients with ISD (UPP < 20 CM OR VLPP < 60 CM), previous continence surgery, or detrusor overactivety were excluded. Cure of occult USI was defined as no leakage on stress test during postop urodynamics at 12 months. Success rate (87.3%) was similar to that of a historical control group who had prolapse with a TVTO (cure 89.7%) or prolapse surgery alone (78%). However, the TVTO group had a 5% mesh erosion rate, with a 7.6% "severe pain" rate. The cure rate for macroplastique with repair, versus surgery alone, was significantly greater (p = 0.05).

Dray et al. retrospectively reported on 73 women who underwent urethral bulking (38 PDMS, 35 collagen) after failed autologous sling or MUS (66%) (200). Macroplastique was injected at either 3 clock and 9 oclock, or 6 oclock, depending on surgeon's preference, whereas Collagen was always injected at 3 and 6 oclock. After an average of 2.6 injections, 26% had complete symptom resolution, 71% had at least partial symptom resolution at their first post-injection follow-up. Pad usage fell from 3.2 pads per day to 2.1 pads/day (200).

Plotti et al. reported on 63 women, median age greater than 75 years, who underwent PDMS, with a mean follow-up of 8.3 years (range 3.5 to 18 years) (201). Cure was defined as resolution of SUI symptoms (including those ''Improved'' on the PGI-I; ''Urine never leaks'' on the ICIQ-SF; and no new symptom or side effect.) Improvement was defined as persistence of stress symptoms but with a decreased number of incontinent episodes (including ''Improved'' on the PGI-I; ''Once a week''/''Daily''/''All the time'' answer to the question ''How often do you leak urine'' on the ICIQ-SF) Fifteen (24%) women were cured, 12 (19%) were improved, and 36 (57%) failed.

Finally, Siddiqui et al (2017) performed a systematic review of English literature regarding Macroplastique and Bulkamid, which is described under Systematic Reviews (202).

4.2.5. Polyacrylamide Hydrogel (PAHG) – BULKAMID

Outcomes of several studies have been summarized in ICI-6 which are now included in the reviews below.

Several systematic reviews of Bulkamid have been published. A major review by Kasi et al (2016) included in ICI-6 (203) involved eight prospective, retrospective, and RCT studies, total = 767 women. In order to achieve adequate efficacy, 186/767 women (24.3%,

range 12-35%) required **reinjection**. Both the number of incontinence episodes/24hr and pad test loss /24hr lost were significantly reduced at one year but only 3 of the 8 studies gave pad test data (which seemed to show cure in all subjects).

The previously mentioned systematic review of Macroplastique and Bulkamid by Siddiqui et al (2017) is considered under Systematic Reviews (202).

4.2.6. Vinyldimethyl-terminated Polydimethylsiloxane Polymer (VDM-PDMS)- UROLASTIC

A theoretical advantage of Urolastic is that it polymerizes in situ into a uniform elastomer which adapts to its environment and theoretically reduces the risk of migration (204, 205). Two studies from the same centre were included in ICI-6 (206, 207). In the latter study, 19 women were followed up at 24 months. Outcomes included Stamey Grade, 1-h pad test, pads/day, incontinence episodes/24-h, and I-QoL questionnaire. "Improved status occurred in 66% at 24-months (vs. 89% at 12 months). About 45% of the patients were dry (Stamey=0) at 24-months (vs. 68% at 12 months). The 1-h pad-weight test showed >50% reduction in 84% at the 12-month follow-up.

Futyma et al (2016). reported an objective success rate after Urolastic injection in 66 women with recurrent SUI of 32.7% at 24 months (208). The completely dry rate was 22.4%. Complications were observed in 25.8%, including an "oval shaped mass" inside the bladder in 4.5%. De Vries et al. reported on 65 women, where 76-88% showed subjective improvement (via chart review) at 12-25 months of follow-up (209). In Dindo et al (2004), complications >Grade II were observed in 24-33% (210).

4.3. Method and Location of Injection

The Cochrane Review concluded that there was no difference in periurethral vs. transurethral delivery, although there was a non-significant trend towards higher early complications with periurethral injection (192). There has been no new information since ICI-6. Several agents have proprietary delivery methods/ devices , such that comparison of delivery techniques across different compounds is not valid.

4.4. Systematic Reviews

Multiple systematic reviews and meta-analyses have been published since ICI-6. Capobianco et al. searched PubMed, Scopus, and Cochrane Central Register for records up to December 2018, and found 42 full texts (of which 21 were selected (211). The pooled subjective cure rate was 26% and 21% at follow-up of ≤1 and >1 year. The pooled objective success rate was 46% and 7%, respectively. Adverse event rate was 0.4%.

In 2017, Siddiquie et al (202) from Birmingham UK published a systematic review of English language studies regarding Macroplastique and Bulkamid using MEDLINE and EMBASE databases from 2006-2016. This was prompted by the removal of MUS from the NHS in the UK, which engendered increased interest in bulking agents. The authors noted that NICE guidelines recommended bulking agents for patients with significantly decreased urethral mobility.

Eight studies of Macroplastique were included; two were RCTs (194, 212). Subjective success was measured by I-QOL, IIQ-7, UDI-6, and VAS. Objective success was measured by urodynamics, 24-hour pad test, cough test, and leakage episodes on diary. Repeat injection was reported in three of the eight studies and ranged from 9% to 44%. Objective cure (given in 6 studies) was 71%% at 3 months, 55% at 6 m, 35% at 10 m, and at 12 months was 42%. The UTI rate was 9%.

Twelve studies of Bulkamid were included (one RCT, (213)). Subjective success = Likert scale, ICIQ, IIQ, and PGIQ, while objective success = urodynamics, 24-hour pad test, and cough test. All studies showed improvement in all subjective indices. Repeat injection was reported in six of the twelve studies and ranged from 8% to 65%. Objective cure (given in 5 studies) were 38%, 47.2%, 73%, 79.3% all at 12 months, and at 22 months cure rate was 19.6%. The UTI rate was 11%.

The most recent and largest systematic review is by Hoe et al (2021) (214) from Melbourne (also partly stimulated by patient avoidance of mesh MUS in Australia). They screened 583 articles from the Ovid Medline, Embase and PubMed databases and included 56 articles in their analysis (214). Higher long-term success rates were found with Bulkamid (42%-70%), Coaptite (60%-75%), and Macroplastique (21%-80%) on qualitative review. UTI rates were similar between agents (4%-10.6%) although temporary acute urinary retention was more commonly associated with Coaptite (mean: 34.2%), and *de novo* urgency in Durasphere (mean: 24.7%). Significant complications such as migration into lymph nodes was reported with Durasphere. Erosion was reported with PDMS, calcium hydroxyl apatite, and VDM-PDMS, with a rate as high as 24.6% in one study of VDM-PDMS. Bulkamid appeared to have a more favourable safety profile, with no cases of erosion or migration of the product. Direct comparisons of bulking agent cure rates could not be performed because of incomplete or highly variable outcome reporting.

4.5. RCTs Comparing Bulking Agents

The Cochrane analysis (updated in 2017) concluded that all bulking agents appeared to provide similar overall improvements as compared to bovine collagen (192). Fourteen trials compared different agents and all results had wide confidence intervals. No improvements were shown to be more or less efficacious than bovine collagen. The authors concluded that the available evidence base remained insufficient to guide practice.

4.6. Bulking Agents vs. Sling Surgery

Several trials included in ICI-6 confirmed that women undergoing anti-incontinence surgery achieved higher continence rates and satisfaction than women undergoing bulking agents (215-217). The incidence of adverse effects, including urinary retention, voiding dysfunction, and UTI, was significantly higher in the surgery group. In the two trials in the Cochrane Review that compared injection therapy with surgical management, better overall objective cure was obtained after surgery vs. injection (RR 4.77, 95% CI 1.96 to 11.64; and RR 1.69, 95% CI 1.02 to 2.79) (192).

Recently, Itkonen Freitas et al. (2020) performed a controlled non-inferiority clinical trial in women with primary SUI who were randomised to TVT or Bulkamid (88). Primary outcome was patient satisfaction and secondary outcomes were reduced urinary leakage and complications at 1-year. Of the 224 women 111 were randomised to TVT and 113 to PAHG. At 1 year, a VAS ≥80 (range 0 to 100) was reached in 95% and 60% of women treated with TVT and Bulkamid, respectively. As a result, Bulkamid did not meet the noninferiority criteria. The cough test was negative in 95% and 66%

of TVT and PAHG cases, respectively (difference 28.6%, 95% CI 18.4-38.5). Not unexpectedly, most perioperative complications (19 TVT vs. 3 PAHG) and all six reoperations due to complications were associated with TVT.

Bach and Toozs-Hobson examined the British Society of Urogynaecology surgical database to analyse 1386 patients who had periurethral bulking and 18,763 who underwent MUS (218). The primary outcome was patient-reported PGI-I for incontinence with secondary outcomes of change in SUI, OAB, and complications. SUI was the most common urodynamic diagnosis (bulking 67%, MUS 77%) but there was a higher proportion of complex diagnoses in the bulking group. The percentage of women reporting "very much/much better" on PGI-I was 59% and 91% in the bulking and MUS groups, respectively. Twenty-eight percent of women felt their SUI symptoms were cured following bulking vs. 77.6% after MUS. There was no difference in outcomes when using periurethral bulking agents as a primary or secondary procedure. There were no intraoperative complications with bulking and fewer post-operative complications compared to MUS (3.6%).

4.7. Role of Bulking in Special Populations

4.7.1. Bulking in the Elderly

Since the publication of ICI-6, a number of studies commented on the results of bulking in elderly women. At a mean follow-up of 8.3 years (range 3.5 to 18) 63 women with a mean age >75 years underwent PDMS injection (201). Cure = complete resolution of SUI symptoms, while improvement was defined as the persistence of SUI with fewer incontinence episodes. Twenty-four percent of women were cured, 19% were improved, 57% failed treatment. Elmelund et al. performed a post hoc analysis of a previously published, randomised, 33-centre study of PAHG vs. collagen injection (219). Cure was achieved after one year if there were no SUI episodes per bladder diary and no SUI symptoms on the ICIQ-UI-SF, while improvement was achieved with ≥50% reduction in SUI episodes. Of the 345 women who were initially randomised 291 were included in this study. A total of 191 women received PAHG and 100 received bovine collagen. At one year 74 women (25%) were cured, 164 (56%) were improved and 53 (18%) showed no effect. On multivariate logistic regression analysis **age 60 years or greater** and fewer than 2.5 daily SUI episodes were associated with cure.

4.7.2. Recurrent SUI; Bulking agents after previous continence surgery

Several studies have been published since ICI-6. Dray et al (2019) reported 73 women who had urethral bulking after failed sling (66% MUS, 27% fascial sling, 7% both). After an average of 2.6 injections (38 PDMS, 35 collagen), 71% had at least partial symptom resolution at their first post-injection follow-up (200). Forty women had long-term follow-up (mean 39.6 months post-injection), but only two of them reported total resolution of SUI symptoms.

Zivanovic et al (2017) included 60 women who had Bulkamid due to recurrent SUI or MUI after a previous MUS, reporting cure based on a negative cough test, <2g urine on a 1-hour pad test, and VAS score improvement by ≥90% (220). Women deemed improved had a loss of a few drops on cough test, 2-10g urine loss on the pad test, and ≥75% improvement on VAS. The combined cure/improved rates were 93.3%, 88.3%, and 83.6% at 1, 6, and 12 months, respectively. Resolution of the urge component was seen in 38.9%. UTI rate was 3.6% at 12 months. Adverse events were <4% of women.

Rodriguez et al (2020) evaluated Macroplastique success after suburethral sling removal for synthetic sling complications (221). Success was defined as a composite score of a UDI-6 question 3 score of 0 to 1 at last visit and no additional anti-incontinence therapy (no objective criteria). In 70 women (mean age 62.7 years), success after the first injection was 46% at a mean follow-up of 46 months. When indicated, a repeat injection yielded an overall 69% success rate for the entire cohort (with 83% of the patients reporting subjective improvement and 78% reporting reduced pad usage). On multivariate analysis, age, body mass index, previous hysterectomy, hormone replacement therapy, type of sling removed, and baseline urodynamic results were not predictors of failure.

Daly et al. presented a retrospective case series of women having their first bulking from 2010-2018, 135 of whom had bulking as a primary treatment and 38 who had a salvage procedure (222). The primary outcome was patient-reported improvement, based on PGII but treatment 'success' defined as 'cured' or 'improved'. Median follow-up was 33 months; complete follow-up was obtained for 114 women (66%). Success was not significantly different between the salvage group (75%; 21/28) and primary group (67%; 58/86) (p=0.407).

4.7.3. Radiation-Associated Incontinence

Dobberfuhl recently reviewed the impact of bulking therapy on irradiated patients, with a focus on the studies in the Cochrane Review by Kirchin et al. (192, 223). Interestingly, of all the surgical treatments for SUI, only bulking agents have been studied prospectively in irradiated women. Plotti et al. observed that 10 women were cured (42%) and 10 improved after PDMS injection (with five of 24 women having previous radiotherapy) (224). Krhut et al. treated 46 women with PAHG, 24 of whom had previous radiotherapy (225). At a mean of 12.4 months of follow-up, complete continence was achieved in 25% of women after radiotherapy (compared with 36.4% of those without radiotherapy). The interval between radiotherapy and injection was a mean of 93 months (range 16-384).

4.8. Complications

As mentioned in several studies above, bulking therapy is infrequently associated with severe complications. The most frequent adverse event is UTI, with dysuria, urgency, urinary retention, and hematuria also reported. Occasionally, the injectables themselves cause unique complications. Chapple and Dmochowski summarized that foreign-body granulomas, erosion and migration/material extrusion, and loss of bulk have been observed in connection with the particle-based products (226). Several of the particle-based agents previously used for bulking have been discontinued or withdrawn from the market due to these complications. The list includes hydrophilic dextran polymer/hyaluronic acid base, polytetrafluoroethylene/glycerine/polysorbate, and ethylene vinyl alcohol copolymer. PAHG (a non-particulate bulking agent) may be mechanistically less liable to these events; however, there are minimal data directly comparing the particle-based and non-particulate bulking agents.

Summary

Only 1 new RCT (of Bulkamid versus TVT) has emerged since publication of ICI-6. While bulking agents provide a treatment option for primary SUI, optimal results may be obtained with repeated injections as effects wane with longer follow-up. The few RCTs that exist suggest that outcomes are similar regardless of

bulking agent used, with no single bulking agent demonstrating superiority to bovine collagen (no longer available). (Level 2b/3)

There appears to be no difference in outcomes whether the transurethral or paraurethral technique is used. (Level 2b). Data suggest that bulking is inferior to surgical treatment for both primary and recurrent SUI (Level 2).

Limited, non-randomised data suggest benefit of bulking agents in special populations, such as women with SUI following pelvic irradiation (Level 4).

The National Institute for Health and Care Excellence (NICE) and The American College of Obstetricians and Gynecologists (ACOG) guidelines suggest that periurethral bulking agents should be considered as one of several treatment options for patients with significantly decreased urethral mobility (Level 2)

Overall complication rates associated with bulking agents continue to be relatively low (Level 2b/3b/4); however, the particle-based agents appear to be associated with adverse events such as extrusion and foreign-body reaction.

Recommendations

Bulking agents should not be offered as first-line therapy for those women desiring a “one-time” durable solution for primary or recurrent SUI (Grade B).

Bulking therapy is an option for selected individuals with SUI (e.g., poor candidates for anti-incontinence surgery or those desiring an office-based, minimally invasive procedure) after appropriate counseling regarding lack of long-term durability (Grade B)

Bulking agents may be offered as therapy for recurrent or persistent SUI following anti- incontinence surgery, although these outcomes are likely inferior to repeat anti-incontinence surgery in the long term, particularly in the presence of Intrinsic Sphincteric Deficiency (Grade C).

Conclusions

While multiple bulking agents are available, their use is typically associated with improvement rather than resolution of SUI, waning effects over time, and a high rate of retreatment. They may have more benefit in women with poor urethral coaptation, such as those with a poorly mobile urethra, previous radiation, and vaginal/periurethral scarring [Grade B]. Their ease of use and minimal anaesthetic requirements should be balanced against potentially high costs, partly due to the frequent need for repeat injections.

Research: Further data regarding subjective and objective success rates in those with normal urethral function versus those with ISD are needed**.**

5. LASER THERAPY FOR STRESS INCONTINENCE

5.1. Introduction

The use of laser-based urogenital therapy has increased in recent years. In ICI- 6, the use of trans urethral laser therapy for USI was briefly described. However, in the only sham-controlled trial of 110 women, 48% of the treatment arm **and** 44% of the sham showed >10 points improvement in their IQOL score (227). These treatments were connected to adverse event effects such as dysuria, urinary retention and post-procedure pain (228). The relevant Cochrane review concluded that there was insufficient evidence to show benefit (229). Recently Gaspar & Brandi (2017) from Argentina studied trans-urethral laser treatment in 22 patients (mean age 57.9y) who all had ISD (VLPP < 60 cm) (230). Two sessions of Er:YAG were given 3 weeks apart. At six months, an ICIQ- of zero ocurred in 46%, with a pad test of < 8 gm in 50% (230). A study of trans-urethral radiofrequency (temperature 65-75° C) in pigs showed that valsalva leak point pressure was greater after treatment ($p = 0.06$) (231).

Also in ICI-6, used of Trans-Vaginal Laser therapy was discussed. As per Fistonic et al (2012), the theoretical aim of non-ablative laser treatment is to induce selective, heat-induced (61°C - 63°C) denaturation of dermal collagen that leads to subsequent new collagen deposition with as little damage to the epidermis as possible (228). Unfortunately, the histological studies that provide this information are often obtained from reports in the field of dermatology (for details see (228)) and Section 5.2 below.

Two main types of laser therapy are used currently: Erbium YAG (2940nm) laser and CO_2 laser.

CO2 Laser is used in gynaecology, dentistry, oral and maxillofacial surgery, is usually intended for cutting, excision, vaporization, ablation, and/or cauterization. This form of ablative therapy creates ablative zones and columns of deep thermal damage (50–125 nm), which increases tissue firmness and increase structural support for tightening and strengthening the vaginal walls.

Erbium-doped: Yttrium Aluminum-Garnet (Erbium:YAG or Er:YAG) uses heat only (60–63°C) to cause shrinkage of mucosal tissue. It was first used in 2000 for treatment of human papilloma virus infections, cervical ectropion, vulva intraepithelial neoplasia, etc and a side effect of vaginal tightening was noted.

Erbium Yag has 10–15 times the affinity for water absorption compared with the CO_2 at a wavelength of 10,600 nm and enables a deeper secondary thermal effect and controlled heating of the target mucous membrane of the vaginal wall. This allows controlled heating of the subepithelial layer without burning the vaginal epithelium. On the other hand, CO_2 lasers (10,600 nm) cause tissue denaturation.

Currently, three different laser modalities have been published for treating SUI: the microablative fractional carbon dioxide (CO_2) laser therapy (10,600 nm) (232); dual-phase erbium-doped yttrium aluminium garnet (Er:YAG) laser therapy (2,940 nm) combining fractional cold ablation and thermal ablation (232); and non-ablative Er:YAG laser therapy (2,940 nm) with SMOOTH mode technology (232) (for details see (228)).

5.2. Histological studies of Laser therapy

Three publications were found that actually investigated histological changes after laser to the vagina in women with stress incontinence. Gonzalez Isaya et al (2018) (233) and Alcalay et al (2021) (234) are discussed below as part of clinical studies. Lapii et al 2017 from Novosibirsk studied biopsies from the anterior vaginal wall taken from 18 women before and 6 weeks after they had two laser treatments (full paper translated from Russian (235)). Light microscopy and electron microscopy were performed but EM photomicrographs were not published. Most of the findings are quite descriptive, not quantitative, and do not actually mention increased density of **collagen fibres**. The epithelial thickness, number of capillaries, and density of capillaries per unit volume were all significantly increased ($p< 0.05$).

Two publications from Italy investigated histological changes after fractional CO2 laser to the vagina in women with vaginal atrophy (***no incontinence***). Vaginal samples were taken either on the same day of treatment (236) or one to two months after CO_2 Laser (237). The same-day study (n=5) showed "mild ablative effects". The longer term study showed substantial thickening of the squamous epithelium with papillae-form projection of the connective tissue rising up under the thickened epithelium. Neither study employed **any stains for collagen**.

5.3. CO2 Laser Therapy for SUI

Gonzalez Isaza et al (2018) from Colombia (233) studied 161 women aged 45-65 with mild stress incontinence. All had four sessions of CO_2 Laser (Mona Lisa) at the urethro-vesical junction every 30-45 days, then further treatments at 12, 24 and 36 months. Drop-out rate was zero. After the 4 treatments, 32% had moderate incontinence. The 1hour ICS pad test fell from a baseline 9.9 gm to 3.5 gms at 12, 24 and 36 months but the "dry rate" was not given. The ICIQ fell from 14.3 (SD+/- 2.65) to 7.5 (+/- 0.94) at 12 months, which persisted at 36 months. These authors obtained *punch biopsies* from the urethrovesical junction in one patient at baseline, 6 weeks and 6 months. Staining with H&E showed thickening of the epithelium and thickening of the underlying connective tissue with papillae-form projections of connective tissue under the epithelium. **Stains for collagen were not employed**.

In 2019, fractional CO_2 Laser (Mona Lisa) was given every 4-6 weeks for 3 treatments in 58 women with SUI, who attended a private facility in Australia (238). The primary outcome was one SUI question on Australian Pelvic Floor Questionnaire (AFPQ); a cough stress test was mentioned but not uniformly reported. Postmenopausal women (44/45) were also on vaginal oestrogen cream. Of the 58 women, 55 were seen at 3 months when 25 women (45%) had no stress leak on AFPQ. At 12-24 months, 36 women were seen (no reason for 22 drop-outs); 10/36 women (28%) had no stress leak on APFQ,

In 2020, Palacios and Ramirez (239) treated 25 women who had stress or mixed incontinence with three CO2 Laser treatments every 4-6 weeks (CO_2RE Intima); outcomes were measured at the time of the third treatment. Two patients dropped out because of vaginal candidiasis (one further follow-up loss). The baseline ICIQ (13.4) fell to 8.2 ($p < 0.001$) The cure rate was not given. Response in stress or mixed incontinence was not significantly different, but severe leakage responded as well as mild or moderate leakage.

Alcalay et al. (2021) from Israel studied 52 patients with proven USI, restricted to mild/ moderate severity (234). Three fractional micro-ablative CO_2 treatments were provided at monthly intervals, but only 42 completed the 12 month follow-up (i.e. 9 months after last therapy) with no reason given. Mean 1 hour pad test fell from 6.3 g (sd 1.6) down to 3.7 g (sd 1.4g), $p =<0.05$, "dry" rate was not given. Bladder diary showed leaks per day fell significantly just after the third treatment, but was no different from baseline at 6 or 12 months. In 29 women who agreed to have 6 month urodynamics, 41% had no USI. These authors also performed baseline and 6 month *biopsies of the posterior vaginal wall*; light microscopy H&E stain showed marked thickening of the squamous epithelium but specific staining for collagen was not performed.

In 2020, Dabaja et al from Israel studied 32 women which satisfied their sample size, based on a 16 point difference in UDI from baseline (240). All had a pure USI diagnosis based on urodynamics and cough stress test (which were also repeated 3 months after the third treatment). Mixed incontinence was excluded, age was limited (18-52 years). All women had 3 treatments, 4 weeks apart, using the Lumenis Acupulse System with the FemTouch vaginal handpiece. Side effects were vulvar sensitivity that lasted up to 3 days (in 30%), no cases of cystitis or vaginitis. The main outcomes were done at baseline and all four follow-ups (Table 6 below). Three months after the third treatment, both UDI and ICIQ showed significant benefit (both $p < 0.0001$), with partial benefit on USI. **However, these benefits were not sustained by 6 months after the third treatment, and data returned to baseline levels.**

This study is one of the few to report an actual sample size/ power calculation, and to give full data for outcome measures eight months after the first treatment, which reveal no benefit whatsoever.

Franić et al. (2021) from Slovenia studied 85 patients with SUI diagnosed on cough stress test (241). They had two sessions of CO_2 one month apart, with follow up 6 months later. However, 37 women (43%) were lost to follow-up, with no mention of the reason. Severity of SUI was significantly reduced on ICIQ from a baseline of 12 (range 4-15) down to 3.5 (range 0 -6.7), at six months ($p < 0.001$) and 45.8% of full participants had no symptoms, cured, on ICIQ. Younger women <39yr had a much better response than older women $\geq$ 60yr.

Table 6: Outcomes following CO_2 laser treatment.(Dabaja et al, 2020) (240)

	Pre-treatment	Post 1Rx	1m post 3Rx	3m post 3Rx	6m post 3Rx
+cough test (N)	25	–	–	23	–
+urodynamics (N)	30	–	–	19	–
No. of pads					
median (range)	**12 (6–18)**	12 (5–16)	9 (2–12)	7 (2–10)	**12 (7–18)**
UDI-6 score, mean (SD)	**45 (20)**	43 (19)	33 (17)	29 (15)	**45 (19)**
ICIQ-UI score, mean (SD)	**16 (4)**	15 (4)	9 (4)	8 (3)	**15 (4)**

Note that two Randomised Controlled Trials of CO2 laser versus oestriol cream have been conducted in women with vaginal atrophy but no incontinence. Cruz et al (2017) showed increased benefit for Laser over oestriol cream in 45 women on a symptom score (242). The VeLVET trial by Paraiso et al (2020) showed no difference for Premarin cream on 4 symptom scores in 62 women, but the vaginal maturation index showed greater improvement on Premarin cream (243).

5.4. LASER Erbium Yag Therapy for SUI

In ICI-6, a large study by Ogrinc et al (2015) of 175 patients with SUI and MUI was discussed (244). One Erbium Yag procedure (see Figure 10) was performed in 12 patients (7%), two treatments in 54 (31%), and three in 109 patients (62%). At one-year, 108 patients (62%) reported no incontinence. On average, they received 2.54 (SD 0.65) procedures. In the 29 patients (16%) whose grade of UI remained unchanged 2.68 (SD 0.55) procedures were given. In 38 (22%) patients, worsening of UI (in terms of UUI) was noted after therapy. The data are difficult to interpret because the ICIQ was used, but the numerical values of this score were compressed into 4 categories of the Incontinence Severity Index. Adverse effects comprised: mild transient discomfort/pain during procedure (6%) or new UUI (4%).

There have been three reports from Taiwon. In 2017, Lin et al studied 30 patients who had 2 sessions of Erbium:YAG laser, 4 weeks apart (245). The 1h-pad test baseline value of 13.2 gm (SD 17.7) fell to 6.1gm (SD 11.6) at 3 months (p = 0.04). At 12 months telephone appointment, the ICIQ fell from baseline of 10 (SD 3.7) to 5.5 (SD 4.2). All patients had OAB symptoms despite a urodynamic diagnosis of USI; they noted that the OABSS fell from baseline of 8.2 (SD 5.0) down to 7.9 (SD 6.0) at 12 months (p = 0.58). The 12 month follow up was a retrospective study, but the percentage of the original numbers who actually answered the telephone follow up was not provided. Figure 10 shows the Erbium:YAG laser equipment.

Figure 10: Photograph of the 2,940 nm Er.YAG laser device. Reproduced with permission from Ogrinc, Senčar and Lenasi (2015) (244).

Also in 2017, Tien et al performed one ErYAG Laser treatment (Fotona, Slovenia) in 35 women with USI; of these, 14 women also had OAB (246). A 20 minute cough stress test (cure < 1 gm) and the UDI 6 (cure = score 0 on question 3) were performed at baseline and 6 months. Three dropouts occurred. The objective and subjective cure rate was 39%.

Also from a different group in Taiwon, Lin et al (2019) evaluated 100 patients with SUI who had three Erbium:YAG laser treatments (interval not stated) (247). Only 41 women completed the protocol, because the remainder were reportedly “much improved after 2 treatments and declined to return”. Main outcomes were the ICIQ and urethral bladder neck mobility on ultrasound. At six months after treatment, the ICIQ fell from 7.2 (SD 4.5) to 3.7 (SD 3.5), p < 0.001. The descent of the bladder neck on Valsalva improved from 16.1 mm (SD 6.4 mm) to 10.5 mm, SD 4.6, p = 0.04 (247).

In 2018, Neimark et al (the same group from Novosibirsk who performed the histology study) treated 98 women (aged 37-63yrs), who had mild – moderate SUI (248). Laser treatment was performed with a 2940 nm Er:YAG laser (Fotona, Slovenia) using a SMOOTH mode. Outcomes were PFIQ-7 and PISQ-12 questionnaires, uroflowmetry, laser Doppler flowmetry and biopsy of the anterior vaginal wall at baseline and 1-2 months after treatment. Only the abstract was given in English, full paper in Russian, which states that “the effectiveness of treatment was 73%”. On PFIQ-7 and PISQ-12, patients with mild incontinence had the greatest benefit. Uroflowmetry parameters improved in most patients. Doppler flowmetry demonstrated improvement of blood flow in the microvascular bed. The authors referred to their previous histology study, saying that “an important feature of the vaginal biopsy after laser exposure was an increase in neoangiogenesis.”

In 2018, Blaganje et al from Ljubljana conducted an RCT of ErYAG laser versus Sham; the same instrument was inserted in the vagina, but no laser energy was applied (249). All 112 women had pure USI; age was limited to 35-65 years. Only one treatment of non-ablative “smooth” pulse was applied, with outcome measures at 3 months. The Sham baseline ICIQ of 12.41 SD 3.3, fell by -1.05 score points. The baseline of the ErYAG laser group was 12.0 SD 4.2, which fell by 3.86 points (p = 0.01 for ANCOVA between groups). The ICIQ score was zero/ dry in 3.6% of sham versus 21.4% of Laser treatment. This appears to be the only Sham- RCT that gives objective outcomes after only one treatment (e.g measures the true biological effect), but the 3 month results are disappointing.

Okui (2019) from Japan sequentially enrolled 50 women to have TVT operation, 50 to have TOT, and 50 to have Er:YAG laser [non-ablative “smooth” Fotona device] (250). Women were allocated “by numerical order of their medical charts”. Urge-predominant MUI was excluded (but MUI was accepted), with no urodynamics. The 3 baseline groups were similar in age and 1 hour pad test (approx. 35 gm). Er:YAG was performed three times every alternate month. At 12 months, the 1 hour pad test was 0 gm in 69%, 68% and 50% in TVT, TOT, and Er:YAG respectively (p< 0.001, data not tabulated). The ICIQ data were only shown graphically and fell from 13 scorepoints in all groups to post therapy value of approximately 2.0 in all groups.

In 2020, Erel et al from Istanbul looked for features that could predict success or failure of Er:YAG (251). After a mean of 2.11 sessions given to 82 women with either pure USI (42) or MUI (40), follow up occurred at a mean of 25 months. The ICIQ fell from a baseline of 13.6 (SD 4.55) down to 7.17, (SD 5.8). Cure rate was not given. Those with pure SUI had greater benefit than MUI (p =0.008). Premenopausal women had greater benefit than postmenopausal women (p=0.032), as did those with a normal BMI (versus those who were obese). Treatment benefit persisted up to 15 months.

5.5. Adverse Events

Most of the studies summarised so far in this section do not indicate any systematic effort to record adverse events.

As per a review from Robinson et al. (2020), a number of complications have been recorded on the MAUDE database from 2015 – 2019 (252). There were 45 separate events recorded, the most common being pain (vagina, bladder, urethral, or unspecified) and 11 patients reported burning or numbness. Some evidence of chronic adverse events was noted, such as long-term pain, numbness, burning, bladder disturbances, dyspareunia, worsening symptoms, aggravation of lichen sclerosis, scarring, and disfigurement.

In 2021, Molina et al from Spain published a case report of a 48 year old woman who developed a complete transverse vaginal septum after 2 ErYAG Laser therapies, with a pseudo-haematocolpos (8 cm diameter collection of blood in the vagina, above the septum) which required surgical division and prolonged vaginal dilatation to restore normal vaginal calibre (253).

5.6. Long term Results

In 2020, Kuszka et al from Germany (232) followed 59 women for a maximum of two years after 5 monthly treatments of ablative Er:YAG. All had urodynamic USI or stress-predominant MUI. Atrophic patients were given vaginal oestrogen. Outcome data were segregated as to whether patients had Stamey grade mild (32 women), moderate (16) or severe (11), resulting in small numbers for each subset. In the mild group, pad weight fell from 7 gm (IQR 6-8) down 2 gm (1-3) and on histogram, approximately 62% were cured (< 2 gm). In the moderate group, pad test fell from 15 gm (14-18) down to 8 gm (3-12). Leakage in the severe group was slightly reduced over 2years (35 gm to 28 gm). No statistical analysis of these changes was provided. This study provided the longest term follow up so far available, but the presentation of the data was disappointing.

This study was the subject of an editorial comment in European Urology by Braga et al (2020) from Switzerland, Greece and Italy (254).

"Although intravaginal laser therapy should strengthen the suburethral and pubocervical fibromuscularis along with their surrounding fascial supports (255), its use in female SUI is a controversial and debated topic. There is currently insufficient evidence to offer intravaginal laser therapy as an effective modality for the treatment of SUI. In fact, no studies comparing erbium: YAG or CO2 laser therapy for SUI treatment to pelvic-floor muscle training …. are available. The study by Kuszka et al (232) has merit in its investigation of subjective and objective outcomes of laser treatment in a 2-yr follow-up period, especially the focus on dose finding. However, data on the number and duration of treatment sessions and the maintenance regimen remain largely arbitrary (255). In addition, the follow-up duration varies considerably, with a mean follow-up period of 6 mo.

In 2018 the US Food and Drug Administration issued a warning against the use of energy-based devices (EBDs), including laser and radiofrequency devices (256). The alert also concerned the use of EBDs for treatment of urinary incontinence. To avoid a scenario similar to that for mesh vaginal surgery for genital prolapse, we urgently need randomised controlled studies to evaluate the safety and efficacy of EBD for treatment of SUI".

Similarly, an IUGA Committee on laser therapy for stress incontinence (and other conditions) published their detailed review (255) of the literature as follows:

Evidence from robustly conducted RCTs with long-term follow-up comparing laser with placebo or hormonal treatment are lacking. Similarly, well-designed case– control studies are required to further investigate potential benefits, harm, and efficacy of laser therapy for treating GSM, VL, and SUI symptoms. The therapeutic advantages of nonsurgical laser-based devices in urogynecology can only be recommended after robust clinical trials have demonstrated their long-term complication profile, safety, and efficacy" (255).

5.7. Conclusions

The mechanisms of action for Laser therapy remain open to question because none of the histopathology studies of its use in incontinence have employed stains for collagen, despite several claims that it stimulates de novo collagen synthesis. The outcome measures presented so far place a heavy emphasis upon improvement, but the "cure" rate is often not provided. Only one "sham" RCT study has been performed, yielding a 21% dry rate at 3 months (versus 4% in sham). Very few reports indicate in the Methods or Results that the authors have systematically elicited adverse events. These deficiencies indicate that Laser therapy has not yet reached the minimum standard required for general introduction of a new therapy.

Recommendation/ Future Research

At this time, laser therapy is not recommended for the treatment of female stress incontinence in the clinical setting.Studies that correct deficiencies regarding mechanism of action, long term cure rate, and adverse events are needed before Laser therapy can be recommended for use outside of Clinical Trials (Grade C).

6. ARTIFICIAL URINARY SPHINCTER FOR WOMEN

While artificial urinary sphincter (AUS) implantation has been used to treat female patients with stress incontinence due to intrinsic sphincter deficiency (ISD) and neuropathic incontinence for almost five decades (257), its adoption by urologists and urogynaecologists varies greatly internationally (258). While In France, it is recommended as the gold standard in women with SUI due to ISD (259), it's use is limited to selected, highly complex patients in the United Kingdom, Canada and most of Europe (260). Because of lack of FDA approval in the USA, it is rarely used there (261) and in Asia (262).

Initially, the AUS was performed as an open procedure. While several high-volume teams reported satisfactory outcomes with open AUS implantation (263-265), this remains a technically demanding procedure with up to 43.8% rate of intraoperative bladder neck injury, up to 25% rate of intraoperative vaginal injury, and explantation rates up to 45.3% after 84 months reported in smaller volume centres (265, 266). However, in large-volume centres, the results for the Open procedure are much more robust. For example, in 2011, Vayleux et al (263) followed 215 women over 22 years; the revision rate was 15% at median of 8.5 years, with a 7% explantation rate; 74% of patients were cured, using 0 – 1 pad per day. In 2014, Phe

et al (267) followed 34 women for 17 years (IQR 12-19 yrs), finding a 20% explantation rate at 15 years, with a social continence rate (0 or 1 pad per day) of 61%.

The largest long-term analysis was published by Costa et al. (264). Over a 20-year period, 376 devices were implanted in 344 women by open approach. At mean follow-up of 9.6 years, 86% of patients were fully continent. Interestingly, the two largest studies reported the lowest rates of intraoperative bladder neck and/or vaginal injury (263, 264). The post-operative complications rates varied widel, from 4.1% to 75% in open series (265). After mean follow-ups ranging from 28 to 204 months, the rates of explantation, extrusion/exposure and mechanical failures in open cohorts ranged from 0% to 45.3%, from 0% to 14.3% and from 0% to 44.1% respectively.

In the 6th Edition of the ICI text, several small reports of laparoscopic implantation of the AUS, and then early reports of robotic implantation, were provided. In this chapter, we provide longer term outcome data for large series of these new technical advances.

6.1. Surgical Principles of the Female AUS

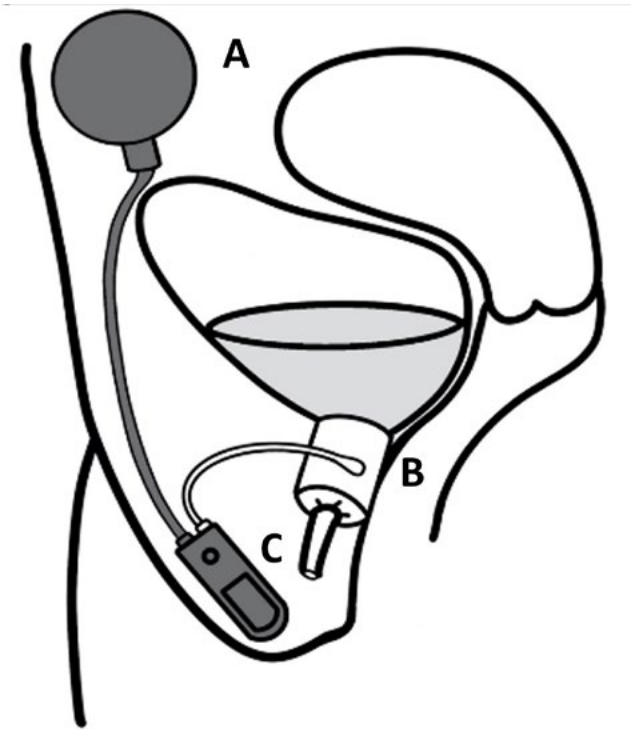

Figure 11: Artificial urinary sphincter for women. A. Pressure regulating balloon in the abdominal cavity. B. Cuff around the bladder neck. C. Pump in the labia majora. Figure thanks to B Peyronnet and C Richard, France.

In order to understand the difference between results for the open, laparoscopic and robotic procedures, a brief summary of surgical principles is needed. The artificial urinary sphincter (AUS) is a silicone device made of three main pieces: a cuff, a pressure regulating balloon (PRB) reservoir and a pump connected altogether with tubing (268). The whole system is filled with fluid**.** **Figure 11**. In females, the cuff is placed around the bladder neck; the pump is placed in the labium majus and the PRB in the abdominal cavity, either intraperitoneal or extraperitoneal (269)(See Figure 11). The rationale for bladder neck implantation is that the tissues are thicker at the bladder neck which may decrease the risk of device related complications (269). During storage of urine, the cuff is filled with fluid and exerts a predetermined pressure on the bladder neck wall circumferentially, which results in closure of the bladder neck and proximal urethra. Hence, the AUS corrects SUI/ ISD by increasing urethral resistance during storage. To void, the patient squeezes the pump located in the labium majus, which pumps the fluid away from the cuff to the reservoir, thus the bladder outlet opens. Therefore, in contrast to pubovaginal slings, the AUS theoretically increases outlet resistance during storage but maintains low outlet resistance during voiding (which has not been proven on urodynamic studies, however).

6.2. Indications

Although the use of AUS varies across the world, there is a global consensus that AUS is almost exclusively used in females with SUI predominantly due to ISD (258, 265, 269). As described in Chapter 4 (Pathophysiology of Incontinence), two main mechanisms may underpin SUI in women: urethral hypermobility and weak urethral closure pressure; those two features are a continuum. AUS serves best in female SUI where ISD is predominant. There is no universally accepted definition for ISD (270), but one relevant feature is the lack of urethral mobility, also described as a fixed urethra (259).

Thus, AUS is indicated in female SUI due to predominant ISD, i.e. with a positive cough stress test and poor urethral mobility with previous anti-incontinence procedures, severe SUI with low MUCP/VLPP. In daily practice, this represents mostly two patient groups: women with one or more failed SUI surgeries and patient with neurogenic ISD (mostly spina bifida, spinal cord injury and cauda equina syndrome), as per the literature (265). Salvage AUS in non-neurogenic patients account for the vast majority of female AUS patients (265). Because AUS may potentially cause less bladder outlet obstruction than other surgical options traditionally offered to these patients (271), it may be of particular interest in those with detrusor underactivity. The only formal contraindication to AUS in females is the inability to manipulate the pump, either due to abdominal obesity, lack of manual dexterity or cognitive dysfunction.

6.3. Surgical Approach

The technical challenge inherent to AUS implantation has likely been one of the main limitations to its widespread adoption. The main technical complexity lies in the placement of the cuff around the bladder neck owing to its location deep in the bony pelvis and the subtle dissection needed to find and follow the surgical plane between the bladder neck and the vaginal wall. This carries a high risk of intraoperative bladder neck or vaginal injury which might increase the risk of device infection/erosion postoperatively. The vaginal approach was largely used in the 1980s' but has been abandoned for more than three decades by most teams due to high rates of device infections/exposure (265).

With the rise of minimally invasive surgery in urology in the 2000s', a few surgical teams started to develop laparoscopic techniques for AUS implantation with the following rationale i) the pneumoperitoneum may decrease the bleeding from vaginal wall veins which often hamper proper vision during the bladder neck dissection ii) videoscopy may allow direct visualisation during the dissection of the posterior aspect of the bladder neck which was impossible with the open approach iii) The overall better vision may decrease the risk of bladder neck/vaginal injury and facilitate the early detection/ repair

of these injuries and improve the teaching/learning of the technique iv) the overall morbidity of the procedures and risk of device-related complications might be reduced (272, 273).

The first series by Mandron (n=25 patients) and Roupret (n=12 patients) reported promising outcomes with > 75% patients dry in both series, 0 and one intraoperative complication respectively and 0% and 8% of explantation/erosion after median follow-up of 12 and 26 months respectively (272, 273). These encouraging findings were recently confirmed by two larger series with longer follow-up. Schroeder et al analysed 49 patients at a median of 4 years, with 14.3% rate of explantations and 83.6% of patients being socially continent (0 to 1 pad per day) (274). Bracchitta et al reported on 74 patients (275) at a mean 44.5 months, in which 78.3% of patients were totally continent (no pad) The extrusion rate was 4%, the vaginal exposure rate was 2.7% and explantation rate was 10.8%.

On the grounds of these promising laparoscopic experiences, several teams started to use a robotic approach since the mid-2010s' (276-280). In the largest series published so far, Peyronnet et al reported 49 cases across five centres with 85.7% having an history of previous anti-incontinence surgery. At median of 18.5 months, 81.6% of patients were fully continent (explantation 2%) (279). An international multicentre experience of 123 patients implanted robotically in 14 institutions from four European countries was presented as an EUA/AUA abstract in 2020, confirming these findings with only four explantations for at median follow-up of 13 months (3.3%) (281).

Although most of the published robotic female AUS series used an "anterior" approach, mimicking what was done in the historical open technique [with an initial opening of the Retzius space to dissect the bladder neck "from above"], a handful of teams have recently reported an alternative "posterior" robotic technique with dissection of the bladder neck being carried out "from below". This involves an extensive dissection of the vesicovaginal space from the vaginal fornix to the posterior aspect of the bladder neck prior to reaching the anterior aspect on each side (280, 282, 283). The outcomes reported were broadly similar to those of the anterior technique although the higher rates of intraoperative urinary tract/vaginal injuries (29.6% and 50% in the Chartier-Kastler and Broudeur series respectively) may raise concerns and should prompt longer term data (280, 283).

6.4. Functional Outcomes: Overview

Since the last Chapter, a 2019 systematic review of the literature was conducted by a group of international experts upon invitation of the ICS (265). Of 886 records screened, 17 met the inclusion criteria. All were retrospective or prospective non-comparative series reporting mostly on open implantation (12/17). The vast majority of patients had undergone at least one anti-incontinence surgical procedure prior to AUS implantation (69.1-100%). The 61-70 cmH_2O pressure regulating balloon was the most commonly used, with the 51-60 cmH_2O and 71-80 cm H_2O being favoured in two and one open series respectively. The median cuff size ranged from 60 to 80 mm (265). After mean follow-up ranging from 5 to 204 months, the complete, social and improved continence rates ranged from 61.1% to 100%, from 71% to 100% and from 81.3% to 100% respectively (265). Seven series, all reporting on open AUS implantations, had a mean follow-up over 5 years (range: 72 to 204 months) (263, 264, 266, 267, 284-286). At the latest follow-up, 61.1% to 85.6% of patients reported being fully continent.

Since publication of this 2019 systematic review, aside from the robotic and laparoscopic female AUS series mentioned, two important studies have been published. Tricard et al analysed 63 women who underwent open AUS implantation up to 2007 (287). At median follow-up of 11.6years, 55.6% of patients remained completely dry, with 25.5% explantation rate. A study focusing on AUS in women aged > 75 years showed (median follow-up 36 months), 68.9% of the 45 patients were continent (288).

Overall, these results suggest that, when remaining in situ, AUS yields satisfactory functional outcomes in female SUI patients, comparable or better than what has been reported in male AUS series.

6.5. Level of Evidence/ Summary

As mentioned above, there is currently no high level of evidence studies published on female AUS (265). All data come from retrospective series or prospective database studies, which is a major barrier to widespread adoption of the AUS. High level of evidence studies are clearly needed to better determine the role of AUS in females. It should be noted that two prospective studies are underway: the SUACT trial (clinicaltrials.gov identifier: NCT02490917) a RCT comparing adjustable periurethral balloons to AUS in females with SUI due to ISD, and the VENUS study (clinicaltrials.gov identifier: NCT04114266), a prospective cohort study on female AUS involving 25 centres throughout Europe and conducted by the EAU Research Foundation. Their findings should shed light on female AUS.

Summary

No high-quality data are available regarding the use of AUS in women with SUI. (EL=3). AUS has been mostly used to treat women with SUI due to predominant ISD, i.e. patients with failed previous anti-incontinence procedures or neurogenic SUI. (EL=3)

In the existing literature, the functional outcomes reported were satisfactory with 61.1% to 85.6% of patients being dry in the long-term. (EL=3)

Safety concerns have been raised in some series with high perioperative complications and explantation rates which seem to be attributable to the technically challenging AUS implantation procedure. (EL=3)

Laparoscopic and robotic implantation techniques have recently been described with promising outcomes in terms of morbidity but with relatively short-term follow-up. (EL=3)

Recommendations

AUS is an option for some women with SUI due to ISD, i.e. with a poorly mobile urethra, most of whom failed previous SUI surgery and some neurogenic patients (Grade C), with implantation by surgeons with appropriate training and expertise.

Patients should be appropriately counseled regarding the likely need for revision over time and the lack of long term RCT data (Grade C).

Research: Longer term data regarding use of laparoscopic and robotic implantation techniques are needed, in relation to cure rates, complications, and explantation rate.

7. STEM CELL TECHNOLOGY AND BUCCAL MUCOSA GRAFTS TO THE URETHRA

Since the last edition of the ICI, there has been progress in the use of stem cell technology in the treatment of female SUI. Translational research in this novel field has evolved from non-primate animal pre-clinical studies to Level 1 clinical data in humans. The findings are summarised below along with historic background information.

7.1. Mechanism of Action

Stem cell therapy is a broad term encompassing both embryonic and adult cell types. Embryonic stem cells are totipotent, whereas adult stem cells are generally unique to the specific tissue they are derived from, with limited capacity for differentiation. Current clinical research in SUI focuses on adult stem cells and can be broadly categorised into the cell types they are derived from:

1. Muscle derived stem cell (MDSC),
2. Adipose derived stromal stem cell (ADSC),
3. Serum (i.e. platelets),
4. Bone marrow
5. Cord blood stem cells.

They all share mesenchymal stem cell (MSC) properties which allow differentiation into smooth muscle or neural cells, that are potentially therapeutic in SUI and ISD.

MDSC and ADSC remain the 2 most studied types of adult stem cells in both preclinical and clinical trials (290), owing to their ability to differentiate into smooth muscle cells in vitro (291) and abundant tissue source that can be easily harvest via muscle biopsy or liposuction with minimal morbidity (292). Sources of MDSC and ADSC in clinical studies are all autologous, which avoids issues of host reaction and rejection. In most studies, after muscle biopsy or liposuction, stem cells are treated by a process of expansion where progenitor cells are incubated and multiplied until appropriate volume of cells are obtained, frozen and later injected back into patients (293). Volume and sites of injection vary between periurethral, transurethral, intrasphincter or submucosal methods.

The mechanism of how stem cells improve continence is still not completely understood, but thought to result from regeneration of the rhabdosphincter and possible repair of neuropraxia (290). In vivo mouse studies show physiological improvements in the urethral sphincter resistance post injection of MSC with smooth muscle incorporating into the sphincter on later biopsy (294). Injections of MSC have also led to enhanced neuromuscular recovery of the pudendal nerve, thus supporting the neuropraxia hypothesis (295). In the porcine model, where urethral histology resembles humans closely, injection of stromal vascular fraction (a type of ADSC) into recently damaged urethra was associated with reduction of urethral injury at day 30 and increased maximum urethral pressure compared to controls without ADSC (296).

In human studies, urethral biopsies are unable to be performed, thus it is unclear whether clinical improvements arise from tissue incorporation of stem cells and increased sphincter function, the bulking effect of cells injected, or a combination of these effects.

7.2. Clinical Trials

Historical aspects of how stem cell evolved from animal studies to early small human studies were discussed in the previous ICI -6 and will not be reiterated here. Of relevance, one systematic review of cohort studies (292) and two double blinded placebo controlled RCTS have examined the efficacy of stem cells in the treatment of female SUI since the last ICI review (297, 298).

The systematic review found 16 small non-randomised studies of varying cohort sizes (n=11-123) with MDSC as the most common cell type used. Cure rates ranged from 11-90% at 12 months follow up, but surprisingly, worsening of incontinence was reported in 8.5% of patients (292). A meta-analysis was unable to be performed due to the high variability in methodology, unclear in- vivo culture technique and cell volume injected and variable concurrent use of collagen bulking agent at the same time.

To date there is only one published placebo controlled RCT of autologous MDSC in women with SUI with 2 year follow up. The study utilised outpatient thigh muscle biopsy and 13 weeks of laboratory culture to produce 150x106 MDSC (containing 84% myocytes and 16% fibroblast) suspended in 2ml patented cryopreservation solution and 2ml normal saline. The solution was injected into the midurethra and intra-sphincter in a circumferential pattern with low side effect profile. Choice of dose was based on a dose finding study of 80 women (293), where higher stem cell volumes injected (200x106) was associated with statistically significant reduction in pad test.

The primary composite outcome of this RCT was a >50% reduction in leakage severity on 24hour pad test at 12 months. Unfortunately, the trial was stopped at 61% recruitment (n=150) due to a high placebo response. Post hoc analysis found this composite outcome to be too liberal, and suggested subsequent studies use >75% reduction stress leak episodes as a primary outcome to reduce placebo effect. While not reaching statistical significance, in the subgroup of patients with recurrent SUI and prior continence surgery, complete continence rate (36.4% vs 16.7%) and >75% improvement in SUI episodes (63.6% vs 16.7%) were higher in the stem cell group compared to controls. This pattern was not seen in the subgroup without prior continence surgery (297).

Very recently, the same group presented preliminary data of another Phase III multicentre RCT of 297 women injected with autologous MDSC (2:1 Stem cell to placebo ratio) with 12month follow up. A high placebo effect was seen again in the control group, when using >50% reduction in leakage as the outcome measure (298). However, patients with severe incontinence (stratified as >10 leaks/ 3 days at baseline) saw a 2-fold increase in complete continence rate compared to placebo (20% vs 11%).

In a subgroup analysis of the same RCT, 75 women with severe recurrent SUI defined as >10 leaks/ 3 day with a history of previous continence surgery, revealed more promising results (299). Using >75% reduction of stress leak episodes as the outcome measure, the stem cell group showed a statistically significant reduction in leakage (40% vs 16%, p=0.037) and significant improvements in QoL (p<0.002) compared to controls. The dry rate was not reported. This and the findings of the previous RCT support the notion that MDSC may have significant therapeutic benefit in ISD and recurrent SUI. This is in line with the proposed stem cell mechanism of action in repair of urethral sphincter damage. Based on the above evidence, Cook Medical ® has obtained the USA Regenerative Medicine Advanced Therapy designation in Dec 2020.

Despite the novel findings discussed above, there is still a lack of long-term outcome data beyond 2 years. Given the relative short-term effect of traditional bulking agents, long term data will help to determine the true efficacy of MDSC.

Summary

The scientific basis of stem cell use for SUI has evolved in the last 5 years with new evidence supporting autologous muscle derived stem cells for treatment of female SUI. However, direct comparisons between stem cell types are lacking and there is currently no consensus on the optimal cell type, location to inject, volume/ concentration of cells, or ideal target population. Long term outcome is also lacking. These areas remain a focus for future studies.

Recommendation/ Research

The use of stem cell technology for treatment of female SUI remains investigational with promising results. Such therapy should only be offered in the setting of clinical trials (Grade D).

7.3. Buccal Mucosa Reconstruction of the Urethra

Urethral extrusion of synthetic midurethral sling can result in devastating complications (300). Removal of the synthetic material is the option of choice in the vast majority of these patients. Immediate reconstruction usually involves direct suturing of the native urethra. However, if the urethral defect is large, direct suturing may involve high risk of urethral stricture. In these situations, the use of autologous tissue may be necessary (300-302). Mainly two types of autologous materials can be used in these situations: local vaginal flap and buccal mucosa graft (303). They are mostly used as onlay and can be either placed on the dorsal or ventral aspect of the urethra (301, 302). Both of these tissues can also be used to repair post- sling excision urethral stricture or urethrovaginal fistula (in case of large urethral defect and along with Martius flap in most instances) (301-303).

Harvesting the buccal mucosa graft entails excising a triangular portion of the mucosa from the inside of the oral cavity on the inner aspect of the cheek, approximately 4 cm x 3 cm. Care must be taken to avoid nerve fibres located under the mucosa, with meticulous haemostasis. The graft is laid down flat, then perforated and stretched gently. While dissecting the peri-urethral tissue, the graft is stored in a moist saline soaked solution (as for the rectus fascia graft harvested for pubovaginal slings). Once the sub-urethral dissection is completed with meticulous haemostasis, the graft is laid under the urethra and tacked into place with 4.0 absorbable sutures. A vaginal pack is kept in position for 24 hours, as haematoma formation is highly undesirable. Prophylactic antibiotics and urinary catheterization are needed for at least 48 hours. Currently available publications (301-303) do not describe long term objective outcomes.

Recommendation

Harvesting of buccal mucosal grafts requires specialised training at a supra-regional centre. The concept of harvesting autologous mucosa to lay under the damaged urethra appears biologically attractive and warrants formal long term series of patients with objective outcome measures. (Grade D)

II. SURGERY FOR NON-NEUROGENIC UUI

1. SACRAL NEUROSTIMULATION (SNS)

1.1. SNS – Technical Considerations

SNS was developed in the early 1980s by Tanagho and Schmidt (304). They showed that continuous stimulation of the sacral root S3 with an electrode connected to an implanted pulse generator could modulate detrusor and sphincter activity (305). Initially, the therapy involved an invasive surgical procedure with a large incision over the sacrum to anchor the lead. Continual improvements in SNS have been introduced and it is now a minimally invasive technique. InterStim® Therapy (Medtronic, Minneapolis, MN, USA) was the first technology licensed by regulatory agencies worldwide for the treatment of urge incontinence (UI) (the subject of this section). The introduction of the percutaneous tined lead (306) has made this procedure easier, improved patient comfort and enabled a longer testing period with less lead migration improving the success rate of the test phase.

The original InterStim™ system had a large implantable pulse generator (IPG) with a battery life of approximately 5-8 years, which was later replaced by the smaller, InterStim™ II SNM system, with a battery life of approximately 4-5 years (see figure 12).

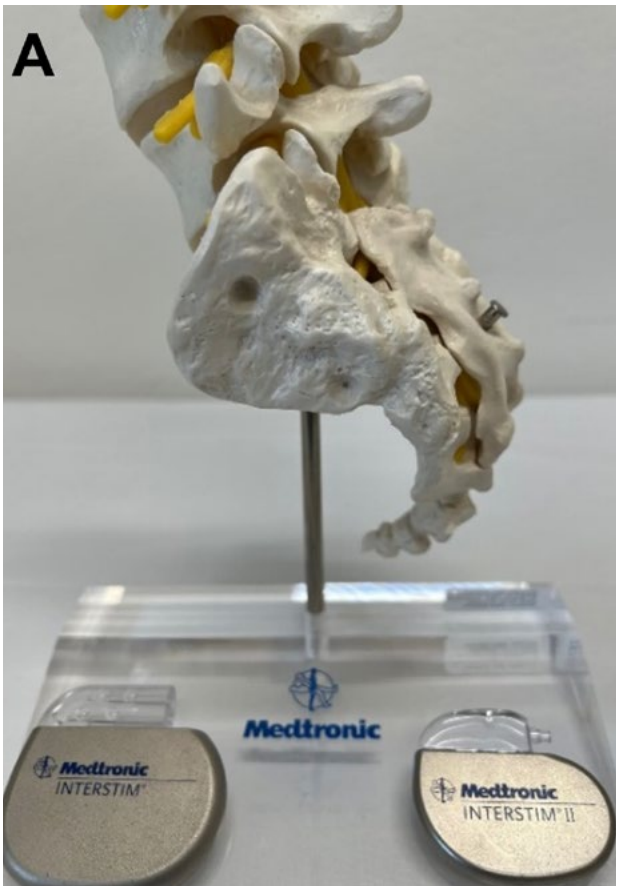

Figure 12: Original and later version of Interstim IPG (courtesy K H. Moore)

More recently, a rechargeable system (InterStim™ Micro system) with new leads that are MRI compatible (InterStim SureScan MRI leads) was developed, allowing full-body 1.5 and 3 Tesla MRI-conditional scans. The new InterStim™ Micro system is a current-controlled system, while the InterStim™ II SNM system is voltage controlled.
Axonics Modulation Technologies, Inc. (Irvine, CA) is a new manufacturer of SNS that has been introduced in Europe and USA. Their new devices (Axonics r-SNM System) are rechargeable and conditional magnetic resonance imaging (MRI)-safe. The Axonics r-SNM System is a current-controlled system, adjusting the voltage automatically to maintain continuous and stable stimulation of the nerve. The implantation technique for both technologies is very similar. An electrode is implanted in the S3 foramen and connected to an implantable pulse generator (IPG). The sequential technique to place a SNM system has been refined (306) and recently well described (308). It involves passing the electrode into the upper medial aspect of the S3 sacral foramen, utilising the ideal curve of the electrodes to place them adjacent to the nerve and allowing low thresholds on all four electrodes, with placement confirmed by fluoroscopic images.

Usually, a test phase determines whether SNS has provided at least a 50% benefit on 2 week bladder diary before implanting the IPG in the upper buttock. The test phase may be performed in two ways: by peripheral nerve evaluation (PNE) using a monopolar short-term electrode which is always removed after the test period and is not designed for long term therapy, or by staged implantation of a permanent, quadripolar tined-lead electrode which is designed for potential long-term use after a successful test period (309). Because PNE may underestimate treatment effect and result in significant false-negative rates, many surgeons utilise the staged implantation of a tined-lead for the first stage (309-312). Although the PNE approach is less invasive, less costly and may be performed in the office setting, there may be problems with lead migration. The conversion rates to IPG implantation in OAB patients are inferior to those with the staged implant (309). More recently, single stage implantation without a test phase has been suggested to improve the patients' experience and reduce complications such as lead infection (313, 314).

1.2. Mechanism of Action

The mechanism of action of SNS is not completely understood. The therapeutic benefits of SNS may arise from the effects of electrical stimulation on afferent and efferent nerve fibers connecting the pelvic viscera and the spinal interneurons to the central nervous system. Little evidence exists demonstrating permanent remodeling, re-innervation or alteration of pathways in the central and/or peripheral nervous systems in humans. SNS seems to predominantly influence sacral afferents and modulate spinal cord reflexes and brain centres involved in lower urinary tract function (315-317). Using functional MRI or positron emission tomography, recent studies have shown that SNS affects activity in supraspinal centres involved in the control of detrusor contraction, bladder filling and micturition timing (318-320).

The impact of SNS on brain activity depends on the level of stimulation. Using functional MRI, Gill et al showed that subsensory stimulation deactivates the pons and periaqueductal grey matter, while sensory stimulation deactivates the parietal lobes but activates the insula. Suprasensory stimulation led to widespread activation, including an increase in activity in the somatosensory region (319). Thus, brain responses to SNM vary with stimulation intensity. In addition, Wenzler et al evaluated the effect of SNM on afferent sensory nerve pathways by recording bladder current perception thresholds (CPTs) and found higher CPT values after SNM therapy, providing further evidence that SNM impacts the sensory function of the bladder (321). These data provide evidence that afferents play a key role in modulating spinal reflexes and brain centres. The fact that neuromodulation techniques with stimulation at different sites in the body (transcutaneous spinal stimulation, transcutaneous/ percutaneous tibial nerve stimulation, and pudendal nerve stimulation) may provide similar effects to SNS is also regarded as evidence for the importance of bladder afferents in SNS (317).

1.3. Efficacy and Safety

The introduction of new technologies and the use of the optimal lead placement technique have impacted on the results of SNS. In this section we mostly discuss studies reporting on SNS technology that is still available in clinical practice.

1.3.1. SNS vs No Therapy

See previous ICI-6 Chapter.

1.3.2. SNS vs Medical Therapy

The InSite trial was a two-phase study including a prospective, multi-centre, RCT comparing Interstim SNS with to standard medical therapy (SMT) eg anticholinergic medication, for patients with refractory **mild to moderate** symptoms of OAB, including urge incontinence (UI) and/or urgency-frequency (UF), within a six-month follow-up period (311). The primary hypothesis of the RCT portion of the study was that SNS is superior to anticholinergic drugs in OAB patients for whom at least one medication had been tried, but other pharmacologic agents were still available. The second phase was a prospective long-term evaluation of the safety/ efficacy of SNS. This was an FDA requirement to evaluate the cumulative five-year rate of AEs including need for surgery, rates of infection and lead migration as well as success/ QOL. See results for one (322), three (323), and five (324) years of follow-up:primary outcome measure for the RCT phase (on voiding diaries at 6-months (311)) was ≥ 50% improvement in average leaks/day or voids/day from baseline, or a return to normal voiding frequency (<8 voids/day). QOL, impact on sexual function and depressive symptoms between groups using the ICI Modular Questionnaire (ICIQ)-OABqol, the ICIQ—Male/ Female Lower Urinary Tract Symptoms-Sex, and the Beck Depression Inventory II were also compared.

Overall, 147 subjects were randomised (70 to SNS and 77 to SMT); 93% were female, mean age 58. Subjects randomised to SNS underwent a staged procedure using InterStim with a 14-day test stimulation period. Of these 70 SNS subjects, 59 underwent test stimulation and 51/59 (86%) received a full implant. The primary ITT analysis showed OAB success was significantly greater in the SNS group (61%) than in the anticholinergic drugs group (42%; P=0.02). Complete continence was almost doubled in the SNS group (39% vs 21% in SMT; P=0.06). Significant improvements in QOL (all P<0.001), sexual function and depression were both superior to SMT. Device-related AE rate was 30.5%; the medication-related AE rate was 27.3% (none serious). The most common SNS device-related AE's were undesirable change in stimulation in 10.2%, implant site pain 8.5%, lead migration/ dislodgment 3.4% , and implant site infection 3.4% . For the 51 SNS full implant subjects, the 6-month post-op surgical intervention rate was 3.9%. The most common OAB medication-AE were constipation in 9.1%, drug toxicity in 6.5% and dry mouth in 5.2%. (Level of evidence 1)

1.3.3. SNS vs OnabotulinumtoxinA (BTX-A)

SNS and BTX-A injection are approved third line therapeutic options for the treatment of refractory OAB (12, 325). SNS is more invasive but has the potential to offer long-term efficacy whereas treatment with BTX-A injections is less invasive but needs to be repeated on a regular basis to provide sustained efficacy. Each treatment modality has its own range of possible AEs. The only head-to-head study comparing the efficacy and safety of the two therapies for OAB is the ROSETTA Trial (Refractory OAB: Sacral Neuromodulation vs Botulinum Toxin Assessment). It was a multicentre, open-label, RCT comparing SNS with Interstim versus intradetrusor injection of 200 U BTX-A in women with refractory OAB (312). Of 386 women randomised, 369 were treated; 364 were available for primary outcome analyses (mean age 63 years). More than 80% of both groups rated themselves as severely or very severely incontinent. In the SNS group, women underwent a two-stage procedure. The rate of clinical response — defined as a reduction of at least 50% in urge leaks on 3-day bladder diary — was similar in the BTX and SNS groups (83% vs 84%), measured at 1 month in the Botox group and during the test phase in the neurostimulation group.

In both the ITT and clinical responders outcome analyses, the BTX-A group had significantly greater mean reduction in daily urge leaks compared to the SNS group (−3.9 vs −3.3 leaks/ day; mean difference, 0.63; 95% CI, 0.13 to 1.14; P =0.01). More patients in the injection group than in the SNS group had complete symptom resolution at 6 months (20% vs 4%; P<0.0001) and a reduction of at least 75% in leaks/day (46% vs 26%; P=0.0002). OABQ scores were significantly improved in both groups but change from baseline was greater in the injection group than in the SNS group (–46.71 vs –38.5; P =0.002). Treatment satisfaction was better in the Botox group than in the SNS group (P=0.01).

At two-years [data available for 260/298 (87%)] (326), there were 72% (115/159) of the BTX-A participants requesting a second injection [median interval 350 days, IQR 242–465] and 48% (55/115) requested a third injection. Median interval between second and third injections was 273 days [IQR = 224–350]. No difference in the reduction of UUI episodes was found between groups over 24 months (-3.88 vs -3.50 episodes/d, [95%CI] =-0.14-0.89; p=0.15]. UUI resolution was similar in both groups. Satisfaction with treatment was higher among women from the BTX-A group, with no difference in QOL.

The UTI rate was higher in the Botox A group versus SNS group at 6 months (35% vs 11%; P<0.0001). In the Botox group, intermittent catheterization (CISC) was needed by 8% of patients at 1 month, 4% at 3 months, and 2% at 6 months. In the SNS group, 3% required surgical revision or removal. At two-years, recurrent UTIs were higher after BTX-A (24% vs 10%; p<0.01). After the second BTX-A injection, 6% needed CISC, with median CISC duration of 29 days [IQR = 17–56]. After the third injection, CISC rate was 2%. Of the 189 Botox participants, 45 (24%) required CISC at any point over two years. In the SNM group, 58% (81/139) required reprogramming, with 17% (14/81) requiring ≥3 reprogrammings (most commonly for decreased efficacy). SNM revision and removals occurred in 3% and 8.6% respectively. Reasons for removal included infection, decreased efficacy, subject's desire and pain.

The authors concluded that both treatments offered sustainable UUI improvement. Women in the BTX-A group had higher satisfaction but with a higher chance of UTI. (Level of evidence 1)

1.4. Long Term Results

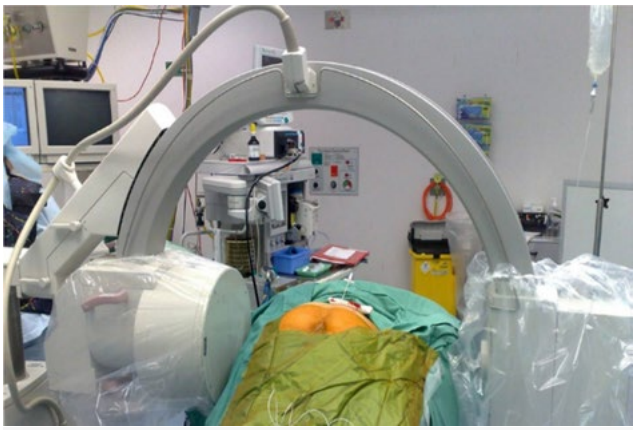

Figure 13: Intraoperative setup for SNS. Courtesy St George Hospital, Sydney

The introduction of new technologies and the use of the optimal lead placement technique have favourably impacted the results of SNS. Groen et al (2011) evaluated the long-term 5 year results of SNS in 60 patients with refractory UI (327). The success rate gradually decreased from 87% at 1 month to 62% at 5 years. Complete continence persisted in 15%. There were 41 patients at the 10-year follow-up; 61% of these were still on active SNS. The 10-year success rates were not different from the 5-year results, suggesting that a deterioration of the results is observed during the first 5 years. A total of 57 AEs occurred in 32 (53%) patients, the majority related to hardware failure and pain or discomfort at various sites. A total of 23 reoperations, including two explantations, were done in 15 patients (25%).

Other long-term studies (discussed in ICI-6) evaluated results of SNS for OAB patients. At 5 years post-surgery, >50% improvement was seen in 68% of those with UI and 56% of those with UF (328-330).

The InSite study was a multicentre prospective trial that evaluated efficacy and safety of SNS with InterStim™ therapy for OAB patients. In ICI-6, results were presented for one (322), three (323) years; five-year (324) follow-up has just been reported. A total of 340 subjects underwent test stimulation, 272 were implanted (91% female, mean age 57 years). Patients with incontinence had an average of 3.1 leaks/day. The success rate was 85% at 1 year and 82% at 5 years. A mean reduction of 2.2 leaks/day was observed after one year, 2.3 leaks/day after three years and 2.0 leaks/day after five years. At five years, subjects with urgency-frequency had a mean reduction of 5.4 voids per day. Sustained QOL improvements were reported from baseline to 5 years in all ICIQ-OABqol domains along with sustained improvements in female sexual function and pelvic pain measures.

At five years, the cumulative rate of AEs related to the tined lead that required surgery after full system implantation was 22.4%. An undesirable change in stimulation was the most common AE, which occurred in (22%), followed by implant site pain in (15%) and product ineffectiveness in (13%). Surgical intervention was performed (30.9%) due to an AE and (33.5%) underwent a surgical intervention due to battery replacement. In total, 19.1% (52/272) of subjects underwent device explantation. The main reason for explant was AE (11%) or lack / loss of efficacy (8.5%). (Level of evidence 2)

The SOUNDS study is a large-scale prospective, multicentre observational study that captured real-world results of SNS, demanded by the French health authority. Results for 12 (331) and 36 (332) months have been reported, but 5 year data collection is ongoing. The study enrolled 291 patients with OAB of which 169 (62%) received a de novo InterStim system, 60 (22%) received a replacement and 45 (16%) patients were tested but did not receive a permanent implant (17 patients were screening failures). For 169 patients receiving a de novo SNS implant, the voids/ day decreased from 12.6 at baseline to 9.1 for the OAB dry subgroup. The leaks/ day decreased from 4.4 at baseline to 1.7 for OAB wet, at 34 months. "Response" was defined as ≥ 50% reduction in leaks/ day for OAB wet, and ≥ 50% reduction in voids per day or <8 voids per day for OAB dry. Response rates at 34 months were 72% in OAB wet and 33% in OAB dry. Complete continence was achieved in 30% of the OAB wet patients.

Device-related AEs rate was 49% (134/274). The most common AEs were implant site pain (6%), implant site infection (4%), battery-related events (5%), device use error (5%), and device failure (7%). Overall, 12% of patients (34/274) experienced a serious AE. Most were managed by lead removal (11%), neurostimulator removal (8%), reprogramming (7%), or antibiotics (6%) or analgesics (4%). Surgical revisions, including replacement, repositioning, or removal of components occurred in 33% of patients who had received a full implant (permanent device removal in 13%.)

There are no studies with long-term data on SNS using the Axonics r-SNM SystemTM but two studies presented two-year outcomes (307, 333). The Artisan-SNM study was a prospective, multicentre, study performed to gain FDA approval. Results for 6 (334), 12 (335) and 24 months (307) have been reported. The study enrolled 129 participants (mean age 59.3 years) with urge incontinence (UUI) who had implantation of the rechargeable Axonics System in a single, nonstaged procedure. At 2 years, 93% were responders (≥ 50% reduction in Urge leaks/ day); 37% were dry. Daily UUI episodes reduced from 5.6 ± 0.3 at baseline to 1.0 ± 0.2. Improvements in ICIQ-OABqol were significant. All subjects were able to recharge their device; 94% reported that recharging frequency and duration were acceptable.

Device-related AEs occurred in 20 (16%) patients and procedure-related AEs occurred in 15 (12%) patients. Uncomfortable change in stimulation was the most frequent AE (9%), usually managed with device reprogramming. Surgical interventions (n=14) were performed in 9%, including lead revision in 2%, neurostimulator revision in 3% and device explantation in 4% (because of infection at INS site, pain and insufficient therapy effectiveness).

The RELAX-OAB study was a postmarket, prospective, multi-centre study in Europe designed to test safety and efficacy of the Axonics system for two years. Data for three months (336), 12 months (314) and 24 months (333) results have been reported, for the 51 participants (mean age 51 years; 75% women) with OAB. At 2 years, 76% (28/37) of the subjects were responders (≥ 50% reduction in urge leaks/day and/or ≥ 50% reduction in voids per day or <8 voids per day). Daily UI episodes reduced from 9.3 ± 0.8 at baseline to 3.6 ± 1.1 at 2 years, with significant improvement in QoL. Device-related AEs occurred in 26% patients (most commonly uncomfortable stimulation 20%), all managed with device reprogramming. Device explantation was needed in 14% [most commonly for insufficient effectiveness].

1.5. Testing Procedure: PNE vs Staged Tined Lead vs Single Stage Implant

As described in Section 6.1, the test phase of SNS may be performed by PNE using a temporary monopolar electrode, or by staged implantation of a permanent, quadripolar tined-lead electrode. More recently, single stage implantation without a test phase has been suggested to improve patients' experience and reduce complications (313, 314). The PNE approach is less invasive, less costly and can be done in the office, but there may be problems with lead migration. The conversion rates to IPG implantation after PNE are inferior to those with the staged implant (309).

In a retrospective study of 92 patients screened for SNS, 35/76 patients (46%) who underwent PNE met the criteria for permanent implantation, compared with 11/16 (69%) patients who underwent screening with the tined lead (337). Of the 41 patients who failed PNE and then had screening with tined lead, 18 (44%) had a successful response and were implanted with SNS. Bannowski et al (2008) examined urodynamic and clinical outcomes of the two different testing techniques. Permanent quadripolar electrodes led to significant benefit in the overall response rate (81.8% versus 47.6%) and urodynamic parameters (max detrusor pressure, bladder capacity) compared to PNE (338).

A prospective single centre study compared the response rate to PNE to that of the stage tined-lead placement test (FSTLP). Of 100 patients with refractory idiopathic OAB or non-obstructive UR, who were screened with both PNE and FSTLP, positive response rate PNE was 47%, versus FSTLP 69% ($P<0.001$). Because of the increased sensitivity of the staged tined-lead placement test for identifying good responders, the most recent prospective studies involving SNS have used this method for the test phase (311, 312, 324, 332). (LE=2)

Single stage implantation without a test phase has been suggested to improve patients' experience, reduce complications and decrease costs of anesthesia and hospitalisation. Lee et al ((2020) found that of 15 consecutive patients who underwent single stage SNM implant with InterStim™ II system, 14 (93.3%) had a ≥50% improvement. The authors calculated total cost savings of $85,366 due to a reduction of 233 minutes in operative time (313). Future studies comparing 1-stage vs 2-stage SNS procedures are awaited.

1.6. Unilateral vs Bilateral SNS

Standard SNS is based on unilateral lead implantation. **Figure 13**. However, there is experimental evidence that bilateral stimulation of the sacral nerves could improve SNS results (339-341). The exact mechanism is still not fully understood, and bilateral SNS remains controversial, see further discussion in ICI-6. A retrospective study of 124 subjects by Pham et al (340) compared unilateral lead technique (55 patients, 44%) to bilateral lead placement. Success occurred in 58% and 76% respectively ($P=0.03$) with no difference in wound infection/ other AEs.

In a prospective randomised crossover trial, Scheepens et al investigated 33 patients who underwent unilateral or bilateral implantation of a temporary test lead (339); 8 were excluded due to lead migration. Of 25 patients analysed, a significant/ comparable response was seen during test stimulation for both methods. The authors concluded that bilateral is in general not superior to unilateral SNS but a few cases may have improved results with bilateral SNS.

A recent multicentric, parallel, randomised, open pilot trial was conducted to compare treatment success rate [improvement of OAB

symptoms] between unilateral and bilateral SNS testing (342). Patients were randomised (bilateral n = 28) or unilateral (n = 27) (342). The primary outcome was the rate of patients with least 50% of clinical improvement at 1 month. The rate of patients presenting at least one significant clinical improvement at month 1 was 62% in the bilateral group, versus 84% in the unilateral group. More complications were seen in the bilateral versus unilateral groups (9 [47%] vs 4 [16%]).

1.7. SNS and Different Programming Parameters

The success of SNS for the treatment of bladder and/or bowel disorders depends not only on the placement of the electrode lead but also on the programming of the neurostimulator. Optimised lead placement focusses on placing the lead along the nerve, allowing more programming options and reducing the need for reprogramming and for changes in the stimulation amplitude. The main programming parameters of SNS are the electrode configuration (selection of the anode and cathode), stimulation amplitude, pulse frequency, and pulse width (the duration of each electrical pulse). In addition, SNS may be continuous or intermittent.

Electrode Configuration: The electrode configuration with the best sensory response at the lowest amplitude is typically chosen. It is usually assumed that the best sensation site is a midline perineal, genital or anal sensation, while leg, buttock, or back sensations constitute a poor response (343). The electrode configuration may be monopolar (when IPG is used as the anode [+]) or bipolar (two contact points used) with no evidence in favour of either one (343). With four electrodes as possible contact points for the cathode, various programs can be used for SNS.

Stimulation amplitude: Optimal lead placement allows for lower amplitude stimulation and lower energy consumption (308, 344). The InterStim™ II IPG works on a constant voltage basis. The Axonics r-SNM System and the InterStim™ Micro system are current-controlled system, adjusting the voltage automatically to maintain continuous and stable stimulation of the nerve. If the impedance is stable, both systems deliver the same amount of energy to the sacral nerve. There is no evidence that one stimulation modality is clinically superior to the other (345, 346).

Pulse frequency: Pulse frequency is typically set at 14 Hz for most urological patients. Beneficial variations of programming have been discussed in ICI-6. It has been shown that frequency changes may have an impact on symptom control. Marcelissen et al evaluated the effect of four different pulse rates in patients with suboptimal response to SNS (347). Although they were not able to show the superiority of any of the different pulse rates tested, they showed that 76% of the patients had an improvement in symptoms by changing the pulse rate. (343, 347).

Pulse width: The standard pulse width is 210 µs (348). When the pulse width is increased, the current or voltage required to stimulate a neural tissue decreases (332).

Continuous vs intermittent SNS: It has been proposed that intermittent SNS could be beneficial for the long-term efficacy and for battery life. A prospective, randomised, multicentre, single-blind, 4 x 4 crossover study was conducted in 2018 by Siegel et al. to see the effect of 4 cycling settings (continuous, 16 seconds on/8 seconds off, 10 minutes on/ 10 minutes off, and 30 minutes on/23.5 hours off) on efficacy, quality of life, and safety (349). Results showed no significant cycling or period effect on UI. There was a statistically significant interaction between cycling and period (P = 0.0032).

Programming parameters in recent prospective studies: In the Insite study (324) with the InterStim™ II system, based on the 140 subjects who reached the 5-year visit and had programming data available: 60.7% were programmed to an amplitude of less than 2 V. In most subjects the pulse width was 210 µs, in 63.6% the stimulation frequency was programmed to 14 Hz and 67.9% were on continuous stimulation. In the RELAX-OAB study (333), based on 39 subjects who reached 2-year visit and had programming data available, the stimulation frequency was programmed to 14 Hz in 82% and the pulse width was 210 µs in 90% of subjects. All participants were on bipolar electrode configurations and all were on were on continuous stimulation.

The circumstances in which reprogramming is necessary have recently been described by Dudding et al. in a systematic review regarding all of the above parameters (343). A recent systematic review evaluated the clinical efficacy of nonconventional stimulation parameters (350). They concluded that altering stimulation parameters may improve efficacy of SNM in implementation of short cycling intervals. (Level of evidence 2)

1.8. Predictors of Outcomes

Most studies investigating predictors of success for SNS in OAB patients are retrospective. Parameters such age, severity of incontinence, obesity, prior medication use, previous spinal surgery, urodynamic findings etc. been analysed.

Yazdany et al (2011) showed that patients with >10 incontinence episodes per day were more likely to have a successful stage I trial compared to those with less than 5 episodes/day (351). Levin et al (2012) reported on the impact of obesity (352). In 149 patients, 80 (53.7%) were obese (BMI mean 37.3): success rates for non-obese patients (83%) was comparable to obese patients (78%).

Peters et al (2015) evaluated the impact of age (353). In a prospective study of 266 patients the rate of IPG implant (89-90%) and explant (9.3-13%) did not vary between different age groups (<40 years, 40-64 and >/=65) but there was a tendency for higher complication rates in younger patients (23% vs. 15% vs. 8.5%, respectively; P=0.08). Angioli et al (2016) reported results of SNS in older patients, mean age 76 years (354). At 12 months, 55.5% of patients reported complete cessation of UUI episodes. Overall, UUI episodes decreased from 6.3/day to 0.5/day

The predictive role of urodynamics was reported by Groenendijk et al (2008) in 111 patients who had permanent SNS after successful PNE: 67 had, and 44 did not have, DO on urodynamics (355). Both groups improved bladder volume at first sensation and at maximum capacity. Resolution of DO occurred in 51% overall., However success in resolved-DO patients was not significantly different from those with persistent DO. Interestingly, patients with UUI and no DO tended to have a higher rate of success (73%) than those with UI and DO (61%) (not statisticaly significant). South et al (2007) had similar results (356). Recently, in 99 patients with idiopathic refractory DO, Nobrega et al (2018) investigated whether urodynamics predicted success of first stage tined lead placement (357). Urodynamic parameters were mean voided volume, peak detrusor overactivity pressure, bladder compliance, capacity, and volume at first detrusor overactivity. None of these parameters was associated with outcome.

Recently Morgan et al (2021) reviewed medical records of 198 women having SNS from 2007 to 2018 for OAB, with or without non-obstructive urinary retention (UR), and fecal incontinence

(FI) (358). At median follow-up of 4.4 years (range= 3.3-14.0 yrs) "success" was entirely subjective. They found that age > 65 years (OR=0.2, 95% CI=0.06-0.8) and prior onaBoNT-A (OR=0.2, 95% CI=0.06-0.9) were negative predictors for completion of stage II implant. Also, prior pelvic floor physical therapy was a significant negative predictor of post-operative success (OR=0.25 95% CI=0.1-0.6) the rationale for this was not explained. There was no correlation between intra-operative motor responses (with either all 4 or <4 electrodes) and device success (358).

High et al (2021) conducted the largest multicentre retrospective study of women with OAB, to evaluate if age and comorbidities were associated with implantation of a SNS device and with long-term therapy outcomes (359). Of 864 patients, 785 (91%) had implantation, which was more likely in younger (62 yrs) than older (67 years) women [OR 0.73]. At a median of 2 yrs (range 0.3 to 15 yrs), success (eg no need for additional therapies) was achieved by 69%. Multiple comorbidities such as cardiovascular disease, chronic pain (narcotics use), diabetes and neurological disorders did not correlate with implantation rates or success. Having past vertebral or disc surgeries or cognitive impairment also did not affect success, but sample sizes were low for this analysis. After SNS, 31% of women had additional therapy, more common in older women. Of the 142 women followed for 5 years, 25% had explantation.

Pizarro-Berdichevsky et al (2018) investigated whether motor responses during intraoperative electrode testing were associated with durability of SNS therapy (360). They retrospectively reviewed 176 lead placements at a single centre, and quantified motor responses into separate subscores, including bellows and toe response subscores (each range 0 to 4), possible maximum score of 8. Primary outcome was the need for revision surgery. Median follow-up was 10.5 months (range 2 - 36 m). Lead revision was performed in 34 (19%) patients. Revision was negatively associated with the total electrode response score (p = 0.027) and the toe subscore (p = 0.033) but not with the bellows subscore (p = 0.183). On logistic regression, patients younger than 59 years and those with a total electrode response score less than 4 were more likely to undergo revision (OR 5.5, 95% CI 2-14 and 4.2, 95% CI 1.4-12.8, respectively).

A systematic review of 78 studies, Jairam et al (2021), investigated factors that could predict the outcomes of SNS (361). In four out of 10 studies, women had a higher chance of success, but in 5 studies, gender was not predictive. Several studies reported younger age as a predictive factor of SNS success. Many factors did not influence SNS outcomes: history of prior back surgery, surgery for stress incontinence, presence of affective symptoms and duration of complaints. However, the majority of the studies had a low level of evidence (3b).

At the International Consultation on Incontinence-Research Society (ICI-RS) meeting in 2019, a Think Tank was convened to discuss how advances in the basic science study of SNS may be translatable into clinical practice to phenotype patients and improve patient selection (Malde et al,2020) (362). The presence of urodynamic DO has not been shown to be related to SNS success. The role of factors such as obesity, comorbidities and medications have not been well studied. The role of psychological comorbidities has yielded conflicting results. The authors concluded that, based on current evidence, the presence of psychological/psychiatric conditions does not seem to be a prognostic factor.

1.9. Effect of SNS on Sexual Function

The effect of SNS on female sexual function has been investigated in mostly retrospective studies. Lombardi et al reviewed nine studies that examined impact on sexual response in OAB (363). Most women were menopausal age, three studies included sexually inactive women. The Female Sexual Function Index (FSFI) was used in six studies, with significant improvement in at least one FSFI domain. In the InSite study, sexual function was a secondary outcome. Women who had SNS noted greater improvement in sexual function based on Female LUTS-sex Q than those having anti-cholinergics after 6 months (311), which was maintained at the 12, 36 months and 5-year evaluations (322-324).

In the Rosetta RCT, onabotulinumtoxinA (n = 190) or SNS (n = 174) a planned sub-analysis focused on sexual function (364). Outcomes were the (PISQ-12) and the IUGA-Revised (PISQ-IR). There was a significant improvement in PISQ-12 score in both the BTX and SNM groups; no difference between groups (p=0.99). (Level of evidence 1-2)

1.10. Magnetic Resonance Imaging (MRI) Recommendations

MRI has been a relative contraindication for patients who have an implanted SNS. Magnetic fields produce currents in electrodes, and heating of the leads has been demonstrated in vivo and in vitro (365-367). Whereas the clinical significance of the small temperature change observed in the leads is questionable, the potential exists to produce nerve damage, and the magnetic field may change the generator itself (368). Until recently, the manufacturer advocated removal of the device before elective MRI (369). The recent introduction of MRI compatible technologies should change the situation. The Axonics r-SNM System is conditional magnetic resonance imaging (MRI)-safe. Also, the InterStim SureScan MRI leads allow full-body 1.5 and 3 Tesla MRI-conditional scans.

However, there is a paucity of real-world data. In a prospective study of Axonics r-SNM SystemTM with 129 participants, at 24 months, a total of 13 MRIs were performed in 12 patients (9%). Eight MRIs were performed on the body/spine/torso, the remaining five MRIs on the head/neck (368). No adverse events or lead migrations were reported after any of the MRIs. The authors did not mention which MRI technology was used in these patients (1.5 vs 3 Tesla).

Patients who received the new models of Interstim II, but not the InterStim SureScan MRI leads, may be eligible to have MRI of the head only. However, the manufacturer indicates that MRI must be performed after certifying eligibility with the manufacturer support team or review the MRI Guideline for the Interstim Neuromodulation Systems. Limited evidence based on small case series indicate that full body MRI may be performed with no harm (370, 371), but is not recommended by the manufacturer.

The safety of nonhead MRI in patients with an implanted SNS system (InterStim II) and its effectiveness one month after the exam was prospectively studied by Guzman-Negron et al (372). Eleven patients had lumbosacral 1.5 Tesla MRI (55% for lower back pain). All SNS devices were turned off before patients entered the MRI scanner. Patients completed validated symptom questionnaires before and after MRI. During the imaging, one patient reported mild discomfort at the site of the implantable pulse generator and two patients reported warmth at the same area. There were no other adverse events and no significant changes in sensory thresholds, stimulation localisation, impedance and battery life.

In a recent study, Karrer-Warzinek et al assessed data from 55 patients with a SNS system (InterStim II) who underwent at least one MRI subsequently (373). A total of 191 MRIs were included in the study, median of 3 scans per patient. The scans were performed with 1.5 Tesla (92%, 176) or 3 Tesla. The majority of 1.5 Tesla (58%) and 3 Tesla (56%) assessed body regions other than the head, including the lumbosacral region, the trunk/ pelvis and the lower extremity. Complications related to the MRI occurred in 2 (1%) scans and consisted of transient electrifying pain and heat sensation during MRI (implantation site of the neuromodulator). The authors concluded that MRI involving body regions other than the head with 1.5 Tesla is safe in patients with SNM (InterStim II) with the device turned off.

1.11. Pregnancy

Electrical stimulation has the potential to induce teratogenicity or abortion and SNS has been considered contraindicated in pregnant women. However, whether it can cause abortion or malformation is not known. Wang (374) reported no adverse effects of electrical stimulation on pregnant rats.

Roulette et al (375) evaluated the outcomes of pregnancy and the results of SNS in women who became pregnant while having SNS. They mailed an online questionnaire to physicians listed in the InterStim enCaptureTM National French Registry. Questions were related to pre-pregnancy health and SNM efficacy, deactivation of the device, its impact on LUTS, childbirth, the infant, its reactivation and postpartum effectiveness. Twenty-seven pregnancies were recorded among twenty-one women. Five (18.5%) women had the device disabled prior to conception. The others had their device disabled during the first trimester and did not reactivate it before delivery. Complications were reported in 25.9% of pregnancies: six women had urinary infections, including three of the four treated for chronic retention of urine (CRU), and 1 woman had pain at the stimulation site. There were 24 live births (including one premature birth and four Caesarians), one spontaneous miscarriage and two voluntary terminations of pregnancy. No neonatal disorders were reported. Effectiveness of sacral neuromodulation decreased in 20% postpartum, regardless of mode of delivery.

Recently, Agnello et al (376) evaluated patients who had SNM devices and became pregnant (14 pregnancies in 11 women). Indications for SNM were urinary retention (7) and dysfunctional voiding (4). Two patients continued two and three pregnancies, respectively, with the device turned off since first trimester. They both had to return to self-catheterization and developed recurring UTI. No major urological complications were recorded in the remaining nine women who kept the device on during pregnancy. A cesarean section was performed in four cases for obstetric reasons; in seven cases it was planned by the urologist/ gynecologist to avoid lead damage/ displacement. Three pregnancies resulted in a vaginal delivery, and no association with term of delivery or duration of labor was observed. No congenital abnormalities related to SNM were reported, and only one patient required device removal because of significant loss of efficacy after childbirth. The authors concluded that SNM during pregnancy appears to be safe, without morbidity for the fetus. (Level of evidence 4)

1.12. Use of Computed Tomography (CT) for Lead Placement

In an attempt to improve the efficacy and accuracy of neuromodulator lead placement into the S3 foramen, investigators have evaluated alternative imaging techniques as compared to fluoroscopic guidance. Amoroso et al used CT with 30 patients in the prone position to identify the location of S3 foramina and guide PNE placement (377). Electrode placement was successful at the first attempt in 36/38 attempts (8 patients had bilateral PNE test). Two cases required several attempts. In one patient who had a nonconsolidated sacral fracture, CT guidance enabled insertion of the electrode inside the only practicable foramen, which would probably not have been possible under fluoroscopic guidance. A positive response to the PNE was obtained in 18/30 patients (60%). The procedure lasted about 45 minutes. Other authors successfully used CT guidance for lead placement in small case series and recommend that it should be considered especially in patients with an altered anatomy in the sacral region (378, 379). (Level of evidence 4)

1.13. Neurostimulation with Pudendal Nerve Stimulation

Pudendal nerve efferent activation directed toward the urethral sphincter is an important mechanism for the control of bladder contractions. In addition, many of the sensory afferent nerve fibers contained in the sacral spinal nerves originate in the pudendal nerve. Thus, the pudendal nerve fibers are important targets for neuromodulating the inhibitory reflex on the micturition reflex (380). Pudendal nerve stimulation has been used with different techniques to treat numerous pelvic floor dysfunctions such as urinary and/or fecal incontinence, urinary retention and constipation. There have been no new reports of this technique since ICI-6.

Summary

There is evidence for long term efficacy for SNS up to five years. (LE = 2). Maintenance of therapeutic effect requires reprogramming and surgical revision rate in a substantial number of patients. (LE= 1)

Preoperative predictors of optimal patient response to this invasive therapy remain unclear except for a positive response to PNE or staged implant (LE=2)

Recommendations

SNS is an effective therapy for selected individuals with urgency/frequency and UUI refractory to behavioural therapy and oral medications (Grade A).

Patients should be counseled regarding the potential for AEs, need for long term monitoring and intervention/adjustment of the implant, and additional surgeries to maintain therapeutic effect. (Grade A)

Research: Longer term data regarding efficacy and the risk of explantation for SNS is needed.

2. IMPLANTABLE POSTERIOR TIBIAL NERVE STIMULATION (PTNS)

In ICI-6, extensive discussion of the mechanism of action of PTNS, and clinical data regarding non-implantable PTNS treatment has been given. In ICI-7, current update for non-implantable devices is given in Chapter 8 (Adult Conservative Management). Recently, two types of surgically implantable posterior tibial devices have

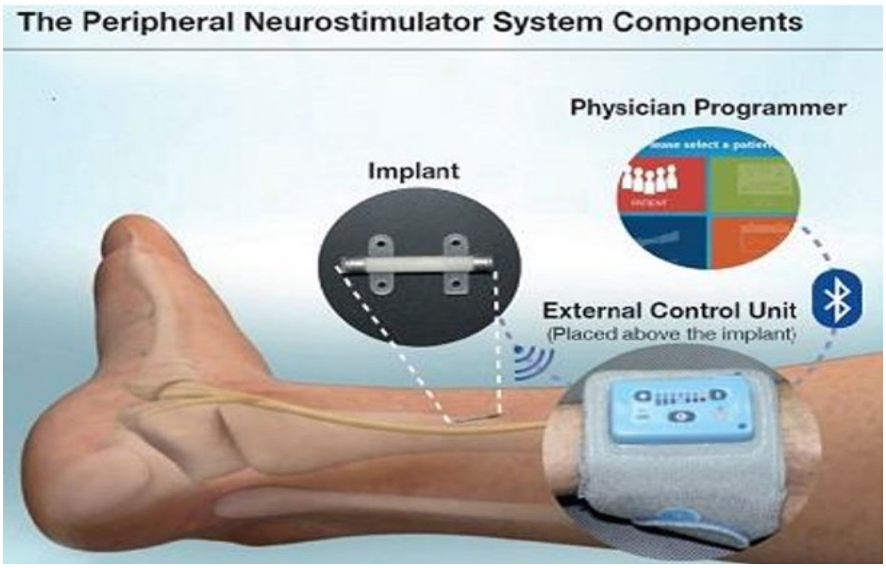

Figure 15: Bluewind Renova Device Reprinted with permission van Breeda et al, 2017 (381)

been employed, which are summarised here. Because PTNS requires 30 minutes of treatment in the office, weekly for 12 weeks, then ongoing treatment at least once per month, the notion of an implantable device that no longer required office visits was appealing. In 2017, van Breeda et al from Nijmegen published the first 3 months follow up of 15 patients, who had the BlueWind Renova device implanted (381). As shown in **Figure 15** , the device consists of a 3.4 mm diameter cylinder with 4 small fixating wings – the cylinder contains an electrical power receiver and 2 bipolar electrodes. Frequency can range from 5 to 40 Hz, pulse width is between 50 – 800 microseconds, amplitude ranges from 0-9 mA. The implantation requires a 5 cm skin incision above and behind the medial malleolus (with preoperative antiobiotics). Test stimulation of the device to ensure a motor response to stimulation was done before fixing the device with non-absorbable sutures. After 4 weeks postoperative wound healing, the External Control Unit (Figure 15) is applied for 30 minutes six times per week. Outcomes were bladder diary with a score for urgency and a score for leakage severity, ICIQ-FLUTS, and UDI. As shown in Table 7a, voids per day, urge episodes, severe urge leaks and pad test loss were all significantly reduced, as were results for the QoL tests.

The same group (Heesakkers et al, 2017) then implanted the same device in 36 patients but after stimulation 6 times per week for 3 months, patients then used the stimulator 3 times per week for 6 months (with the same parameters). Outcomes were 3day bladder diary, OABQ, and the number of pads per day. Success was defined as $\geq$ 50% reduction in reduction in number of leaks/day OR number of voids/day, OR episodes with degree of urgency>2. Two patients were not treated, one withdrew from the study, and one had device explanted due to pain and swelling with suspected infection but negative cultures. As per Table 7A, clinical response occurred in 71%, with significant benefit in voids/ day, leaks/ day and pads/ day ($p < 0.05$). However, implant site pain and suspected infection and wound complications occurred in 47%, which the authors pointed out is lower than the adverse event rate for sacral neuromodulation implants. Most recently, Dorsthorst et al. (2020) continued to follow these subjects: all 34 participants in the above study were invited to rejoin for a 3year continuation study, of whom 20 agreed, reason not given for the other patients declining. The baseline demographics/ OAB features of those who continued and those who declined were very similar. Outcomes remained 3day

Table 7A: Outcomes for Bluewind Device

Study	Design	N value	Results	Comments
Van Breeda et al. (2017) (381)	3-month prospective study	Bluewind (n=15)	Decrease in 24-hr frequency (11.8 to ->8.1, p = 0.002), urge episodes (6.5->2.0), severe UUI leaks (2.8->0.3), pad test (243->55gm) p = 0.038	AE: prolonged antibiotic treatment (20%), pain (20%). Removal of implant in 1 patient (7%)
Heesakkers et al. (2018) (382)	6-month multicentre prospective study	BlueWind (n=34)	71% of participants had >50% response Voids/ day 12 >9.4 Leaks/ day 6.6 > 3.9 Pads/ day 3.1 > 2.2	AE: Implant site pain (13.9%), suspected infection (22.2%), wound complications (8.3%)
Dorsthorst et al. (2020) (383)	3-year prospective study	BlueWind (n=20)	75% overall success rate. 73% improvement in QoL scores	Removal of 1 implant No reports of implant migration. Treatment frequency varied from once every 4-6 wks to 1-2 per day.

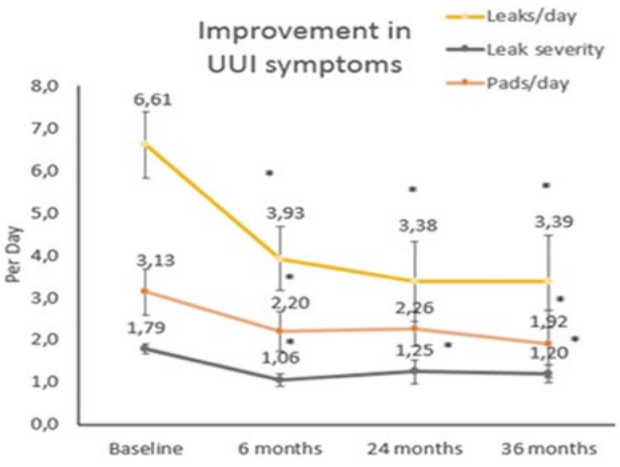

Figure 16: Improvement in the wet OAB symptoms during BlueWind continuation study period in the PP analysis. * indicates p < 0.05 Reprinted with permission from Dorsthorst 2020 (383)

bladder diary and OABQ with same definition of treatment success, which occurred in 75% (Table 7a).

The response seen for leaks per day, and pads per day, as shown in Figure 16 above, were obviously significant. Continued benefit on OABQ was shown in 75% of patients in the extension study, and there were no additional explantations, no serious adverse effects, and no new surgical interventions.

The E-coin device is smaller than the BlueWind device, being the size of a US quarter (25c) coin. The cathode is located at the centre of the device, with circumferential anodic ring, thus creating a wide electrical field. It is implanted under local anaesthetic (using a pre-designed template shown in Gilling et al, 2021 (384)). Once activated after 4 weeks of wound healing, there is no externally applied stimulator needed (unlike the BlueWind device). A trained field clinical engineer programs the device, with pulse amplitude of 0.5 – 15 mA, pulse width 0.2 ms. Therapy was delivered for 30 minutes every 2 days for 12 weeks then every 15 days thereafter.

Preliminary 3 month data were reported by MacDiarmid et al (384), 20% of subjects were continent (Table 7B). The same 46 participants from the USA and New Zealand were followed for 12 months. All had at least one episode of urge incontinence per day. Outcomes were 3day bladder diary, I-QOL and PGII. 26% of patients were continent (Table 7B) with significant reduction in urge leaks. There were 8 cases possible infection / pain that responded to treatment.

Figure 17: eCoin Device

A similar small device prototype was originally published in 2013, and 7 patients were followed up for 9 years clinically and on x-ray of the lower limb. Safety was remarkably adequate with only 2 minor adverse events (tenderness at the implantation site, and sporadic sensory impulses), but this device discontinued manufacturing for technical reasons (386).

Summary

Implantable PTNS devices appear to yield quite significant reduction in urge leakage with improved QoL and overall, about 70% clinical response, with one follow up study at 3 years. The rate of adverse events differs considerably between devices. With the recent advent of Trans Cutaneous PTNS, which patients can also use at home after initial instructions, the chief benefit of these implantable devices (no requirement for office visits) will require further comparative analysis.

Table 7B: Outcomes for e-coin devices

Study	Design	Intervention	Results	Comments
MacDiarmid et al. (2019) (385)	6-month multicentre prospective study	eCoin (n=46)	70% of participants had >50% decrease in episodes of UUI. 20% were continent. I-QOL scores improved by mean of 48%.	1 participant developed wound cellulitis treated with antibiotics.
Gilling et al. (2021) (384)	12-month follow-up prospective study	eCoin implantable device (n=46)	65% of participants had >50% decrease in episodes of UUI. UUI 4.2 reduced to 1.7 p< 0.001 **26% were continent.** I-QOL scores improved by mean of 86%. 70% better on PGII	1 participant experienced 1cm posterior migration of implant, 8 cases of possible infection which responded to treatment
Janssen et al. (2013) (386)	9-year follow-up study	Urgent-SQ implant (n=8)	7 patients still had implant. 6 out of 7 patients had response on stimulation.	Implants were intact with no migration and/or displacement. 1 report of localised ankle discomfort.

Recommendations/ Research

Implantable PTNS devices appear to show promise but require longer term objective evaluation in studies involving larger numbers of patients. Grade C

3. AUGMENTATION (ENLARGEMENT) CYSTOPLASTY (AC)

3.1. Enterocystoplasty

Enterocystoplasty is the main form of AC and involves a segment of the bowel that is removed from continuity with the fecal stream, detubularised, and patched into the bisected bladder. This method increases bladder capacity and decreases bladder pressure caused by uninhibited detrusor contractions. Virtually any portion of the GI tract can be utilised for entero-cystoplasty, and each segment has its own unique favourable properties as well as inherent complications (387, 388).

Other than idiopathic OAB, indications for enterocystoplasty include mainly small capacity bladders due to fibrosis, tuberculosis, radiation, chronic infection or neurogenic DO (NDO) (389) and as a last resort in refractory OAB. With the introduction of therapies such as SNS and BTX-A, there has been a dramatic decline in the use of AC, with only one additional publication since the 5th ICI.

3.1.1. Efficacy and safety

There is no RCT published to compare the efficacy/ safety of AC with other methods. The 2015 AUA/SUFU Guideline Amendment for Diagnosis and Treatment of OAB (Non-Neurogenic) in Adults recommend that AC should only be considered in extremely rare cases (390).

In 2013, El-Azab et al (391) compared UDI-6, IIQ-7 and OAB-Sat questionnaires after AC versus injection of BTX. Patients chose their treatment on personal preference (N= 31 including 16 for BTX and 15 for AC). At six months, significant benefits in LUTS and QoL occurred after both treatments but were greater in patients who underwent AC. The AC group had worse scores on the UDI-6 voiding difficulty question (1.7 vs 0.81 for the BTX group; p= 0.004). Four (26.7%) patients required CISC after AC and two in the BTX group. The need for repeat treatments was the primary reason for dissatisfaction in those who received BTX. (LE= 4)

Apart from the inherent risks of open, laparoscopic or robotic abdominal surgery, associated with bowel and bladder anastomoses, AC carries several distinct long-term risks. These include kidney or bladder infections, new-onset recurrent UTIs, metabolic derangements, mucus production, and, in rare cases, bladder tumours (392). As a segment of bowel is used for AC, the available absorptive surface area of the bowel is reduced, and the incorporation of bowel segments into the urinary tract may have metabolic consequences (393). Hyperchloraemic metabolic acidosis can occur if ileal and/or colon segments are used, as well as malabsorption of vitamin B12 and bile acid after the use of ileal segments. Blackburn et al demonstrated a reduction in serum B12 level with time following ileocystoplasty in 44% of their patients at 7-year follow-up (394).

The incidence of secondary malignancies that may develop as a long-term consequence of bladder augmentation remains a concern. The carcinogenesis pathway is still not clearly understood. In 2016, Biardeau et al (392) systematically reviewed the risk of malignancy after AC. The probability to develop a malignant tumour ranged from 0 to 5.5%, the estimated incidence ranged from 0 to 272.3 per 100,000 patients/year. Adenocarcinoma was the commonest (51.6%) type. Malignant lesions predominantly occurred at the entero-urinary anastomosis (50%). Mean latency period was 19 years and most tumours were diagnosed more than 10 years after AC (90%). Long-term surveillance by cystoscopy is still controversial because of its lack of efficiency. Tumours were often diagnosed at an advanced stage within surveillance protocols, because of other LUTS symptoms (64.1%). The authors recommended that studies regarding carcinogenesis and surveillance strategies should be performed to develop a more efficient follow-up protocol and allow early diagnosis. The authors cautioned that the level of evidence of the studies was usually poor and results should be interpreted with caution. (LE=4)

3.1.2. Other Evidence

Most reviews on AC feature patients with a neurogenic bladder (388, 395). The few reports that have examined the results of AC in adults with idiopathic OAB are case series (LOE=4).

Several variations on the standard AC have been described, most of which were applied to children or adult patients with neurogenic DO or contracted bladders, and are reviewed in the last chapter ICI-6. Overall, due to its invasive nature and potential for long-term adverse effects, AC is considered to be one of the last choices of treatment in refractory IDO cases (390).

Summary

There have been no randomised controlled trials, double blind or sham-controlled trials or long-term cohort studies which have examined the effects of enterocystoplasty for the treatment of idiopathic OAB. (LE=4)

Recommendations

Enterocystoplasty for idiopathic OAB should only be considered in rare cases where other therapies have been deemed unsuccessful or are not suitable. (GRADE D)

Patients undergoing enterocystoplasty should be counselled regarding the potential life altering changes postoperatively (e.g. need for self catheterisation, etc.) and the need for long term follow-up (GRADE D). See previous ICI Chapter for details.

3.2. Autoaugmentation

Initially described by Cartwright and Snow in 1989, auto augmentation of the bladder was developed as an alternative option to AC, especially in children with neurogenic DO. The procedure is discussed in ICI-6, with no new reports published.

Summary

There have been no randomised controlled trials, double blind or sham-controlled trials or long-term cohort studies which have

examined the efficacy and safety of autoaugmentation for the treatment of adult idiopathic OAB. (LE=4)

Recommendation

Autoaugmentation is not recommended as a therapy for adult idiopathic OAB. (GRADE D)

III. URETHRAL DIVERTICULA

Urethral diverticulum (UD) is an outpouching of the urethral lumen into the surrounding periurethral connective tissue. This is a relatively rare condition with an estimated annual incidence of 17.9/1,000,000 (396). UD are thought to arise from repeated obstruction, infection and subsequent rupture of periurethral glands into the urethral lumen, resulting in an epithelialised cavity that communicates with the urethra (397). Iatrogenic damage to the urethra may also play a role, as up to 20% of women with urethral diverticula are noted to have a history of prior urethral surgery, dilation, or traumatic delivery (398). Iatrogenic UD formation associated with MUSs has also been reported (399, 400). The clinical manifestations of UD are often vague and variable resulting in a prolonged time to definitive diagnosis (401).

Urinary incontinence occurs in between 20 and 60% of patients with UD at presentation (402, 403) and which may be mixed, stress, urgency or paradoxical (insensate) incontinence. It may also present with a vaginal mass, irritative LUTS, dyspareunia, pain, dysuria, recurrent urinary tract infections, watery vaginal discharge and post-micturition dribble (402, 404, 405). About 20% of patients are asymptomatic (403).

At presentation, SUI is more commonly associated with UD than urge leak. Those with post-micturition dribble may have insensate incontinence due to urine accumulation in the pouch during normal voiding, with subsequent discharge of the accumulated urine out through the urethra upon movement (406). Finally, persistent or de novo incontinence may occur after surgical repair. Patients having autologous sling concomitantly with UD repair have a lower risk of needing subsequent continence surgery, compared to those undergoing UD repair alone (407).

1. PREOPERATIVE ASSESSMENT INCLUDING URODYNAMICS

Careful history, physical examination, and appropriate tests are needed to evaluate suspected UD. Imaging modalities including ultrasound **(see Figure 18**) (408, 409), voiding cystourethrography (410), and MRI (411, 412) help to define the UD anatomy and to plan surgical intervention. Cystourethroscopy will most commonly reveal the ostia of the UD in the dorsolateral midurethral segment.

Urethral pressure profilometry has also been utilised by some authors in the assessment or diagnosis of UD noting a biphasic pattern, or pressure drop at the level of the lesion during the study (413, 414).

Video- urodynamics are often used to assess patients with UD and LUTS (413-415). Approximately 50% of women with UD will have

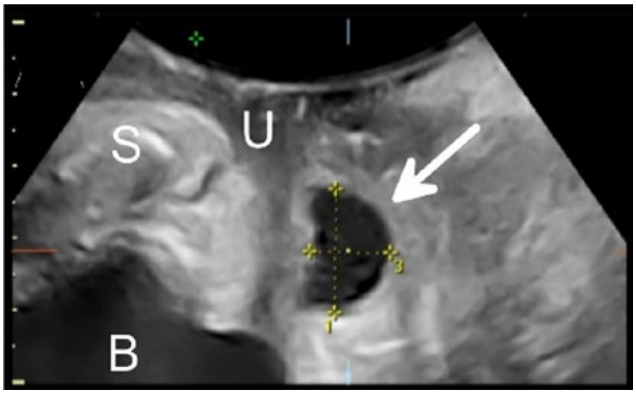

Figure 18: Ultrasound of Urethral Diverticulum where arrow is pointing to U = Urethra, S = symphysis pubis, B = bladder. Figure courtesy of HP Deitz

Urodynamic Stress Incontinence (USI) (416). Fluid accumulation in the UD may be seen on fluoroscopy and will help to delineate the size and location of the diverticulum (e.g. whether it is circumferential or just a simple pouch). Resting and straining images on fluoroscopy may show an open BN at rest, suggesting a compromised proximal sphincter mechanism that may further support the need for continence surgery.

2. UD AND STRESS INCONTINENCE

UD are most often located at the level of the midurethra thus co-existent incontinence is usually USI. The midurethral location of UD often overlaps with the external sphincter but UD may also extend proximally toward the BN at the proximal sphincter mechanism, or completely around the urethra (417). The more proximal, larger, complex lesions are at greater risk for postoperative SUI (412, 418, 419).

Patients with symptomatic USI are generally offered simultaneous continence surgery, after discussion. One series showed good results with BN suspension (416), but more recent series use autologous pubovaginal slings in such patients (401, 407, 420, 421) with success in >90% of cases in some series (420, 421). The high likelihood of curing the USI must be balanced against the longer operative time, convalescence, and risks of needing CISC or aquiring de novo DO. Note that resolution of USI may occur in about 50% of cases after surgical excision UD alone (407, 422). The mechanism underlying this is not clear but may result from elimination of post-void dribbling, or due to reconstruction and bolstering of a damaged sphincter mechanism during UD repair (422).

Midurethral synthetic slings are not recommended as a continence procedure at the time of urethral diverticulectomy (423). Synthetic material adjacent to a fresh suture line in the setting of potentially infected urine may increase the risk of urethral erosion and vaginal extrusion of the sling material, as well as urethrovaginal fistula and foreign body granuloma (EL=4).

Urethral diverticulectomy alone may be associated with de novo incontinence in 7-16% of cases. Risk factors for de novo SUI may include the size of the diverticulum (>30 mm), more proximal location (418, 419), and wide excision (419). Another important cause

is iatrogenic urethrovaginal fistula, occurring in up to 6% of cases (398, 404, 418, 419, 424).

Significant postoperative de novo SUI may occur in 7-16% of those undergoing urethral diverticulectomy without a concomitant continence procedure (418, 419). Risk factors for de novo SUI may include the size of the diverticulum (>30 mm), more proximal location (418, 419), and wide excision (419). Another important cause is iatrogenic urethrovaginal fistula, occurring in up to 6% of cases The pathophysiology of this is not well understood. It may be due to surgical trauma to the sphincteric mechanism during UD excision/repair or unmasking of "occult" SUI in the setting of partial obstruction from the UD (425), especially when the UD is proximal and greater than 3cm in size (426). UD repair may be bolstered by placement of a Martius flap (427) which may reduce the chance of de novo SUI (422).

3. UD AND URGE INCONTINENCE

UD may also be associated with storage symptoms and urge incontinence. Bladder outlet obstruction due to the mass effect of the UD, urinary retention, or irritative LUTS e.g. urgency and urge incontinence may present secondary to UD (425). Pain and dysuria associated with UD may also result in acquired voiding dysfunction.

Stav et al (2008) reported that storage symptoms decreased significantly from 60% to 16% after diverticulectomy (418) but at least one small series reported no improvement in urgency and UUI (410). Other long term studies have shown rates of postoperative urgency of 54% (424), and de novo urge incontinence in 36% (419). Such symptoms may herald UD persistence, UD recurrence, de novo urethral obstruction or may simply reflect persistent preoperative symptoms unrelated to surgery.

Summary

The evidence pertaining to UD and urinary incontinence consists of retrospective, poor quality small- to medium-size case series with limited follow-up (428) demonstrating that urinary incontinence and other voiding dysfunctions are significantly associated with this condition (EL=3). Surgical repair of UD will often improve associated urinary incontinence and other lower urinary tract symptoms, but de novo or persistent lower urinary tract symptoms are possible.

Recommendations

Patients with UD should be carefully questioned and investigated for co-existing voiding dysfunction and urinary incontinence. (Grade C)

Patients with UD without SUI should not be offered concomitant prophylactic SUI surgery at the time of urethral diverticulectomy. (Grade C)

Following appropriate counselling, bothersome SUI can be addressed at the time of urethral diverticulectomy with concomitant non-synthetic sling (Grade C)

Patients should be counselled regarding the possibility of de novo or persistent lower urinary tract symptoms including urinary incontinence despite technically successful urethral diverticulectomy. (Grade C)

IV. CONFOUNDING VARIABLES

Confounding variables were discussed as a separate issue in the last ICI-6 chapter. However, as per the Introduction to this chapter, we have systematically included such variables (age, obesity, previous continence or spinal cord surgery, co-existence of detrusor overactivity preoperatively, and Intrinsic Sphincteric Deficiency under the discussion for each procedure, wherever they appear in the literature.

V. CLINICAL TRIAL OUTCOMES USED IN UI RESEARCH

The reported outcomes from surgery for urinary incontinence have recently been scrutinised, following concerns raised regarding the failure to capture important long-term results. A 2017 Cochrane review examining outcomes from mid-urethral sling surgery, perhaps the most commonly performed continence surgery, described the quality of published evidence as "moderate at best" (103). In 2020, a UK parliamentary review looking at mesh inserted for SUI (and pelvic organ prolapse) criticised the quality of evidence in this area and commented that "There is no reliable information on the true number of women who have suffered complications" (429). In 2019, Doumouchtsis et al further underlined this in a study which examined outcomes from 108 RCTs about treatment of stress incontinence, finding that several important outcomes were under-reported (430). These included pain, sexual dysfunction, dyspareunia and surgical site infection. Despite the widespread reporting of outcomes relating to cure or improvement, the authors noted significant heterogeneity in the outcome measures used. In another study of outcomes reported from 66 stress incontinence surgical trials, similar findings were noted (431): for both "subjective cure" and "quality-of-life" more than 20 separate terms were used. Both of these studies called for the development of a core outcome set which could be used by researchers to facilitate both comparison of different treatments and meta-analyses of clinical trials.

Currently, outcome measures for SUI surgery remain non-standardised in clinical trials. Unlike cancer treatments with a readily defined outcome, or even prolapse surgery where an anatomic outcome can be objectively assessed, SUI is a quality-of-life condition which can be difficult to measure. However, objective quantitation of the severity of urine loss on pad testing remains useful, and essential for research studies. Because surgery for SUI can improve or worsen other LUTS such as detrusor overactivity or incomplete emptying, the most meaningful evaluation we can make often comes from randomised trials where the same outcomes for different treatments and complications rates are applied.

It would appear that the same degree of heterogeneity is found when the health- economic analyses of surgical trials for incontinence are examined. In a systematic review of economic evidence which looked at 26 economic evaluations the authors concluded that "methods used for the economic evaluation of surgical treatments for SUI vary widely in terms of study design, analysis type, compared alternatives, time horizon, costing methodologies and

effect outcomes" and called for consensus in order to improve economic evaluation (432).

1. HISTORY OF SUI MEASURES

Surgical outcomes are broken down into subjective and objective measures. Early reports of outcomes for SUI surgery were largely subjective. Often, they were nothing more than surgeons asking the patient at the post-operative appointment if they were "better". Of course, both the patient who decided to have the surgery, and the surgeon who did the surgery, were invested in the outcome: hence success rates greater than 95% were not uncommon. This physician-reported subjective outcome has been severely criticised. In a very early systematic review of SUI surgery, Jarvis (1994) commented that such subjective assessments of cure are clearly unsatisfactory for robust scientific assessment (433). The AUA SUI Guidelines Panel report (1997) noted the paucity of clinical studies that met minimal criteria for good science in the conduct of clinical studies (9). The panel **recommended 5 year outcomes** with specific measures including history/questionnaire, physical exam, diary, pad test, post void residual urine volumes, and assessment of complications/morbidity, including urinary retention, and de novo urgency (9). Ten years later when Rovner et al reviewed the literature no articles met all criteria, but most complied with at least half of the recommendations (434).

Most SUI studies now report both subjective and objective measures and most of the Cochrane reviews of SUI surgery compare subjective and objective outcomes. The Standardization Committee of the International Continence Society (ICS) is the main body that has governed terminology and outcome measures in the field of urinary incontinence since 1978. Objective parameters typically include stress tests, pad tests, voiding diaries, urodynamic studies and the advantages and disadvantages of these measures are included in Table 12. Over time urodynamic studies have been used less commonly as an SUI surgical outcome, because objective measurement of degree of leakage is accurately determined by the less-invasive pad test.

The voiding diary was often used in the past, but only measures output. The Bladder Diary is a more useful outcome measure because it indicates:

- The number of leaks per 24hr (or convert to leaks per week by averaging)
- The number of voids per day ("frequency")
- The episodes of nocturia (after patient goes to bed, must be indicated)
- Whether patients fluid restrict (often for fear of urge leak)
- Whether patients are drinking more than 2 litres/day ("over-drinking")
- Factors that precipitate leak, such as cough/ sneeze/ lifting are written down

The 7-day diary is the most sensitive and accurate, but compliance is poor. As the first 3 days and the last 4 days of a 7-day test correlate well (r = 0.9), the 3-day Diary is the most common research tool.

The One-Hour Pad Test was introduced 1983 and recommended by the ICS in 1988. The patient is asked to attend with a comfortably full bladder (which they may be reluctant to do). They are given a pre-weighed continence pad, then given 500 ml water to drink over 15 min, then perform a standard series of activities to provoke leakage (which can be onerous). The wet pad is re-weighed.

Unfortunately, the 1-h pad test has poor sensitivity (up to 40 % false negative rate). It was, however, the first objective method that could be used to define mild (1–10 g leakage per 1 h), moderate (11–50 g/h), and severe (>50 g/h) incontinence; thus, it was used in many publications.

The 24-Hour Pad Test was designed because of the problems with the 1-h test. It is conducted at home, in "real-life" conditions. The patient is given a set of (usually 5) pre-weighed pads in sealed plastic bags (**See Figure 19**). The pads are worn at home for 24 h, whilst ordinary provocative activities are carried out, and the patient returns the pads, which are re-weighed (436). The amount of leakage does not evaporate in the sealed bag for up to 2 weeks, so they can be returned via post. The 24-h pad test is more sensitive than the 1-h test (10% false negative rate).

Normal ranges on the 24-h pad test are controversial. In small samples of women (n = 23–78), using simple kitchen scales, the normal values were 3–10 g. Later, the normal values were redefined (n = 120) using scales accurate to 0.1 g which revealed a median value of 0.3 g (95th centile 1.3 g) was obtained (436). The test correlates with the ICIQ (437).

The 24hour pad test can also be used to define mild (1.3 – 2.0 gm), moderate 21 – 74 gm), and severe leakage (>75gm). This helps to define women with "mild" leakage who are more likely to respond to conservative therapy, versus severe leakage that is more likely to require surgery (438). Even so, Richter et al (2011) showed that

Table 12: Female SUI Objective Outcome Measures

Measure	Advantages	Disadvantages
Cough Stress test	Noninvasive, Inexpensive Specific for stress incontinence A positive test is predictive for urodynamic stress incontinence (435)	Should be standardised (position of patient Volume to be 'comfortably full', at least 200ml, often done at 300+ ml
Pad test (1 hr or 24 hr)	Quantitative; raw data can be compared pre-op and post- op then compared via T-test etc.	Not SUI specific 1hour test requires nurse time 24hour test requires patient compliance
Bladder diary (3 day or 7 day)	Can differentiate stress from urgency events.	7day diary is burdensome but most sensitive
Urodynamics	Can detect urodynamic stress incontinence and DO	Invasive, uncomfortable, expensive

larger pad weights were predictive of greater risk of surgical failure (439).

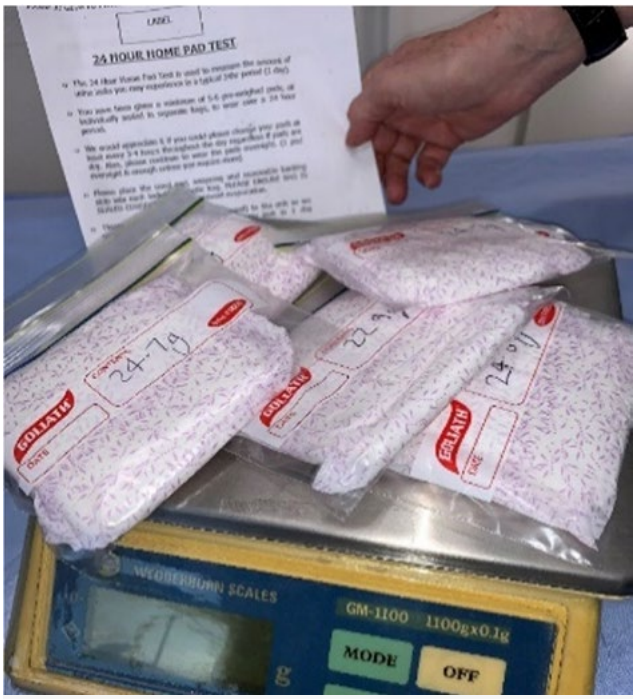

Figure 19: Five pre-weighed pads in sealed zip log plastic bags for 24hr Home Pad test.

2. PATIENT REPORTED OUTCOMES

While many of the subjective self-reported measures can be considered "patient reported", the concept of true Patient Reported Outcome Measures (PROMs) is more complex and encompasses a more global assessment. PROM's should measure patient impressions in a more global context by encompassing 4 domains: 1) Symptoms, 2) Functioning, 3) General Health Perception and 4) HRQOL. The NIH recently established the Patient Reported Outcomes Measurement Information System (PROMIS) for women with urinary incontinence (440). The International Consultation on Incontinence has adopted the use of PROM's and established the ICI Modular Questionnaire (ICIQ) Project that includes the assessment of a wide spectrum of urinary, bowel and vaginal symptoms along with their impact on HRQOL. **Table 13** demonstrates PROM's which have received an A grade from the ICI for female SUI outcomes from prior Consultations.

The *ICIQ-SF* was validated by the ICI many years ago. It records incontinence symptoms and severity, with a simple quality of life question. The final ICIQ comprises three scored items (maximum score 21) and a self-diagnostic item on the impact of the incontinence upon the patient's "bother". It is probably the most widely used outcome test for general urinary incontinence (www.iciq.net).

3. COMPOSITE MEASURES

There are deficiencies with any single subjective or objective SUI research outcome measure. Therefore, multiple measures are often included which are not used by any other others which makes definitive conclusions difficult. For this reason, especially with the advent of clinical trial networks, investigators have increasingly used composite outcomes **(Table 14**).

Table 13: Female SUI patient reported outcomes with ICI Grade A recommendations

Tool	Measures	Items
ICIQ FLUTS	QOL, Treatment outcome	34
ICIQ-UI SF	Symptoms and impact	4
IIQ (Incontinence Impact Questionnaire)	Impact of UI on HRQOL	30
IIQ-7	Short version of IIQ	7
I-QOL (Incontinence QOL)	Incontinence specific QOL	22
ISS (Incontinence Symptom Severity Index)	Severity of storage and voiding symptoms	8
KHQ (ICIQ-LUTSqol) King's Health Questionnaire	Symptom impact of LUTS	21
LIS (Leicester Impact scale)	LUTS QOL	21
UISS (Urinary Incontinence Severity Score)	Severity and impact of UI	10
LUSQ (Leicester Urinary Symptom Questionnaire	Presence and severity of storage abnormalities	10
PGI-I (Patient Global Impression of Improvement)	Symptom bother	1
PGI-S (Patient Global Impression of Severity)	Symptom bother	1
PPBC (Patient Perception of Bladder Condition)	Impression of bladder condition	1
UDI (Urogenital Distress Inventory)	Symptom bother related to UI	19
UDI-6	Symptom bother related to UI/LUTS	6

Table 14: Examples of composite primary outcomes used in RCT's of SUI surgery with more than 200 subjects.

1st Author, Year (ref)	Surgery	Composite Outcome
Ward, 2002 (90)	TVT vs. Burch	No USI and Negative pad test
Albo, 2007 (14)	Fascial sling vs Burch	Negative pad test and No UI on 3 day diary and Negative cough stress test and No self-reported SUI on MESA and No SUI retreatment
Barber, 2008 (130)	PVS vs. TO	Abnormal bladder function defined by presence of Incontinence symptoms of any type Positive cough stress test Retreatment of SUI Elevated PVR
Rinne, 2008 (126)	TVT vs TVT-O	Objective Negative stress test Negative pad test Subjective condition-specific quality of life Q and general EQ-5D Q.
Wang W, 2009 (136)	TVT vs TVT-O	Negative cough test Negative pad test Reduction by 50% of incontinence episodes
Richter, 2010 (121)	PVS vs TO	Objective Negative stress test Negative pad test No SUI retreatment Subjective No self- reported SUI symptoms No UI on 3day diary

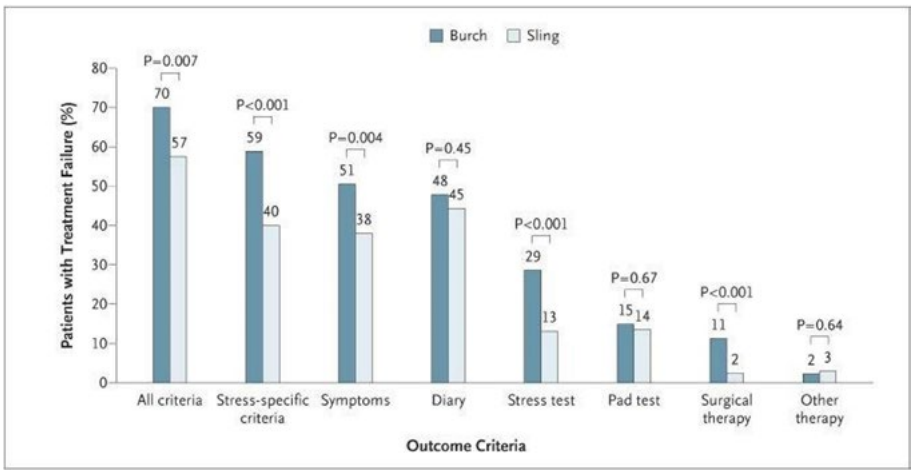

Figure 20: Proportion of subjects with treatment failure at 2years according to different criteria in the UITN randomized trial comparing Burch vs. Autologous sling (14)

While they do provide more comprehensive assessments, composite outcomes often create a stricter definition of success and thus lower success rates especially if all of the components of the composite must be satisfied. Investigators should also consider reporting the results of the individual components of the composite measure. An example of the reporting of individual composite components is shown in Figure 20.

4. SURVIVAL ANALYSIS REPORTING FOR SUI OUTCOMES

When assessing outcomes, it is important to determine if the study used a survival type analysis (typically reported on a Kaplan-Meier graph which follows patients over time) or just assessed the patient at one specific postoperative time point. In these survival analysis types of studies an assumption is made that once a patient reports

incontinence she will continue to have incontinence and she is considered a failure for the course of the study. This may not fit the natural history of SUI symptoms, which can change over time. Survival analysis reporting will lead to lower success rates than single time reporting and may not be consistent with the patient's reported outcome.

5. SUCCESS RATES ARE DEPENDENT ON THE RIGOR OF THE ASSESSMENT

Further complicating the issue of outcome assessment is that few of our SUI treatments make a woman completely dry and therefore success rates decline with the rigor of the assessment. An example of both a rigorous outcome measure and a survival analysis approach is found in the UITN's randomised trial of Burch vs PVS which was criticised for low overall success rates of less than 50% in both arms (14). In this study a composite measure was used which included administering a 3 day diary, a 24hour pad test and a 15-question incontinence survey (MESA) every 6 months for 2 years. Any positive response during any assessment resulted in a failure for the duration of the study. In this study with composite rigorous assessments and survival analysis methodology, the low overall success rates of less than 50% were however inconsistent with patient satisfaction rates of 78 and 86% in the 2 groups (14).

If the definition of SUI surgical success is too rigorous outcomes will not meet face validity. In 2001, the NIH defined cure of stress urinary incontinence as: 1) resolution of the stress incontinence symptoms; 2) resolution of the sign (negative full bladder cough stress test, performed under the same conditions as before treatment); and 3) no new symptoms or side effects which could include new urinary symptoms such as urinary urgency, frequency, urge incontinence, with or without urodynamic changes of DO (detrusor instability); change in sexual function; development or worsening of POP; adverse effect on bowel function; onset of urinary tract infections; surgical complications, etc. (441). As Hilton noted in an editorial, if this definition was applied to the United Kingdom TVT vs Colposuspension RCT, cure rates in the 2 arms would be 6 and 9% (442).

6. MIXED INCONTINENCE AS A CONFOUNDER

Many patients undergoing stress incontinence surgery also have urgency incontinence (mixed UI) and this urgency component may worsen, remain the same, or improve after SUI surgery. Hence continence surgery failures often result from worsening or de novo urgency incontinence. The true "pure" SUI patient is rare. In support of this, in the SISTeR trial where all women were reported to have pure or predominant SUI for study inclusion, the range of women with mixed incontinence ranged from 8.3% if mixed incontinence required DO on urodynamic studies to as high as 93.3% if they reported "yes" to any urgency incontinence question (443). The inclusion criteria for studies vary, the amount of mixed incontinence in the sample varies, thus comparison between studies can be inaccurate.

Any instrument that is stress incontinence-specific may give results about the surgery's effect on stress leakage but may not give an accurate assessment of what the surgery did for overall LUTS (urgency, frequency, urgency incontinence, or voiding difficulties). Therefore, an overall bladder assessment tool is recommended for measuring SUI surgical outcomes. Patient reported bladder outcomes with ICI Grade A recommendations are shown in Table 13 and include the: ICIQ-UISF, ISS, KHQ, UISS, PPBC, UDI, and UDI-6. However, several scores exist for urgency incontinence, chiefly the OABQ.

7. GLOBAL MEASURES

Another outcome that has recently gained popularity is the patient global impression of severity (PGIS) and the patient global impression of improvement (PGI-I). Use of such global assessment instruments provides a single response which is easy for the patient and clinician to understand (444). Furthermore, the measurement is all encompassing since the subject takes success and complications into account when responding. The PGI-I was part of the composite primary outcome in the UITN randomised trial evaluating preoperative urodynamics (435).

Summary

The last two decades has seen a massive expansion in the field of SUI research. While initially criticised for poor quality research, significant advances have been made especially in the development of clinical trial networks that have allowed large scale multisite surgical studies necessary for high quality studies. We have also seen a maturation of outcome tools including validated patient reported outcome instruments. The standard clinical trial for SUI now is a prospective randomised comparative efficacy trial using patient reported outcomes as a component of the primary outcome. However further standardisation is needed to allow for data-pooling and meta-analyses of different trials.

Recommendations

Patient reported outcomes using ICI Grade A bladder symptom and incontinence-specific quality of life instruments should be utilised in stress incontinence clinical trials (Grade D).

A cough stress test standardised to bladder volume and patient position provides an objective assessment of the presence of absence of stress continencee (Grade D). However a weighed 24 hour pad test pre operatively and post operatively provides quantitative continuous data which is more suitable for statistical analysis (Grade A)

Composite measures address inadequacies of any individual stress outcome measure, but rates using these composite measures are often lower than any individual measure, so the individual components must also be reported. (Grade D)

VI. RESEARCH RECOMMENDATIONS

As regards autologous pubovaginal sling, further long-term objective and subjective outcome data should be collected for the less invasive "Sling on a String" versus the traditional PVS, particularly in relation to the likelihood of voiding dysfunction/ CISC and de novo DO.

As regards the laparoscopic colposuspension, further objective and subjective data regarding success rates at 18 m – 5 years needs to be obtained.

As regards trans-obturator rmid urethral slings, further longer term data regarding risks of groin pain, need for groin dissection to entirely remove trans-obturator tapes, and risks of repeat continence surgery are needed.

As regards bulking agents, further data regarding subjective and objective success rates in those with normal urethral function, versus those with ISD, are needed**.**

As regards Laser Therapy, Studies that correct deficiencies regarding mechanism of action, long term cure rate, and adverse events are needed before Laser therapy can be recommended for use outside of Clinical Trials.

As regards Artificial Sphincter for urinary incontinence in women, longer term data regarding use of laparoscopic and robotic implantation techniques are needed, in relation to cure rates, complications, and explantation rate.

The use of stem cell technology for treatment of female SUI remains investigational. Such therapy should only be offered in the setting of clinical trials.

As regards Sacral Neuromodulation, longer term data regarding efficacy and the risk of explantation is needed. The safety of MRI investigation, and pregnancy, in patients having the more recently developed devices, needs to be continually monitored and reported.

As regards Implantable PTNS devices, longer term objective evaluation in studies involving larger numbers of patients is needed.

APPENDIX A: Validated SEAPI scoring system (Stothers, 2004 (32))

1. Stress related leakage	2. Emptying ability	3. Anatomy	4. Protection	5. Inhibition
0–no urine loss	0–no obstructive symptoms	0–no descent during strain	0–never used	0–no urge incontinence
1–loss with strenuous activity	1–minimal symptoms	1–descent, not to introitus	1–only used for certain occasions	1–rare urge incontinence
2–loss with moderate activity	2–significant symptoms	2–descent through introitus with strain	2–used daily for occasional accidents	2–urge incontinence at least once a week
3–loss with minimal activity or gravitational leakage	3–voiding only in dribbles, or urinary retention	3–through introitus without strain	3–used continually for frequent accidents or constant leakage	3–urge incontinence at least once a day

WHERE: 1, 2 AND 5 ARE DETERMINED BY PATIENT HISTORY, 3 BY PHYSICAL EXAMINATION OF BLADDER NECK DURING COUGH AND VALSALVA MANEUVER, AND 4 RELIES ON PATIENT REPORTED USE OF PADS OR DEVICES FOR

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COMMITTEE 12

SURGERY FOR NEUROLOGICAL URINARY INCONTINENCE

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Sekido, Noritoshi (Japan)
Stoffel, John (United States)
Trigo Rocha, Flavio (Brazil)

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ABBREVIATIONS

AD	Autonomic dysreflexia
AUS	Artificial urinary sphincter
BCI	Bladder contractility index
BoNT/A	Botulinum neurotoxin type A
BOOI	Bladder outlet obstruction index
DSD	Detrusor-sphincter dyssynergia
EAU	European Association of Urology
EMDA	Electromotive drug administration
FDA	Food and Drug Administration
GR	Grade of recommendation
IC/BPS	Interstitial cystitis / bladder pain syndrome
ICI	International Consultation on Incontinence
ICUD	International Consultation on Urological Diseases
IIQ-7	Incontinence Impact Questionaire-7
IPSS	International Prostate Symptom Score
I-QOL	Incontinence quality of life (questionnaire)
LE	Level of evidence
MeSH	Medical Subject Headings
MMC	Myelomeningocele
MS	Multiple sclerosis
MSA	Multiple system atrophy
NIDRR	National Institute on Disability and Rehabilitation Research
NLUTD	Neurogenic lower urinary tract dysfunction
OAB	overactive bladder
PD	Parkinson's disease
Pdetmax	Maximum detrusor pressure
PdetQmax	Maximum detrusor pressure during maximum flow rate
PVR	Post-void residual
QOL	Quality of life
RCT	Randomised controlled trial
SADF	Sacral deafferentation
SARS	Sacral anterior root simulation
SCI	Spinal cord injury
SNM	Sacral neuromodulation
TD	Transdermal
TURP	Transurethral resection of the prostate
UDI-6	Urinary Distress Inventory-6
UTI	Urinary tract infection
VUR	Vesico-ureteral reflux

I. INTRODUCTION

There was no independent chapter dealing with surgery for neurological urinary incontinence in previous International Consultation on Incontinence (ICI) reports, but the topic was covered partly in the very broad chapter on "Neurologic urinary and faecal incontinence". The structure of this newly implemented chapter has been developed and agreed by the chapter authors using the Delphi method. The chapter fully focus on neurological patients and complements information provided for the non-neurological population in other ICI chapters.

Due to the complex, still not fully understood multilevel control of the lower urinary tract, many neurological disorders such as multiple sclerosis (MS), Parkinson's disease (PD), stroke, spinal cord injury (SCI), spina bifida, diabetic neuropathy, Alzheimer's disease, etc. frequently result in neurogenic lower urinary tract dysfunction (NLUTD). The site and nature of the lesion in the neurological axis determine the type of lower urinary tract dysfunction which is reflected in the patient's symptoms (Figure 1) (1).

Little has changed in terms of the description of the different types of lower urinary tract and pelvic floor dysfunction that occur with specific neurological disorders since the last edition (6th edition, 2017) of the consultation. For a more detailed description, the reader is referred to pages 1093-1308 of the previous edition.

The aims of the neuro-urological management are to preserve upper urinary tract function, to control urinary tract infection, to improve quality of life, and to maintain a low-pressure bladder that is both continent and capable of emptying completely (1-4). These goals are ideally achieved without an indwelling catheter or a stoma, and in a manner that is socially and vocationally acceptable to the patient, whilst avoiding complications such as recurrent urinary tract infections, urethral strictures, calculus disease, hydronephrosis, and renal failure.

In daily practice, it is straightforward to base the neuro-urological management on the clinical and urodynamic dysfunction pattern to determine the appropriate therapeutic strategy to preserve both upper and lower urinary tract function, and to achieve or maintain urinary continence. In patients with detrusor overactivity, the therapeutic concept is to convert the overactive into a normoactive or underactive detrusor. Although antimuscarinics are the pharmacological treatment of choice, they have limited effectiveness and many patients discontinue their use because of adverse events. Beta-3 adrenergic agonists have recently been introduced as an alternative to antimuscarinics for treating the non-neurogenic overactive bladder, but research into its application in the neuro-urological patients is still limited. For refractory neurogenic detrusor overactivity, intradetrusor onabotulinumtoxinA injections are a highly effective, minimally invasive, and generally well-tolerated treatment that improves health-related quality of life. In the case of failed onabotulinumtoxinA treatment, augmentation cystoplasty is an established treatment option, but requires abdominal surgery with interposition of an intestinal segment (usually ileum) into the bladder and/or partial replacement of bladder by an intestinal substitute. In highly selected patients, cystectomy with continent or incontinent urinary diversion becomes necessary as a salvage procedure.

In patients with an under-active/acontractile detrusor and/or with detrusor-sphincter dyssynergia (DSD), intermittent (self-)catheterization is recommended to assist bladder emptying. Passive voiding by abdominal straining (Valsalva manoeuvre) or, particularly, by suprapubic downwards compression of the lower abdomen (Credé manoeuvre) is not recommended since it creates un-physiological and high intravesical pressure which puts the upper urinary tract at risk and causes compression of the urethra, i.e., a functional obstruction resulting in an inefficient emptying. Nevertheless, some patients are not able and/or not willing to perform intermittent self-catheterization and therefore an indwelling transurethral or suprapubic catheter is potentially the only alternative.

In patients with refractory neurogenic detrusor overactivity and/or neurogenic voiding dysfunction, sacral neuromodulation may be a valuable treatment option. However, the evidence is limited, and it is unclear which neurological patients would be most suitable.

In the case of stress urinary incontinence due to low bladder outlet resistance, electrical stimulation of the pelvic floor can help to restore urinary continence in patients with incomplete lesions. In some neurological patients, the implantation of an autologous urethral sling or an artificial urinary sphincter may become necessary. However, it needs to be considered that artificial urinary sphincters generally do not continue working indefinitely and the probability for revision surgery is high.

In conclusion, there is no uniform management strategy for neuro-urological patients and a rather individualized, patient-tailored approach aiming to achieve an optimal quality of life and to protect the upper and lower urinary tract is needed for this special patient population (1-4).

II. METHODS

1. METHODS AND LITERATURE SEARCH

A literature search was performed by the chapter authors using the Agency for Healthcare Research and Quality (AHRQ) database, BIOSIS, the Cochrane Library, Embase, MEDLINE, Science Citation Index, and Scopus to identify studies published from January 1st 1946 to June 30th 2021. Search terms included Medical Subject Headings (MeSH) and keywords for interventions and surgeries related to neurogenic lower urinary tract management. No language restrictions were applied. Studies were reviewed by chapter authors and characterized as systematic reviews and meta-analysis of randomised controlled trials (RCTs), RCTs, non-randomised cohort studies, case control studies, case series, and expert opinion. Levels of evidence and grades of recommendation were determined according to the International Consultation on Urological Diseases (ICUD) system which can be mapped to the Oxford system (5).

2. LEVEL OF EVIDENCE (LE)

LE 1: Meta-analysis of trials or a good quality RCTs

LE 2: Lower quality RCTs or meta-analysis of good quality prospective studies

LE 3: Good quality retrospective and case series studies

LE 4: Expert opinion

3. GRADE OF RECOMMENDATION (GR)

GR A: Assigned to LE 1 unless dangerous, unethical, or prohibitively expensive

GR B: Assigned to LE 2 and 3 or majority evidence from RCTs

GR C: Assigned to LE 4 or majority evidence from LE 2/3 studies or expert opinion

GR D: Assigned when no recommendation can be made

The Delphi method was used by sub-chapter authors identify expert opinion levels of evidence. The Delphi method was also used when reviewing sub-chapter recommendations by panel of additional chapter authors to finalise chapter recommendations.

III. SURGICAL TREATMENTS

1. BOTULINUM TOXIN INJECTIONS

1.1. Botulinum toxin injections into the detrusor

1.1.1. Efficacy

Ten years have passed since botulinum neurotoxin type A (BoNT/A) intradetrusor injections became the newest approved treatment for urinary incontinence in adult neurological patients with inadequate response to (or reduced tolerance of) an antimuscarinic medication (US Food and Drug Administration (FDA) approval) in the onabotulinumtoxinA (Botox®) format. Similar approval has been granted in European countries and worldwide. Several systematic reviews (6-11), meta-analyses (12-16), and RCTs (LE 1) (17-24), two active comparator-controlled trials (LE 1-2) (25, 26), four LE 2 studies (27-30), as well as numerous LE 3 studies have confirmed the efficacy of BoNT/A in the treatment of refractory neurogenic detrusor overactivity incontinence. Clinical improvement is accompanied by significant ameliorations in bladder function, as urodynamic parameters that matter in the management of neurogenic detrusor overactivity, namely maximum cystometric capacity, maximum detrusor pressure and reflex volume, gain substantial benefits (6, 7, 10, 31). Almost all studies have published on two BoNT/A preparations, onabotulinumtoxinA (Botox®) and abobotulinumtoxinA (Dysport®) (7, 8). Although both products are efficacious in neurogenic detrusor overactivity, onabotulinumtoxinA has been more comprehensively studied than abobotulinumtoxinA (7). Two LE 1 studies have been published reporting abobotulinumtoxinA (23, 28). The two formats are not interchangeable and there is scarce data on direct comparisons for dose, efficacy and safety, at least in urological indications. A retrospective case-control study concluded that intradetrusor injections of abobotulinumtoxinA 750 units provided better outcomes than injections of onabotulinumtoxinA 200 units in patients with neurogenic detrusor overactivity. The authors found similar success rates of abobotulinumtoxinA 750 units and onabotulinumtoxinA 300 units but the interval between injections tended to be longer with onabotulinumtoxinA 300 units (32). An LE 3 study suggests that onabotulinumtoxinA may be more efficacious than a novel BoNT/A preparation, Prosigne® (Chinese botulinum toxin serotype A), in the treatment of refractory neurogenic detrusor overactivity (33).

The mean duration of efficacy of a single injection is 6-16 months for onabotulinumtoxinA and 5-12 months for abobotulinumtoxinA (7). The FDA regulatory trials (275 and 416 patients, respectively) demonstrated a mean duration of effect of 37-42 weeks for onabotulinumtoxinA compared to 13 weeks for placebo (19, 21). Complete continence was achieved in 36-38% and 40-41% respectively with the 200 units and 300 units doses of onabotulinumtoxinA as opposed to 7.6-10% with placebo. Interestingly, significantly higher post-treatment continence rates have been reported in single-centre studies with both preparations (a mean 71% with onabotulinumtoxinA and 65% with abobotulinumtoxinA) (7). Similarly, reduction in the number of daily leaks was significantly superior in LE 3 compared to LE 1&2 studies (80% versus 63%, p=0.01) (8), but the majority of LE 3 studies had used 300 units onabotulinumtoxinA. Several retrospective studies (30, 34-44) and a single prospective trial (45) now attest to the sustained efficacy of repeat treatment sessions with either of the two formulations. In prospectively followed-up patients opting for repeat injections, the median duration

of effect was ≥9 months, with one in four patients enjoying an even more lasting effect of at least one year (45).

The concomitant use of antimuscarinics does not appear to provide additional benefit (46), although this needs to be confirmed in specifically-designed studies. In those taking antimuscarinics, onabotulinumtoxinA initially reduces the dose of antimuscarinics needed, but this tends to increase again at longer follow-up (47, 48). A head-to-head comparison between onabotulinumtoxinA 300 units and oxybutynin 5mg transdermal (TD) in a small RCT of neurologically stable, self-catheterising patients with SCI showed clear superior improvements in the number of incontinence episodes, maximum cystometric capacity, maximum detrusor pressure, bladder compliance and quality of life in the toxin group (all p<0.001 except for p=0.006 for bladder compliance) (26). However, all patients had been on oral antimuscarinics before the study, and it is not clarified whether they had oral oxybutynin as first treatment in the past (since this was the treatment of choice in the country of origin). This may be reflected in the 10-fold increased probability of complete-dry rates (60% with onabotulinumtoxinA as opposed to only 6% with oxybutynin).

Earlier systematic reviews and meta-analyses reported failure rates of 5-25% for onabotulinumtoxinA and 10-32% for abobotulinumtoxinA (7). Clinical predictors of success/failure in neurogenic detrusor overactivity are increasingly being investigated. A study of patients with SCI proposed that the level of injury may be important as patients with thoracic and lumbar injury had better clinical and urodynamic outcomes compared to cervical injury patients (49). A longer duration of MS has been proposed as a predicting factor for treatment failure (14) (LE 3). In PD patients, a lower pre-operative post-void residual (PVR) and a lower maximum detrusor pressure during maximum flow rate (PdetQmax) were associated with treatment success, while in male patients both the bladder outlet obstruction index (BOOI) and the bladder contractility index (BCI) were associated with treatment failure. Also, a higher pre-treatment PVR was associated with increased risk of post-injection need for intermittent catheterisation (50). The evidence linking treatment failure with the formation of neutralizing BoNT/A antibodies has been conflicting; a wide range of antibody formation rates following treatment has been reported (0-35%) (51-54). A small, mid-term, controlled study in children (LE 1-2) found no association between antibody formation and treatment failure, but reported an increased rate of antibody formation in those receiving repeat versus single injections (71% versus 38%) (55) up to 4 months post treatment. In the long-term, antibody titres returned to control levels. The long-term extension study of the registrational RCTs for onabotulinumtoxinA found a very low percentage of neutralizing antibodies development (8/381 patients, 2.1%) (56). The low number of patients did not allow for clinical associations, but the median time between injections in patients who developed antibodies was 5 months, less than the study average of 9 months. By contrast, a large retrospective study reviewing 2'700 injections in 414 patients found a correlation between neutralizing antibody formation and the duration of BoNT/A therapy (p=0.015), the mean number of BoNT/A injections (p=0.011) and the time interval between BoNT/A injections (<7 months, p=0.022). Significant differences were also seen in urodynamic parameters where the formation of antibodies was seen more commonly in patients with lower post-treatment values of maximum cystometric capacity (<225 mL, p=0.038) and higher detrusor pressures (>45 cmH2O, p=0.040) (57). Patient-related factors also affect adherence to treatment; in a long-term study with a mean 12-year follow-up, 21% of patients discontinued treatment due to inadequate efficacy, but another 19% opted for other treatments (antimuscarinics, sacral neuromodulation) despite the toxin's efficacy (44). In another study, only 59.3% of SCI patients were satisfied with repeat treatments and only 20% continued after a fourth injection, with 33.9% reporting inadequate efficacy and 6.8% discontinuing due to adverse events (43). More recent studies have examined long-term continuation rates up to 10 and 15 years after the first injection. A Danish study of SCI patients reported 59% (95% CI 50.0–67.8) probability of continuing treatments after 5 years and 50% (95% CI 40.1–59.3) after 10 years. Younger patients (31–50 years old) were more likely to continue treatment compared with those aged >50 years (p=0.008) (58). Another mixed population (SCI and MS patients) 10-year study with a mean follow-up of approximately 7 years and a mean of 9 injections per patient reported treatment failure rate of 26% with discontinuation occurring after a mean 76 months (59). Finally, in a 15-year study, occasional or consecutive failures were seen in 46.6% of patients (60). In another study of long-term outcomes in patients with neurogenic detrusor overactivity the failure rates were 12.6% after 3 years, 22.2% after 5 years and 28.9% after 7 years (61). The study proposed that the presence of pre-treatment urinary incontinence, higher maximum detrusor pressure, a higher number of febrile urinary tract infections (UTIs) and decreased bladder compliance were related with a higher probability for treatment failure.

Nevertheless, in treatment failures toxin switch could be more effective than re-injection with the same toxin (51.7% versus 24.1%). Patients treated with a switch from abobotulinumtoxinA to onabotulinumtoxinA and those treated with a switch from onabotulinumtoxinA to abobotulinumtoxinA had similar success rates (52.9% versus 50%) (62).

1.1.2. Disease-specific outcomes

The majority of the studies involved participants with neurogenic lower urinary tract dysfunction due to SCI or MS, often mixed, while smaller case series investigated efficacy in patients with PD, multiple system atrophy or cerebrovascular accident (63-67) (50, 68, 69). Comparisons of efficacy between neurological subpopulations are generally lacking, although a small LE 3 study suggested better continence outcomes and more significant improvements in maximum detrusor pressures in SCI patients compared to those with cerebrovascular accident (66). The largest RCTs which involved MS and SCI patients conclude that the toxin is highly efficacious in both subpopulations (19, 21). A lower placebo effect in the SCI subpopulation could be noted, although the studies were not designed for head-to-head comparisons. More recent studies explored the effect of lower doses (100 units onabotulinumtoxinA) in patients with MS (69) or PD (50), results are reported in the following section.

1.1.3. Doses

The FDA registration studies demonstrated a similar efficacy and adverse event profile for the 200 units and 300 units onabotulinumtoxinA doses, suggesting a plateau in the efficacy of the toxin. Similar conclusions were drawn by a smaller randomised study (30). Providing the best benefit/risk ratio, the 200 units onabotulinumtoxinA dose was recommended for the treatment of refractory neurogenic detrusor overactivity incontinence (19) (21). To date, only 2 real-life studies have investigated the effect of switching from the earlier used 300 units to the newly approved 200 units onabotulinumtoxinA (70, 71). In the former, although 94% of patients continued to experience symptomatic improvement, 25% reverted back to the original 300 units dose. Somewhat greater reductions in daytime frequency and nocturia were recorded with 200 units versus 300 units (87.5% and 81.3% respectively *versus* 75% and 75%) but lesser urgency improvements (75% versus 81). At three-year follow–up, 82% of patients who had switched to the lower dose were happy and keen to continue receiving 200 units onabotulinumtoxinA

(70). In the latter, no significant differences were found between the 2 doses in urodynamic parameters, proportion of patients with incontinence, daily pads number, frequency of bladder emptying or in the use of concurrent neurogenic detrusor overactivity medication (71). A LE 2 study suggested a trend towards better clinical and urodynamic improvements with 750 units as opposed to 500 units abobotulinumtoxinA (51). Other, non-randomised and inadequately powered studies (LE 3) (27, 28, 72) could not identify a clear dose-response for higher doses of abobotulinumtoxinA, although 1000 units abobotulinumtoxinA might produce a beneficial effect of greater duration than that with 500 units (28).

Novel data exists on lower doses. Following a pilot LE 3-4 study suggesting that 100 units onabotulinumtoxinA could be effective in MS patients and minimize unfavourable side-effects, particularly the need for intermittent catheterisation (67), a randomised, double-blind, placebo-controlled phase III study in non-catheterising patients with MS demonstrated significantly greater improvements in urinary incontinence episodes, urodynamic parameters and quality of life in patients who received active treatment. Complete cure of urinary incontinence was achieved in 53.0% of onabotulinumtoxinA-treated patients as opposed to only 10.3% of the placebo arm. Intermittent catheterization rates were 15.2% for onabotulinumtoxinA compared to 2.6% for placebo, and these were lower than previously reported with onabotulinumtoxinA 200 units (73). A LE 1 dose-response study confirms a more significant clinical benefit of the 200 units dose as opposed to the 50 units and 100 units doses of onabotulinumtoxinA in patients with SCI (22). The largest to-date study on PD patients used 100 units of onabotulinumtoxinA in 24 patients and achieved a subjective improvement in 79.2% but complete resolution of incontinence in only 29.1%. Despite the lower dose used, the post-void residual increased significantly (from 17.6 to 125.3 mL, $p<0.001$) and 12.5% of the participants required intermittent catheterisation after the 1st injection. The overall incidence of intermittent catheterisation was 10.2% including repeat injections (50). These results are contradicting earlier reports of preserved micturition with either 100 units (65) or 200 units (63, 68) onabotulinumtoxinA in smaller case series in which post-void residual increased but did result in the need for post-treatment intermittent catheterisation.

1.1.4. Effect on quality of life (QOL)

Both preparations have been shown to improve patients' QOL in RCTs. The Incontinence QOL (I-QOL) questionnaire has been used in the majority of LE 1 studies. Patients with neurogenic detrusor overactivity incontinence receiving a single injection of 500 units abobotulinumtoxinA, diluted in 25 mL saline and injected into 25 injection sites, had a more significant change in clinical, QOL and urodynamic parameters when compared to placebo at 26 weeks, in addition to reduced use of anticholinergics (18). Similarly, 200 units and 300 units onabotulinumtoxinA administered into 30 injection sites improved QOL scores significantly more than placebo in all LE 1 studies (19-21, 74-76). Moreover, onabotulinumtoxinA-treated patients achieve their treatment goals at significantly higher proportion than placebo-treated patients (LE 1) (77). Fully published data on QOL following repeat treatments is sparse; in a 3-year extension study of the registration trials, QOL improvement was sustained with repeat injections (up to six) in parallel with clinical benefits (56).

1.1.5. Administration technique

A large variance in the number and volume of injections has been described. However, in the majority of studies onabotulinumtoxinA was given at 30 injection sites (range 10–40) at a dilution of 10 units per 1mL per injection site (total volume of 30 mL, range 3–30 mL), as described in the original publication by Schurch et al. (78). The same dilution and number of injection sites was used when administering either 300 units or 200 units onabotulinumtoxinA in the registrational trials. Administration of abobotulinumtoxinA is less standardised (10–30 injection sites, total volume of 5–30 mL), but a total 30 mL given at 30 injection sites appears to be the most common again (7). The effect of these variables on outcomes has little been studied. A recent LE 1 study compared 15 to 30 injection sites (abobotulinumtoxinA 750 units or the equivalent placebo) and concluded that a reduction of injection sites does not affect efficacy (23). Urodynamic results were more robust than the clinical ones, the small sample size possibly affecting the statistics. A randomised, non-controlled study on onabotulinumtoxinA existing only in short report format (79) compared 10 to 30 injection sites (300 units onabotulinumtoxinA), and found no significant difference in number of incontinence episodes or cystometric capacity, but a significant reduction in post-procedure pain in the 10 injection-sites group. More recently, however, in a non-randomised non-controlled study of a mixed neurogenic / idiopathic detrusor overactivity population minimisation of the number of injection sites to 3-4 did not affect efficacy of the treatment as the complete continence rate was as high as 81%, and the mean duration of effect was a spectacular 34.9 weeks, comparable to earlier studies which typically used more injection sites (80). Another non-RCT using 100-300 units onabotulinumtoxinA in a mixed neurogenic / idiopathic detrusor overactivity population explored a further reduction of the injection sites to only 1-3 and reported also very satisfactory results, with 87% of the patients with neurogenic detrusor overactivity reporting subjective success of the treatment, 52% achieving complete continence and a mean duration of effect of 31 weeks (81).

The vast majority of studies reported injections into the detrusor sparing the trigone, as in the original technique (78). There is, however, now LE 1 evidence to suggest that combined detrusor and trigonal injections may produce better continence rates than detrusor injections alone, more significant improvements in incontinence episodes, symptom severity, detrusor pressures and volume at first desire to void (29, 82). In addition to these parameters, another LE 1 study found higher improvements in the mean voided volume, the percentage of patients with detrusor overactivity and the duration of first detrusor contraction in the patient group where 40 of the total 200 units onabotulinumtoxinA were injected in the trigone compared to the intradetrusor only injection group (82). There is also LE 1-2 evidence suggesting that submucosal injections are comparable in efficacy to intradetrusor injections, with the exception of voided volume (83) and detrusor compliance (84). An impressive difference was found, however, in patient satisfaction favouring the suburothelial injections (88.8% versus 64.3% of patients satisfied) (84). Furthermore, a meta-analysis found no differences in the incidence of vesico-ureteral reflux, haematuria, general weakness, bladder discomfort, increased post-void residual, and urinary tract infection between submucosal injections and intradetrusor injections (85).

Alternative delivery techniques into the bladder are being investigated, however, to date, almost exclusively in non-neurological patients (overactive bladder (OAB) and interstitial cystitis / bladder pain syndrome (IC/BPS) patients) (see review (86)). These include intravesical instillation of BoNT/A encapsulated in liposomes (87), via electromotive drug administration (EMDA) (88), TC-3 hydrogel embedding BoNT/A and low energy shock waves to promote intravesical BoNT/A delivery to the urothelium (86). In small, short-term, placebo-controlled trials (89, 90) (LE 1-2), intravesical instillation of liposomal onabotulinumtoxinA (200 units) improved micturition frequency and urgency severity scores over placebo at 4 weeks, but not urgency episodes or urgency incontinence. No urinary re-

tention episodes were reported though. However, in a placebo-controlled trial, liposomal onabotulinumtoxinA could not produce better improvements in bladder pain than placebo in patients with IC/BPS (86). The EMDA method has been tested in a pilot LE 3-4 study in children with myelomeningocele. Significant improvements were reported in maximum cystometric capacity, detrusor pressure, urinary incontinence, vesico-ureteral reflux and even faecal incontinence (91), but results need to be confirmed in controlled trials. The TC-3 hydrogel method has produced promising results in a RCT in OAB patients and in a single-arm prospective cohort study in IC/BPS patients (see review (86)). Finally, in a small case series, although histopathological findings showed that low energy shock waves help BoNTA pass through the urothelium it did not result in a significant clinical effect in IC/BPS patients (see review (86).

1.1.6. New indications in neurogenic detrusor overactivity

In patients with neurogenic vesico-ureteral reflux due to SCI, the co-administration of onabotulinumtoxinA with a bulking agent (Macroplastique) resulted in significantly higher treatment rates of vesico-ureteral reflux in the combination group, while urodynamic parameters significantly worsened in the monotherapy group, suggesting a protective role for onabotulinumtoxinA from the post-vesico-ureteral reflux treatment changes occurring in the bladder (92). In addition, in patients with long-stay catheters and refractory bladder pain and catheter bypass leakage, the majority of whom were neurological patients, intradetrusor injections of 200 units onabotulinumtoxinA achieved adequate management of symptoms in 94% of patients and a significant reduction in urine leakage in 83% of them (93). Finally, results of the ENTEROTOX study suggest that BoNT/A could be used as salvage therapy in cases of failed augmentation cystoplasty for refractory neurogenic detrusor overactivity; 58% of the study patients had a clinically significant outcome and requested re-injection, with significant improvements also in key urodynamic parameters (maximum cystometric capacity and maximum detrusor pressure) (94).

1.1.7. Safety

The treatment appears to be overall safe in currently used doses and techniques. The most common adverse event is the significant increase in PVR in patients not using intermittent catheterisation prior to treatment. In onabotulinumtoxinA placebo-controlled trials, 12-22%, 30-47%, and 42-49% of patients in the placebo, 200 units, and 300 units groups, respectively, initiated intermittent catheterisation post-treatment (19) (21). Rates of de novo intermittent catheterisation appear to be reduced after repeat treatments: in a 4-year study with up to six onabotulinumtoxinA injections, de novo intermittent catheterisation rates were 29.5, 3.4, and 6.0% (200 units), and 43.0, 15.0, and 4.8% (300 units) for treatments 1-3, respectively; de novo intermittent catheterisation rates were 0% for treatments 4-6 (56).

Although earlier studies had reported a reduced incidence of UTIs in patients with neurogenic detrusor overactivity treated with BoNT/A (39, 95, 96), recent large RCTs (19, 21) as well as systematic reviews (9) and meta-analyses (12) suggest a higher incidence of UTIs in those treated with onabotulinumtoxinA as opposed to placebo-treated patients. This might be associated with the increased rate of de novo intermittent catheterisation in the onabotulinumtoxinA-treated population. In prospective, long-term, follow-up trials UTIs remained the most common adverse event, but with no increased incidence over time (45, 56). Long-term controlled trials could clarify these apparent discrepancies. Importantly, however, there appears to be significant inconsistency regarding the definition of UTI in the BoNT/A studies, with only half (54%) using diagnostic criteria for a UTI, albeit with a wide range of definitions, most of which did not comply with either the EAU criteria or the National Institute on Disability and Rehabilitation Research (NIDRR) standards (97).

A debate regarding the role of preoperative asymptomatic bacteriuria and the need for antibiotic prophylaxis is ongoing. The treatment of asymptomatic bacteriuria in patients with neurogenic detrusor overactivity is not recommended, and it appears to be very common among patients treated with BoNT/A (38.8-73% in urine specimens taken before treatment) (44, 98). However, there is conflicting data about its association with post-BoNT/A development of UTIs; one study found it to be associated with a 16-fold risk for post-BoNT/A UTI (98) while another found no difference between those with and without asymptomatic bacteriuria (44). Both studies, however, agreed that pre-treatment asymptomatic bacteriuria was not associated with the efficacy of the treatment (98) (44). Nevertheless, as the use of peri-operative antibiotics can reduce the risk of post-BoNT/A UTIs by almost 5-fold (99) and febrile UTIs were found to be associated with treatment failure (61) it has been proposed that treatment failures should be screened for occult UTIs and that fierce UTI prevention strategies should be followed (100).

Pain/discomfort from the procedure might be an issue for patients with preserved sensation. An RCT demonstrated that an alkalinized lidocaine solution could significantly reduce the pain from the procedure compared to a lidocaine-only solution (2.37 ± 0.31 versus 4.44 ± 0.36, $p<0.01$). Pain scores were similar one hour after the procedure (24).

Haematuria, constipation and flu-like symptoms have also been described (7, 19, 21), while inclusion of trigonal injections does not appear to produce vesico-ureteral reflux (LE 2-3) (29, 101, 102). A study in SCI male patients found a post-treatment decrease in the volume of ejaculate accompanied by improvements in semen quality, sperm mobility and vitality, as well as semen culture (103). Further research is needed to confirm these results and explore whether they are due to local re-organization of autonomic function which also affects the reproductive system.

The most serious adverse event is generalized paraparesis / fatigue, which has been described in 0.005% of patients receiving onabotulinumtoxinA and in 0.026% of patients receiving abobotulinumtoxinA (7). The effect resolves spontaneously after 4-6 weeks and appears to be dose-related, with most cases reported in those patients injected with 750-1000 units abobotulinumtoxinA or 300 units onabotulinumtoxinA (21, 37, 104).

As BoNT/A studies in skeletal muscles have identified autonomic, histological and other secondary effects (105, 106), further investigation is needed on safety issues, especially after repeat injections (6). Preclinical studies provided evidence for transport of the toxin from the bladder to the central nervous system and vice versa (107, 108). A single study to-date prospectively examined distant effects post-BoNT/A bladder injection using single-fibre electromyography: One-third of the patients had findings of neuromuscular jitter post-treatment, but there was no placebo arm or pre-treatment data for comparison (109) (LE 3). Frequency and severity of autonomic dysreflexia episodes were reported to be reduced following onabotulinumtoxinA bladder injections (LE 3)(110). Other studies produced histological evidence of reduced or no additional fibrosis after one or multiple injections, including in children (111-113).

Future research should highlight the gaps in our knowledge of long-term treatment with focus on patient-reported outcomes and satisfaction, safety and tolerability issues as well as technical aspects

such as alternative techniques of application, ways to minimize post-treatment voiding dysfunction in patients who void freely and larger studies in select patient populations.

1.2. Botulinum toxin injections into the external sphincter

Sphincter injections were historically the first application of BoNT/A in the lower urinary tract (114), but there is still inadequate evidence to support its use. The most commonly injected volume is 4mL of either the onabotulinumtoxinA or the abobotulinumtoxinA preparations. Usually 100 units onabotulinumtoxinA or 150 units abobotulinumtoxinA have been delivered transperineally or transurethrally (115, 116). No direct comparison of injection techniques exists; there is low evidence (LE 4) to suggest the two delivery approaches are equally effective (115).

In a LE 1 study, the effects on DSD of botulinum toxin versus placebo was studied in 86 MS patients (117). The study employed a single transperineal injection of onabotulinumtoxinA, 100 units in 4 mL normal saline, or placebo, into the striated sphincter with electromyography guidance. The primary endpoint was PVR at 30 days. The secondary endpoints included voiding and urodynamic variables. OnabotulinumtoxinA failed to decrease PVR in this group of MS patients, although it increased voided volume and reduced pre-voiding and maximum detrusor pressures. These findings differ from those in patients with SCI and may be due to lower detrusor pressures in MS patients. A small LE 1-2 study (n=13 patients) showed a superior effect of onabotulinumtoxinA over lidocaine 0.5% injected in the urethral sphincter in MS patients (116). Another small (n=21 patients), controlled study (LE 1-2) in cerebrovascular accident patients with urethral sphincter pseudo-dyssynergia reported superior clinical efficacy in the active treatment group (91% response rate and higher improvements in QOL and symptom scores with 100 units onabotulinumtoxinA) despite highly significant urodynamic benefits noted in the control group (reduction in voiding pressures and increase in maximum flow rates) (118). In MS patients there is also LE 3 to suggest that a combination of detrusor and sphincter injections may facilitate bladder emptying (119). In children with neurogenic detrusor overactivity and DSD due to myelomeningocele there is LE 1-2 from a single study to suggest that sphincter injections additional to the detrusor injections accomplish significant improvements in post-void residuals, as well as more significant benefits in urinary incontinence, constipation, vesico-ureteral reflux and creatinine levels (120).

Since the ICI update of 2012 there have been only LE 3 studies investigating the effect of urethral BoNT/A injections in neurogenic DSD (121-126). A study in SCI patients with neurogenic detrusor overactivity and DSD compared urethral injections of 100 units onabotulinumtoxinA to intradetrusor injections of 200 units onabotulinumtoxinA depending on the main symptoms (voiding dysfunction versus neurogenic detrusor overactivity incontinence) and found less patient satisfaction in the urethral injection group (60.6% versus 77.3% in the intradetrusor injections group) as well as greater improvements in the Urinary Distress Inventory-6 (UDI-6) and Incontinence Impact Questionnaire-7 (IIQ-7) scores in the intradetrusor injection group, despite significant urodynamic benefits in both groups (121). Not unexpectedly, patients in the urethral injection group were dissatisfied due to increased degree of post-onabotulinumtoxinA incontinence whereas the intradetrusor injection group suffered higher rates of post-treatment voiding difficulty.

A multicentre study of SCI patients who received 200 units onabotulinumtoxinA into the detrusor and 100 units onabotulinumtoxinA in the urethral sphincter reported significant reduction in mean maximum detrusor pressure, maximum urethral closure pressure, duration of first detrusor contraction and DSD for up to 12-weeks post-treatment (122). Additionally, the authors claim significant improvements in the I-QOL questionnaire, voided volume, urinary incontinence episodes and complete dryness which were sustained 16 weeks post-treatment.

Another 3 studies investigated predictive factors of successful treatment of DSD by urethral BoNT/A injections. In all 3 studies, 100 units onabotulinumtoxinA were injected in the urethral sphincter. No robust video-urodynamic factors could be identified as predictors of successful treatment except for an open bladder neck during voiding in a cohort of 95 patients with non-neurogenic or neurogenic detrusor underactivity (16). A lower efficacy was reported for the neurological population, but with similar duration of effect of a little over 7 months. This result contradicted another study by the same group of researchers which reported significantly shorter duration of effect in the neurological population (9.55 ± 4.18 versus 7.44 ± 2.91 months, p=0.033). This study found that a significantly smaller volume at first sensation of filling (p=0.046), greater detrusor pressure (p=0.027), higher maximum flow rate (p=0.017), and smaller post-void residual (p=0.006) were predictors of efficacy, together with an open bladder neck upon video-urodynamics (85). Another cohort of SCI patients found that poor outcome was related to the presence of concomitant bladder neck dyssynergia, the absence of detrusor contraction in standard cystometry, the severity of DSD, and the pre-treatment PVR (125). Finally, in another mixed patient cohort higher maximum flow rates and smaller PVR were predictive of successful results in patients with neurogenic voiding dysfunction (126). The efficacy rate was reported to be about 60%.

Overall, the highest level of evidence for studies exploring the efficacy of urethral sphincter BoNT/A injections in treating neurogenic DSD remains within RCTs or quasi-RCTs in comparison to placebo or active comparators which were considered to be of limited quality due to the small sample sizes, the heterogeneity in the protocols, and with a high risk of bias (127). Thus, results of this Cochrane review still stand that intraurethral BoNT/A injections improve some urodynamic parameters at 30 days post-injection but future high-quality research is needed to establish the efficacy and the optimal parameters for a successful treatment outcome in neurogenic DSD.

2. INVASIVE NEUROMODULATION / NEUROSTIMULATION

2.1. Sacral anterior root stimulation (SARS) combined with dorsal rhizotomy

Neurostimulation of the sacral anterior roots in humans, was introduced by Giles S. Brindley from London, UK, in the early 1970s. He aimed at restoring bladder emptying in patients with NLUTD due to SCI by electrical stimulation of the sacral nerves (S2-S4). By selective stimulation of these sacral roots, micturition was induced by detrusor contraction. Together with the company Finetech Ltd a silicon embedded implant was developed that consisted of an array of electrodes, connected to a subcutaneous receiver that could be stimulated by electromagnetic transmission from an external transmitter (128, 129). The first implantation was performed in a human in 1976 (130). However, at that moment the treatment did not address the problem of detrusor contractions and incontinence between episodes of micturition. Later, Brindley together with Sauerwein from Bad Wildungen, Germany, combined the implantation of the electrodes with posterior rhizotomies at the S2-S4 levels. These rhizotomies result in sacral deafferentation (SDAF) as the sacral

reflex arch is interrupted hence abolishing the reflex contractions of the detrusor at low filling. Hence urinary incontinence is abolished and bladder capacity and compliance significantly increased. The combination of sacral anterior root stimulation using the Brindley stimulator and posterior rhizotomy has become known as the Brindley procedure (130, 131). The mechanism of action is based on the so-called “post-stimulus voiding” which is characterized by an intermittent stimulation pattern that allows the urethral sphincter to relax while the detrusor pressure remains elevated. The result is an intermittent flow pattern until complete bladder emptying.

2.1.1. Indications

Suprasacral lesions are typically characterized by the presence of detrusor overactivity and DSD and are associated with high risk for upper urinary tract deterioration (130). For those patients who do not respond adequately to conservative treatments of the detrusor overactivity (antimuscarinics or onabotulinumtoxinA), sacral deafferentation eventually in combination with the implantation of a sacral anterior root stimulator may be a suitable alternative to other irreversible procedures such as augmentation cystoplasty or urinary diversion (4).

From a purely medical perspective, SDAF is indicated in patients with or at risk of:

- Autonomic dysreflexia
- Renal failure
- Urinary incontinence
- Recurrent UTIs
- Difficult or traumatic bladder catheterization
- Failure of conservative bladder management with persistent low compliance
- Failure of conservative therapy because of unacceptable side effects

From the point of view of bladder function the requirements for SDAF and SARS are:

- Motor and sensory complete SCI (informed consent should be obtained as loss of sensation in the segments S2-S5 will occur)
- Patients with SCI can be candidates if the lesion is non-progressive or very slowly progressive
- Intact spinal reflex arcs in the S2-S4 segments
- Intact detrusor function (no organic fixed fibrosis, no acontractility because of overdistension)
- Security of a long term therapeutic program for the SCI patient
- Support and understanding of family and friends given the irreversible nature of the rhizotomies with in male patients loss of reflex erections (132)

Advantages of dorsal rhizotomies include: detrusor areflexia which provides continence, significant increase in bladder capacity and compliance, correction of DSD and abolishment of autonomic dysreflexic attacks triggered by the bladder and rectum. However, section of all six of the S2-S4 posterior roots abolishes reflex erection. Also, genital sensation and reflex ejaculation is lost if these were present, and the patient has to be informed of these consequences.

SDAF and SARS are contraindicated for patients with the following characteristics:

- Poor or inadequate bladder reflexes
- Active or recurrent pressure ulcers
- Current sepsis
- Implanted cardiac pacemaker
- Not fully matured skeletal structure

Different approaches have been described to perform the rhizotomies and the electrode implant, the main ones being the intradural and extradural technique, each of them has its pros and cons. An increased risk of cerebrospinal fluid fistula and an increased risk of incomplete rhizotomies and motor nerve injury is described for the intradural and extradural technique, respectively. However, some authors have recently reported similar results with the extradural approach without comparatively higher rates of motor injury or incomplete rhizotomies (133). Combined approaches (intradural rhizotomies and extradural electrode placement) have been reported but are not frequently used.

2.1.2. Results

Since this surgical technique includes rhizotomies of the dorsal roots S2-S4 (SDAF) plus the implantation of an electric stimulator for the ventral roots S2 to S4 (SARS), both storage and voiding disorders are treated with one single procedure: the first part of the operation (SDAF) produces sensory deafferentation by interruption of the sacral reflex arch which suppresses detrusor overactivity and DSD thus achieving low bladder pressure and also decreases autonomic dysreflexia (134). With the second part of the surgery (SARS), patients regain physiological urination, mediated by a stimulated detrusor contraction, thereby eliminating urethral catheterization, the use of antimuscarinics and prophylactic antibiotics. With long term follow-up a decrease of the number of UTIs and associated complications has been observed, reducing the number of hospitalizations and the associated costs (135). This outcome has a relevant positive impact on the QOL of the operated patients (136).

During the last 40 years more than 2’000 patients were implanted (137). Many groups have since reported their experiences with the Brindley procedure some of them with a follow-up of up to 12 years. The treatment was found to be able to achieve a continence rate of 57% to 100%, increase the bladder capacity by 122% to 375%, reduction of PVR <50 mL in 70% to 91% of patients, and decrease the incidence of UTIs (132, 133, 138, 139).

Bladder compliance and storage detrusor pressure have been reported to be improved with SDAF/SARS (139, 140). Krebs et al compared pre- and post-SDAF/SARS urodynamic parameters and found that detrusor compliance and storage detrusor pressure values at short-term follow-up after surgery were greater than 20 cmH2O and smaller than 40 cmH2O, respectively. This indicates a return to physiological values. Furthermore, they found an increasing and decreasing tendency in bladder compliance and storage detrusor pressure, respectively, during the long-term follow-up period (141). This indicates that further improvement of the urodynamic parameters seems to continue after SDAF.

The stimulation of the anterior root especially of S2 may facilitate erection and the stimulation can maintain the erections, which otherwise would be of short duration. Vignes et al. (142) informs that although the device is effective for erections in 60% of patients, it is only used for this purpose by 30% of them. Its utility is better evidenced in the initial period (as for bowel function) but in the longer term the stimulation is rarely used.

Castaño et al reported that 88% of patients use the device to assist in bowel function, while other authors indicate that the neurostimulator is used in up to 91% of patients for bowel evacuation (133).

In a cross-sectional study in which 93 patients with the Brindley stimulator were compared with a matched control group of 70 pa-

tients, the implanted patient group had a significantly better Specific Impact of Urinary Problems score, a better general QOL index (Qualiveen), a better continence rate, and fewer UTIs, even for those patients who for some reason no longer used the neurostimulator. These patients continued to have the benefits of the rhizotomies as the quality of life and clinical parameters were better (136).

With regard to complications, Brindley et al. (131) reviewed the outcome of 50 patients, and reported 7 cases of pain over the sacral dermatomes during micturition with the neurostimulator. In 2 patients, the pain was severe and they abandoned the use of the device. The potential risk of pain also underlies the principle that the procedure should be performed only in patients with complete SCI or in some well selected incomplete SCI patients.

The damage of the motor roots is one of the most serious complications since it puts at risk the effect of stimulation. Brindley reported any grade of anterior root damage in 23 of 50 patients (131), although most recovered by 1 year. Cerebrospinal fluid leaks also occurred in 14 patients. To minimize cerebrospinal fluid leaks, Brindley and Sauerwein (143) also attempted extradural implantation, especially in patients with previous arachnoiditis, which may pose significant technical difficulties for intrathecal procedures. The trade-off is an increased risk of anterior nerve root damage. More recently, a study comprising 104 patients who had undergone extradural implantation reported significant improvement in bladder capacity, urinary incontinence episodes and UTIs without any increase in the incidence of anterior root damage (133).

2.2. Sacral neuromodulation

Sacral neuromodulation (SNM) has become a widely adopted treatment modality for non-neurogenic urgency urinary incontinence, urgency-frequency syndrome, non-obstructive urinary retention, and faecal incontinence since its FDA approval in 1997, 1999, 1999, and 2011 (144). However, the efficacy of SNM in patients with NLUTD remains unclear. It is important to mention that RCTs in the neurological population are still lacking (145), that means the level of evidence of the published studies is low, the risk of bias is significant, the sample sizes are small, the patient population is heterogenous, and there are relevant variations in terms of outcome parameters as well as technique.

SNM mechanism of action relay on the effects of electrical stimulation on afferent and efferent nerve fibres connecting the bladder and pelvic floor to spinal interneurons and central nervous system (146). This is attained by the permanent or intermittent electrical excitatory impulse at a central or peripheral somatic sensitive nerve in order to restore the normal afferent signal from the detrusor to spinal cord by restoring the balance between the excitatory and inhibitory control (147). Since SNM influences sacral afferents and modulates spinal cord reflexes and brain centres which control the lower urinary tract, this therapy is usually indicated for patients whose neural system is intact or only partially damaged (148).

Van Ophoven et al. (145) updated the systematic review and meta-analysis by Kessler et al. (149) and evaluated SNM for NLUTD over 20 years' experience. Forty-seven studies were included in the systematic review and twenty-one studies (comprising a total of 887 patients) in the meta-analysis of SNM testing. The pooled success rate of SNM testing was 66.2% (95% CI 56.9–74.4). Twenty-four studies with a total of 428 patients were included in the meta-analysis of permanent SNM. The success rate of pooled permanent SNM was 84.2% (95% CI 77.8–89.0). The most common adverse events were loss of effectiveness, infection, pain at implant site, and lead migration with adverse event rates of 4.7%, 3.6%, 3.2%, and 3.2%, respectively.

In patients with SCI undergoing SNM for NLUTD, another recent meta-analysis shows success rates of 46% and 76% for the test and permanent phases, respectively (150). Recommendations from the ICS best practice statement recommends SNM limited to AIS D and E and an additional benefit in the outcomes if the presentation is upper motor neuron injury since this one does not affect afferents integrity and contractility of the detrusor (147).

According to a review by Puccini et al. the success rate of SNM testing was around 60%, with a final subjective cure rate of 45% and a global satisfaction of 85% in patients with MS (151) being more successful in patients with neurogenic detrusor overactivity and DSD rather than an underactive detrusor. Recent publications reported not very encouraging results of SNM for patients with PD and spina bifida (144).

SNM is a safe and reversible minimally invasive procedure with a low risk of nerve damage or surgical site infection (152). Most typical complications are primary failure, pain, discomfort, and lead migration. Barriers for applying this therapy in NLUTD were mainly related to magnetic resonance imaging incompatibility, size of the implantable pulse generator, and battery depletion. Newer devices are up to 80% smaller than previous models, they are also rechargeable with a longer battery life which can last up to 15 years. Additionally there are compatible with magnetic resonance imaging (153). However, the characteristics of ideal patients for a rechargeable device are still unclear since they patients require manual dexterity to manipulate and recharge the device for optimal performance. Therefore, an ideal patient selection is crucial.

2.3. Other invasive neuromodulation techniques

Other invasive neuromodulation techniques such as epidural spinal cord stimulation (154, 155), deep brain stimulation (156), and invasive pudendal (157) and tibial (158, 159) nerve stimulation may have beneficial effects on the lower urinary tract but specifically designed high-level evidence studies are needed in neuro-urological patients.

3. URETHRAL, PROSTATIC AND BLADDER NECK SURGERY

3.1. Urethral / prostatic stents

In 1990, Shaw *et al.* proposed using a wire mesh stent (Urolume) to treat patients with spinal injury presenting with DSD (160) (LE 3). Since then, various stents have been used. Table 1 lists the types of stents used for DSD, according to classification criteria (161, 162). They can be placed in the prostatic urethra, through the striated sphincter or more distal in the sub-sphincteric urethra.

Table 1. Stents used in neurogenic DSD

Temporary stents					
Stent	**Expansion method**	**Size**		**Material**	**Maximal duration (months)**
		Calibre (French)	**Length (mm)**		
Not specific to the striated sphincter First-generation					
Urospiral (163)	Non expandable	21	40-80	Stainless steel	<12
IUC (164)	Non expandable	16-18	25-80	Polyurethane	<6
Second-generation					
Memocath (165)	Heat	22/34	30-70	Nitinol	<36
Specific to the striated sphincter					
Diabolo (166)	Self-expansion	18	38	Medical steel	>12
Permanent stents					
Stent	**Expansion method**	**Size**		**Material**	
		Calibre (French)	**Length (mm)**		
Urolume Wallstent (167)	Self-expansion	42	20-40	Steel alloy	
Titan (168)	Balloon	43	19-58	Titanium	
Memotherm (169)	Heat	42	20-80	Nitinol	
Ultraflex (170)	Self-expansion	42	20-50	Nitinol	

3.1.1. Temporary prosthetic sphincterotomy

Temporary stents make it possible to carry out a therapeutic test to check the feasibility of condom catheter use, check that placing a foreign body in the urethra does not induce autonomic dysreflexia and ensure the patient accepts the mode of micturition. Moreover, during this testing period, it is possible to study how the bladder empties in the seated position, and assess the necessity of additional treatment for smooth muscle sphincter dyssynergia at the level of the bladder neck. As this treatment is simple and reversible, it is possible to propose it very early to the patients, rendering the patient autonomous with regard to carer-assisted catheterization, if this were the prior mode of micturition and leaving the possibility to discuss any fertility and sexual issues, and considering the possibilities of preserving sperm. For patients with SCI, early temporary stent placement (within six months of trauma) theoretically has the added advantage of waiting for recovery of upper limb motility to enable intermittent catheterisation. After using a temporary stent, the patient may choose the mode of bladder emptying, i.e. return to the former state, change to another temporary stent, replace it by a permanent stent, or choose surgical sphincterotomy.

By definition, temporary stents should be self-retaining, easy to remove and must not epithelialize. Only the temporary stent Diabolo (166) is specific for the external urethral sphincter. The results of two types of temporary stenting (test) for incontinence have been published in the same series (171) (LE 3). In a retrospective study of 147 patients, the authors demonstrated a significant effect on incontinence throughout the mean 10-month test period, with very low morbidity (15%). The temporary stents were removed easily from all patients without sequelae. After this period, 62.6% of patients chose permanent sphincterotomy, usually by means of a permanent stent. Memokath is another device that has been studied in neurological patients (172-177) (LE 3-4). Several authors report complications (32-100%) using this stent, which seems to induce a lot of bladder stones and is quite difficult to remove, especially if it is left longer than 18 months. When used as second-line treatment following failed sphincterotomy, Memokath successfully reduced PVR, but failed to improve urodynamic parameters including bladder capacity, detrusor leak point pressure, bladder compliance, and maximum detrusor pressure (172).

3.1.2. Permanent prosthetic sphincterotomy

Permanent stents are designed to integrate with the urethral wall (178). They resist the striated sphincter and prevent its closing during reflex contraction. They can be removed if necessary, or at the patient's request, with recovery of striated sphincter contraction (179, 180). Permanent stents are made of biocompatible materials such as nitinol (a nickel and titanium alloy) and titanium. They usually consist of a mesh comprising a single thread (e.g. Urolume) or several threads (e.g. Ultraflex). None of the stents are specifically adapted for the urethral striated sphincter. Three have been reported for treating neurological patients with DSD: Urolume, Memotherm and Ultraflex. All can be placed under local anaesthesia. Table 2 summarizes the principal series published on these devices. Only Urolume was studied according to strict prospective criteria (181) (LE 1-2). Using stringent clinical and statistical methods, they classified the stent as LE 1 for effectiveness and morbidity in DSD with a 5-year follow-up. 160 patients with SCI (mean age 36.3 years) in 15 North American centres, were treated prospectively with Urolume for DSD. Urodynamic parameters for voiding pressure, PVR and functional bladder capacity were measured before treatment and then annually up to 5 years afterwards. Mean voiding pressure, the primary criterion, was significantly lower 5 years after stenting. PVR decreased significantly and was sustained after 5 years. Mean bladder capacity remained constant. Hydronephrosis, suffered by 28 patients before surgery, disappeared in 22 (78.6%) and was improved in the remaining. Autonomic dysreflexia resolved in 70% of cases. The indwelling catheters could be removed in 63

Table 2. Main series of permanent prosthetic sphincterotomy

	Stent	Year	LE	n	Efficacy (%)	Mean follow-up (Months)	Migration (%)	Complications
Pannek et al. 2011 (172)	Memokath	2011	3	22	78	10	18	32
Mehta et al. (175)	Memokath	2006	3	29	89	21	23	42
Hamid et al. (187)	Memokath	2003	3	25	89	20	28	48
Vaidyanathan et al. 2002 (177)	Memokath	2002	4	10	90	20	10	100
Low et al. 1998 (174)	Memokath	1998	3	24	54	16	33	38
Shah et al. 1997 (176)	Memokath	1997	3	14	78	24	NA	NA
Game et al. 2007 (171)	Nissenkorn/Diabolo	2007	3	147	NR	10	29	30
Denys et al. 2004 (170)	Ultraflex	2004	3	47	81	19	22	15
Juan Garcia et al. 1999 (169)	Memotherm	1999	3	24	100	15	16	17
Rivas et al. 1994 (188)	Urolume versus sphincterotomy	1994	2	46	79	16	15	0
Chancellor et al. 1999 (181)	Urolume	1999	2	160	84	60	28	20
Chancellor et al. 1999 (189)	Urolume versus sphincterotomy	1999	1	54	81	24	9	0
Hamid et al. 2003 (173)	Urolume	2003	3	12	77	144	NR	16
Abdul-Rahman et al. 2010 (186)	Urolume	2010	3	12	80	144	0	80

of the 86 (84.9%) patients catheterized before surgery. The percentage of positive urine cultures remained unchanged after stenting. No cases of peri- or post-operative bleeding, soft tissue erosion or bladder lithiasis were observed during the study. Fourteen cases of prosthetic encrustation occurred; one during the first year; three during the second year; three during the third year; two during the fourth year and five in the fifth year. Urothelial reaction was reported in 44.4% of cases, but 93.3% of these were mild and none required treatment. No erectile dysfunction was reported. Stents had to be removed from 24 patients (15%), four of whom received new implants. 80% of the patients considered their situation improved by stenting, and 84% of physicians considered the treatment effective. 47 patients required supplementary treatment on the bladder neck (endoscopic incision in 20 cases). In the mid-term, prosthetic sphincterotomy using a Urolume stent appears to be satisfactory. However, the situation is not so clear over the longer-term. It is not always easy to remove the stent, especially from patients who have not been monitored regularly. Some teams report highly complex surgery for stent removal, especially in the event of associated urethral stenosis (182-185) (LE 3). A small study (n=12) following patients up to twenty years after insertion, suggests a high rate of complications, as 5/6 patients who completed the 20-year follow-up developed bladder neck dyssynergia requiring incision, 2 patients developed obstructive encrustations within the first year of insertion and another patient developed bladder cancer (186). However, in those patients who completed the 20-year follow-up, sustained significant improvements in maximum detrusor pressure and duration of detrusor contraction were recorded.

3.1.3. Prosthetic versus endoscopic sphincterotomy

Whether patients should be offered prosthetic or endoscopic sphincterotomy is not yet agreed. Endoscopic sphincterotomy is the preferred standard treatment for DSD when intermittent catheterisation cannot be performed. Two prospective studies carried out in the US in 1994 indicated that prosthetic sphincterotomy was at least as effective as standard sphincterotomy in patients with SCI, and offered advantages in terms of morbidity, duration of hospitalization, and costs (188, 190). The two studies were not randomised. Follow-up was short (mean 15 months), with a potential risk of bias, since the conclusion that external sphincter balloon dilatation is as effective as endoscopic and prosthetic sphincterotomy is not borne out by long-term outcomes (191).

A prospective, multicentre, randomised study comparing endoscopic sphincterotomy with prosthetic sphincterotomy was published in 1999 by Chancellor and Rivas, using the Urolume stent (189). Fifty-seven patients in three specialised SCI centres were included. The study concluded that prosthetic sphincterotomy was as effective as endoscopic sphincterotomy and required shorter hospitalization. Polguer et al published their experience with the Ultraflex (n=11) and Memotherm (n=11) during 56 months in patients with DSD. Complementary procedures after stenting included five stent prolongations or displacements (mean interval 7.6 months), six bladder neck incisions (12.2 months), three urethrotomies (42 months), an ten obstructions treated by laser (47.3 months). Eight patients had a change of their urinary pattern: four underwent ileal conduit diversion, one had a continent urinary diversion, one chose intermittent self-catheterisation, two were under indwelling catheterisation waiting for another treatment. Stent retrieval was either harmful or impossible for four of them. Three patients were free of complementary procedures. They conclude that nitinol urethral stent was an effective treatment initially. However, after years urethral stenosis and hypertrophic growth of the urethral mucosa usually require extra endoscopic procedures (0.31 per patient per year). They recommend yearly endoscopic follow-up (192).

A recent study in 41 male patients with neurogenic DSD identified maximum detrusor pressure as a predictor of the success of either

prosthetic or endoscopic sphincterotomy. Twenty-six patients had a sphincteric stent placement (Memokath) and 15 had endoscopic sphincterotomy. The combined success rate was 76%. Significantly higher mean preoperative maximum detrusor pressure was recorded in patients with immediate successful outcomes (59.6 versus 29.7 cmH_2O; p=0.002), but also at 6 months (p=0.008). The threshold of 40cmH_2O for maximum detrusor pressure was associated with even higher success rates (≥90%). The technique used (stent placement or incision) had no impact on immediate or 6-month success rates (193).

3.2. Sphincterotomy

The aim of sphincterotomy is to produce reflex micturition into a condom catheter which acts as a pressure relieve valve, thus protecting the upper urinary tract. For the last thirty years, endoscopic sphincterotomy has been the technique of choice for patients who cannot or do not want to perform intermittent catheterisation. It is invasive, irreversible and the patient has no adaptation period (194, 195) (LE 3).

Sphincterotomy recommendation supposes a diagnosis of a neurological cause of DSD that is complicated by hydronephrosis, vesico-ureteral reflux, autonomic dysreflexia or recurrent UTIs secondary to poor bladder emptying. Patients should have failed or refused intermittent catheterisation. Main contra-indications are (196, 197):

- Impossibility to retain a condom catheter. All sphincterotomy techniques (including stenting) are contra-indicated in men who cannot retain a condom catheter (hence also for women). A semi-rigid penile prosthesis can be placed to help retain the condom catheter (198) (LE 3). However, patients must be informed that there is a 20% to 30% risk of erosion and infection of the penile prosthesis for those with SCI, as opposed to only 2.7% in the general population (199, 200) (LE 3).
- Detrusor acontractility or hypocontractility. Patients with SCI and no reflex detrusor contraction during urodynamics are poor candidates for the various techniques of sphincterotomy.
- Patients who wish to father children and are candidates for vibrostimulation or electro-ejaculation and an artificial insemination program.

Emmett et al. (201) first described in 1948 cervico-prostatic incisions as endoscopic sphincterotomy in patients with SCI, but later realized that the problem lay in the striated sphincter. External sphincterotomy was performed in 1958 by Ross et al. (202). They carried out cold-blade surgery and placed a catheter (22-26 French) for tamponade, since nearly all patients required transfusion (one of the ten patients in the series died after surgery). A few attempts at surgical sphincterotomy via the perineal and subpubic myotomy routes were tried later, but due to their complexity and frequent serious complications these approaches were abandoned (203, 204). Sphincterotomy with electrocoagulation was finally found to be the best technique. Besides the conventional transurethral electrocautery sphincterotomy, Perkash first reported in 1994 the use of contact neodymium-doped yttrium aluminium garnet (Nd:YAG) laser with similar results (205).

Endoscopic sphincterotomy morbidity includes haematuria, which can be abundant and sometimes difficult to control, requiring transfusion in 2-13% of patients (LE 2-3). Incision at the twelve o' clock position, first described by Madersbacher and Scott in 1975 (206), seems to offer the lowest risk of haemorrhage, with three and nine o' clock sphincterotomies entailing the highest risk (207) (LE 4).

Post-operative impotence is also a common complication. Rates of up to 56% were reported in early series (208-211) (LE 3). More recent series (Table 3, LE 2-3), most using a median, or slightly deviated incision, have not affected sexual function. However, it should be noted that the population concerned may have many other reasons (neurological, psychological, etc.) for suffering from erectile dysfunction. When sphincterotomy is accompanied by complete incontinence there are obvious reasons for psychological difficulties during intercourse. This issue must be discussed with the patient before surgery. The fear of this sequel sometimes causes the patient to decide against surgery. The use of an incontinent prosthesis as first-line therapy can enable the patient to gain insight into this potential consequence of endoscopic sphincterotomy.

If striated sphincter section fails, the possibility of bladder neck stenosis should be investigated. This is seen in 2% to 21% of the patients (LE 2-3). Bladder neck incision may then improve voiding but will result in permanent incontinence. Before surgery, the surgeon must make sure that the patient accepts this situation and can use a condom catheter.

Results of endoscopic sphincterotomy are summarized in Table 3 (LE 2-3). Any analysis is made difficult by the absence of unequivocal criteria of success. Some patients are improved by sphincterotomy, even with a PVR of 200 mL. Most authors use indirect urodynamic criteria to evaluate success (decrease in detrusor pressure during voiding, decrease in PVR). The most obvious result is the improvement in autonomic dysreflexia observed in tetraplegic patients. It also appears that the intervention reduces the rate of symptomatic UTIs, although chronic bacteriuria is not improved (181). The reported results concerning resolution of hydronephrosis and vesico-ureteral reflux differ, and in each series, there are very few patients. Another essential point, well known in practice but rarely reported, is the recurrence of neurogenic DSD in many patients (195, 212, 213) (LE 3). Riccotone et al. (213) reported 82% recurrence of symptoms after ten years of follow-up (LE 3). Juma et al. (195) describe similar results after 11 years, with patients undergoing an average of 1.7 sphincterotomies (LE 3). Pan et al. (214) reported a mean duration of benefit of almost seven years, which could be sustained with a repeat procedure. Some impairment of the upper urinary tract can be developed in 30-68% of patients (195, 214), so regular monitoring after surgery is advised.

There is little evidence available to address predictive factors for a successful sphincterotomy. In a retrospective study by Pannek et al. (172), although detrusor leak point pressure and retrograde perfusion pressure were found to be superior to PVR in predicting sphincterotomy success, results were not statistically significant. On the other hand, a retrospective study by Hourié et al. (193) including patients who underwent surgical sphincterotomy (with electrocautery or laser) or urethral stent placement, showed that 90% of patients with a preoperative maximum detrusor pressure (Pdetmax) >40 cmH_2O achieved a successful outcome (PVR <150 mL) that was maintained at least 6 months after surgery; in contrast to 41% of patients with a Pdetmax below this figure (p=0.003). Another study by Takahashi et al. (215) also highlighted that the mean preoperative Pdetmax in the group that continued using a condom catheter after sphincterotomy (81.5 ± 6.0 cmH_2O) was significantly higher than that in the failure group (49.9 ± 8.5 cmH_2O).

Vainrib et al. (216) published their long-term data on 97 patients who underwent bladder neck incision with external sphincterotomy over a period of 40 years. During the period reviewed, a solitary redo bladder neck incision with external sphincterotomy was done in 46 patients, a second redo bladder neck incision with external sphincterotomy was done in 23 patients, and a third redo bladder neck incision with external sphincterotomy was done in 7 patients

with success rates of 50%, 68.2%, and 85.7%, respectively. The most common reasons to indicate a redo bladder neck incision with external sphincterotomy were elevated PVR and recurrent UTI. Remarkably, all patients had a normal serum creatinine level at the end of the follow-up. Mean elapsed follow-up after the last redo bladder neck incision with external sphincterotomy was 119 months (range, 6-408 months) for all patients evaluated. Mean durability of successful redo bladder neck incision with external sphincterotomy was 109.1 months.

Table 3. Studies of endoscopic sphincterotomy (all studies report on SCI patients)

	LE	Number patients	Mean Follow-up (months)	Success criteria	Redo rate
Pan et al. 2009 (214)	3	84	76	• Absence of recurrent urinary sepsis • No evidence of DSD in video-urodynamics • Stable upper tract on imaging • Eradication of detrusor overactivity • Primary procedure success rate: 32% • Secondary procedure success rate: 43%	35.70%
Perkash 2007 (217)	3	46	65	• * Previous sphincterotomy in 32.6% • Decrease systolic and diastolic blood pressure during urodynamics • Improved autonomic dysreflexia (91.3%) • Decrease in mean PVR • Decrease in maximum voiding pressure (not statistically significant)	4.35%
Chancellor et al. 1999 (181)	2	26	24	• PVR decrease • Hydronephrosis (100%), VUR decrease (100%) • Improved micturition comfort (80%) • Improved autonomic dysreflexia (100%)	8%
Catz et al. 1997 (218)	3	32	NR	• * Previous sphincterotomy in 43.75% • Significant decrease in PVR (84%) • Decrease in UTI (74%) • Disappearance of hydronephrosis (66%) and VUR (40%) • Improved autonomic dysreflexia (100%)	NR
Fontaine et al. 1996 (219)	2	92	20.6	• Decrease in hydronephrosis, VUR (100%, 90%) • Significant decrease in PVR, micturition pressure (83.7%) • Decrease in febrile UTI (76.7%) • Improved autonomic dysreflexia (93.2%) • Subjective improvement in 73%	8.10%
Noll et al. 1995 (194)	3	105	55.2	No statistical management of the data, but: • Improved autonomic dysreflexia (42% to 17%) • Decrease in mean PVR (180 to 70 mL) • Decrease in leak point pressure (from 97 to 37 cmH2O) • Decrease in frequency of UTI (8.1 to 3.6 per year)	30% standard sphincterotomy 15% laser sphincterotomy
Rivas et al. 1995 (220)	2	22	14	• Improved autonomic dysreflexia (44%) • Significant decrease in PVR, voiding pressure • Decrease in hydronephrosis (40%)	13.60%
Juma et al. 1995 (195)	3	63	132	• Renal function (creatinine): normal in 97% of patients • Upper urinary tract complications in 30% of patients: VUR, renal calculi, renal scaring, hydronephrosis, kidney atrophy	50.80%
Vapnek et al. 1994 (212)	3	16	39	• Eight patients using condom catheters • Eight patients with suprapubic cystostomy: recurrent UTI (high PVR), autonomic dysreflexia, skin problems	31.30%
Carrion et al. 1979 (221)	3	60	6-12	• VUR disappeared (86%) • Significant decrease in VUR: 75% • Decreased PVR: 65%	1.60%

DSD: detrusor-sphincter dyssynergia; LE: level of evidence; NR: not reported; PVR: post-void residual; SCI: spinal cord injury; UTI: urinary tract infection; VUR: vesico-ureteral reflux.

3.3. Urethrotomy

Urethral strictures are one of the most feared complications in neuro-urological patients because they could hinder lower urinary tract management. However, the available literature on the topic is scarce. Urethral strictures are thought to occur due to repetitive urethral trauma. They are more common in patients with indwelling urinary catheters (222, 223), although some authors have reported a higher rate in patients on intermittent catheterisation (224). Furthermore, it has been suggested that urethral strictures are more common in patients on intermittent catheterisation when they have had a previous indwelling transurethral catheter (225). Strictures appear more commonly in the bulbar urethra, but the penile urethra and the urethral meatus can also be affected.

Management of urethral strictures can be conservative with urethral dilatation or surgical with direct vision optical internal urethrotomy (226, 227).

Krebs et al. (224) (LE 3) identified 415 patients undergoing intermittent catheterisation, from which 105 men were diagnosed of stricture by a retrograde urethrography. However, only 38 men underwent internal urethrotomy (9.2%) due to intractable difficulties with intermittent catheterisation. During surgery, the stricture was incised at 12 o'clock with a cold knife, and if there was no bleeding, the catheter was removed after 24 h. Urethrotomy was repeated up to 5 times in 36.8% of patients with a median follow-up of 14 years. In the study by Cornejo-Dávila *et al.* (227) (LE 3), 14/333 patients on intermittent catheterisation (4.2%) developed urethral strictures. Twelve of them underwent internal urethrotomy with a single cold cut at 12 o'clock, and a 16-Fr silicone Foley catheter was placed for two weeks. At a mean follow-up of 1 year, no recurrence was noted.

3.4. Urethroplasty

The literature on urethroplasty (urethral reconstruction) in patients with NLUTD is sparse and there are only a few series involving a limited number of patients making comparisons among studies difficult.

Urethroplasty in the neurological patient has been considered a challenging procedure not only surgically but also due to postoperative complications and the high risk of recurrence, depending on the type of urethral injury, evidenced by the poor success rates historically reported (228-230). Different approaches have been described depending on injury characteristics such as erosion, stricture length, combined defects, tissue characteristics, previous interventions and the surgeon's experience. Penile grafts or skin flaps, primary closure in some cases of erosion, excision and primary anastomosis, and novel techniques for diverticula management has been used (231-234). There is no consensus of which technique will represent a better option for each patient, some classical concepts can be extrapolated from the urethral stricture management in the general population, and depending on the location, length, past medical history and surgeon's experience would be considered to take an appropriate decision (232, 234).

There is no actual evidence to emit any weighted recommendation about the proper surgical management of urethral stricture in SCI patients and limited information has been published about it.

Schreiter et al. in 1989 reported on 96 patients with complex urethral stricture who underwent a mesh graft urethroplasty using a split thickness skin graft or foreskin (228), but patient characteristics are not presented in this study, therefore outcomes in certain patients are difficult to acquire. In females, there are some reports that describe success rate for urethral closure up to 66% (229), appearing to be a promising approach for female urethral injury in patients with SCI.

Although urethral surgery in neurological patients has a generally high failure rate, some of the best series has shown success rates up to 70%, and as high as 85% for urethral stricture management as described by Casey in 2008 (230, 233, 234).

Anterior urethra seems to be the most affected urethral location after analysing the current available data. The most common site of injury is bulbar urethra followed by penile urethra, different series have reported up to 90% affection of bulbar urethra (230, 231, 233, 234). Erosion and stricture are the most common affection as showed in Table 4.

Techniques must be individualized depending on urethral lesion (erosion, stricture, diverticula, fistula, etc.), length, location, but it seems that urethroplasty using buccal mucosa graft, excision and primary anastomosis might be used as a safe and successful management in selected neurological patients (233, 234).

Many patient related factors can affect surgical outcomes, such as poor nutrition, low hygiene, lack of social support, environment and persistent insults to the involved tissues, all of them would probably contribute to negative results. When these issues cannot be adequately addressed, perhaps initial diversion is the best choice.

Table 4. Urethroplasty in patients with NLUTD

Study	Number of patients	Neurological disorder	Aetiology	Type of injury	Site of injury	Management	Result	Comments
Andrews et al. 1998 (229)	18 (women)	MS=6 SCI=6 Other causes=6	Traumatic due to indwelling catheter	Not described	Female urethra	Closure=18	Success rate 66%	12 patients were dry and 6 leaked after management
Secrest et al. 2003 (230)	18	SCI=16 Other causes=2	Traumatic due to intermittent catheterisation	Erosion=4 Stricture=6 Diverticula=1 Fistulae=3 Combined=3	Erosion anterior urethra=9 Stricture bulbar urethra=2 Penile urethra =2 Not described= 2	Urethroplasty=13 Diverticulectomy=2 Extensive reconstruction=1 No reconstruction=1 Skin flap, Byars flap=1	33% success rate	11 patients required further urinary diversion
Ronzoni et al. 2004 (233)	48	SCI=48	Traumatic due to indwelling catheter	Diverticula=48	Bulbar urethra=43 penile urethra=5	Urethroplasty Monseur modified technique=48	Non clear results reported with this management	26 patients reported positive outcomes 15 years after procedure
Casey et al. 2008 (234)	23	SCI=16 Others=7	Traumatic due indwelling catheter=10 Traumatic due to intermittent catheterisation=5 Others=8	Erosion=10 Stricture=7 Others=6	Penile=15 Bulbar=7 Penobulbar=1	Erosion Primary closure=5 Urethroplasty=5 Stricture Urethroplasty=7 (EPA=4, BMG=3) Others=6 (diverticulectomy=4, primary fistula closure=2)	Overall success in 69% patients	60% success for erosion 85% success for stricture 66.6% for diverticula and fistulae
Meeks et al. 2009 (231)	11	SCI=11	Traumatic due indwelling catheter =9 Not described=2	Erosion=11	Penile urethra=11 No stricture identified	Primary closure=6 Urethroplasty=3 (substitution with penile skin graft)	63% success rate	4 patients had recurrence, more frequent with flap use

SCI: spinal cord injury; MS: multiple sclerosis; EPA: excision and primary anastomosis; BMG: buccal mucosa graft

3.5. Transurethral resection or incision of bladder neck and other de-obstructive surgeries

3.5.1. Transurethral resection or incision of bladder neck

Currently, patients with NLUTD who cannot void safely from a video-urodynamic standpoint are usually managed with intermittent catheterisation instead of undergoing transurethral resection of bladder neck (TURB) or transurethral incision of bladder neck (TUIBN). Therefore, most studies cited in this section are relatively old retrospective studies, which means that many studies include subjects treated before the widespread use of intermittent catheterisation. These include:

- SCI: 7 studies in the 1970's (235-240), 2 in the 1990's (241, 242), and 2 in the 2010's (216, 243)
- MS: 3 studies in the 1970's (244-246) and 1 in 1980's (247)
- Diabetes mellitus: 1 study in 1970's (248)
- Other aetiologies: 1 study in 1970's (249)

3.5.1.1. Spinal Cord Injury (SCI)

TURBN and TUIBN are performed to achieve a balanced bladder function as well as a decrease in the incidence of recurrent UTI and an improvement of an impaired upper urinary tract in patients with NLTUD who are managed with an indwelling catheter or with

voiding despite an unbalanced bladder. The subjects in each study are mainly male and relatively small in number: less than 50 cases, 5 articles; 50 to 100 cases, 3 articles; and more than 100 cases, 3 articles. Only one study (243) clearly mentioned that demonstrating detrusor bladder neck dyssynergia on video-urodynamics was an indication for TUIBN. It should be kept in mind that 9 of 11 studies on SCI included patients undergoing sphincterotomy and/or transurethral resection of the prostate (TURP). As expected, in SCI, sphincterotomy is needed to overcome a concomitant functional obstruction at the membranous urethra due to DSD when TURBN/TUIBN fails or they occur in a combined manner. Although complete high-level SCI would frequently require a sphincterotomy (237), whether it should be performed simultaneously or sequentially remains to be determined. In TURBN, a 3- to 9-o'clock resection is a popular procedure (235, 236, 239), while circumferential resection as well as resection of prostate tissue down to the verumontanum is also reported (237, 242). In all but one (6-o'clock incision, (238)) TUIBN, 5- and 7-o'clock incisions are performed.

3.5.1.1.1. Transurethral resection of bladder neck (TURBN)

3.5.1.1.1.1. Efficacy

It should be noted that endpoints and the time of evaluation for TURBN are not standardized, and that many studies include patients with simultaneous as well as sequential sphincterotomy. The main efficacy outcomes are:

- Catheter free: 75% (235) or 35% (TURBN alone) to 58% (TURNB followed by sphincterotomy) (242)
- Balanced bladder: 12% (TURBN alone) to 58% (TURBN followed by sphincterotomy) (242)
- Free of UTI: 60% (235)
- Sterile urine: in upper motor neuron lesion, 17% (males) and 33% (females); in lower motor neuron lesion, 50% (males) and 25% (females) (236)
- PVR <100 mL: 20% (235) to 55% (TURBN alone) (239) and 50% (235) to 79% (TURBN combined with sphincterotomy) (239), in upper motor neuron lesion, 67% (male) and 17% (female); in lower motor neuron lesion, 50% (male) and 75% (female) (236)
- Improvement of hydronephrosis: 74% (235)

3.5.1.1.1.2. Re-operation

The rate of re-operation varied: 9.4% (235), 13% (236), and 18% (239). O'Flynn et al. (237) reported that of 139 SCI patients who underwent bladder outlet surgery including sphincterotomy, 72 patients (52%) underwent various secondary procedures. Fifty-six per cent of these 72 patients initially underwent TURBN, while 31% of them initially underwent TURBN combined with sphincterotomy (237). Moreover, secondary procedures were more likely to be necessary in complete and high-level lesions; 59% of complete cervical lesions, 57% of complete thoracic lesions, and 50% of complete lumbar lesions, required a secondary operation (237).

3.5.1.1.1.3. Complications

Although complications were not reported in a standardized manner in the cited literature, postoperative bleeding, ejaculatory dysfunction, and sepsis as well as renal dysfunction occurred with low frequency (235-237, 239-242).

3.5.1.1.1.4. Predictive factors

Fellows et al. (239) reported that a closed bladder neck on cystourethrogram did not predict efficacy of TURBN, while cervical SCI patients with maximum urethral closure pressure higher than 100 cmH_2O never benefited from TURBN. Al-Ali et al. (241) reported that based on their previous operative outcomes, they planned to perform TURBN combined with sphincterotomy for complete SCI or SCI above T9 and TURBN for incomplete SCI below T9; this was the only prospective cohort of the cited reports in this section. As a result, no patients required an additional sphincterotomy after TURBN with a decrease in PVR (320 mL to 30 mL) and a decline in infected urine (70% to 23%) (241).

3.5.1.1.2. Transurethral incision of bladder neck (TUIBN)

Morrow et al. (250) performed TUIBN combined with sphincterotomy on 75 patients with NLUTD (SCI: 72, myelomeningocele (MMC): 2). Seventy-seven per cent of the patients who needed indwelling catheterisation preoperatively were freed from catheter, while all the 32 patients who had large PVR preoperatively showed a clinically significant decrease in post-void residual. Hydronephrosis improved in 88% of the patients who had hydronephrosis preoperatively. The incidence of UTI decreased in most patients, while sterile urine persisted in the long-term in only 8 patients. Twenty-three per cent of the patients who underwent surgery for the intention of removing the indwelling catheter and 6.3% of the patients for the intention of decreasing PVR needed re-operation. In terms of complications, post-operative bleeding and urethral injury occurred in 9.3% and 1.3%, respectively. In addition, they evaluated erectile function in these patients (239), which showed complete/permanent loss of, diminished, and unchanged/improved erectile function in 8.2%, 16.8%, and 74.8%, respectively.

Sharpe et al. (240) reported that after TUIBN in 21 female patients with NLUTD (SCI and MS: 50% each), 33% of them achieved PVR <50 mL as well as urinary continence without medication and UTI, while 48% of those achieved PVR <50 mL with carbachol as well as one UTI or one minor procedure. Although only two patients needed repeat TUIBN, UVF and stress urinary incontinence occurred in 3 and 1, respectively. Two other retrospective studies (216, 243) were published in 2010's.

Ke et al. (243) evaluated outcomes of TUIBN in 22 SCI patients (above mid-thoracic-level) with detrusor bladder neck dyssynergia by video-urodynamics with or without autonomic dysreflexia (AD) (216). A decrease of more than two points in IPSS QOL was obtained in 83% of the patients, while 86% of them became able to empty their bladder by reflex voiding with an open sphincter. DSD and AD disappeared in 27% and 88%, respectively. High detrusor pressure (>15 cmH_2O) was improved in 70% of the patients with high detrusor pressure, while mean detrusor pressure (45.7 to 26.1 cmH_2O), and mean maximum flow rate (Qmax) (3.7 to 8.3 mL/s), and mean PVR (288 to 110 mL) improved significantly in them. Moreover, in the patients with low detrusor pressure (<15 cmH_2O), all the patients showed a significant increase in mean detrusor pressure, and mean detrusor pressure (6.0 → 26.9 cmH_2O), mean maximum flow rate (0.46 to 12.1 mL/s), and mean PVR (369 to 117 mL) improved significantly. Eventually 82% of the patients became catheter-free or decreased the frequency of CIC. No postoperative complications were encountered. The AIS scale, level of SCI (between cervical and thoracic cord), time from SCI, type of DSD, and the presence or absence of AD did not affect the clinical outcomes.

Vainrib et al. (216) performed TUIBN combined with sphincterotomy in an earlier period and the suitable procedures based on the findings of VUDS in the later period. They retrospectively reviewed outcomes in 97 SCI patients. Success rates were 53%, 50%, 68%, and 86% after 1st, 2nd, 3rd, and 4th, operation, respectively. Postoperative bleeding was a main complication, and urosepsis occurred in one patient.

3.5.1.2. Multiple sclerosis (MS)

Jakobsen and collaborators (244-246) as well as Petersen et al. (247) retrospectively reviewed outcomes of TURBN for patients with MS, which were published in the 1970's and 1980's. The indications for TURBN were not clearly mentioned in their studies.

Jakobsen et al. (244-246) performed various surgeries that mainly included 3- to 9-o'clock TURBN in the earlier period and circumferential TURNB in the later period in 139 MS patients. At 6 months postoperatively, 50% of the patients with complete urinary retention were rendered catheter-free, while 97% of patients with occasional retention were rendered retention-free (244). Voiding difficulties decreased in more than 60% of patients, and about 50% of patients did not complain of any voiding symptoms postoperatively (244). The mean reduction in PVR was 30% (244). Sixty-one per cent of the patients with urgency urinary incontinence improved with 35% becoming continent (245). Urinary continence was maintained in 34 of 35 patients who were continent preoperatively (245). Eventually 23% of the patients showed complete resolution of storage/voiding symptoms or very mild residual symptoms (245). Pyuria and symptomatic UTI disappeared in 36% and 70% of the patients, respectively (244). The re-operation rate was 53% (251). Complications reported were postoperative bleeding (6.5%), UTI (2.2%), sepsis (0.7%), and fever (19%) (246). It should be noted that 33% of the patients showed neurological progression during the observation period (244).

Peterson et al. (247) evaluated 21 female detrusor overactivity patients (MS: 18, other aetiologies: 3). At 3 months postoperatively, urinary incontinence episodes were significantly reduced (2.5 to 1.3 times/d) with 58% of the patients improved. Although improvement in symptoms did not correlate to urodynamic findings, urodynamic studies revealed a significant increase in volume of the first detrusor overactivity and effective bladder volume with a 33% reduction in PVR in patients showing symptomatic improvement.

3.5.1.3. Diabetes mellitus

Zincke et al. (248) reviewed outcomes of TURBN in 39 patients with PVR more than 50 mL: 23 patients had diabetic cystopathy, 11 had diabetic cystopathy with benign prostatic hyperplasia, and 5 had diabetes mellitus with benign prostatic hyperplasia. PVR was reduced to less than 50 mL in 56% and to 50−200 mL in 13%, while sterile urine was achieved in 53%. Eventually, excellent to good results were obtained in 74%. Postoperative urinary incontinence occurred in two patients.

3.5.1.4. Other aetiologies

Petri et al. (249) reported outcomes of TURBN or TUIBN in 86 neuro-urological patients with various aetiologies (MMC, MS, SCI, lumbar prolapsed disc, cerebrovascular disease, abdominoperineal resection, and abdominal radical hysterectomy), in which the indication for the procedures was large post-void residual or UUI. Symptomatic improvement was attained in 72% and 80% in TURBN and TUIBN, respectively. PVR disappeared in 38% and decreased in 41%, while urinary incontinence decreased from 8% to 3%. Sixty per cent of the patients had persistent UTI preoperatively, and sterile urine was achieved in 18% postoperatively. Re-operation was performed on 2%. Postoperative bleeding and VVF occurred in one patient each.

3.5.2. Other de-obstruction surgeries

Apart from TURBN and TUIBN, most studies evaluated outcomes of TURP for benign prostatic hyperplasia as de-obstruction surgeries in NLUTD (236, 251-260). Laser enucleation as well as vaporization of benign prostatic hyperplasia, urethral lift, and prostatic stent have not been evaluated in patients with NLUTD.

3.5.2.1. Spinal cord injury (SCI)

Only one study retrospectively evaluated outcomes of TURP in 17 SCI patients (236). Although the indication for TURP was unclear, sterile urine was attained in 18% and 17%, respectively, of patients with upper and lower motor neuron lesion, and PVR decreased to less than 100 mL in 64% and 50%, respectively.

Koyanagi et al. (252, 253) retrospectively reviewed outcomes of radical TURP in 89 SCI patients. Radical TURP is different from conventional TURP because authors resected not only the transition zone but also the peripheral zone, which was named surgical sympathectomy or modified sphincterotomy by the authors. The indications for radical TURP were 1) inability to void after maximum conservative management, resulting in permanent indwelling or intermittent catheterisation, 2) inability to void efficiently as well as safely (PVR rate >20%, Qmax <1.7 mL/min, detrusor pressure >70 cmH2O); or 3) the presence of hydronephrosis, renal impairment, bladder deformity, VUR, and prostatic reflux on imaging studies. Success was defined as stable voiding efficiency, catheter-free status, and no exaggeration of upper urinary tract deterioration. The final success rate including 12 patients undergoing additional procedures was 90%. Mean PVR rate (44% to 9%) and mean maximum flow rate (0.9 to 3.4 mL/s) significantly improved. On imaging studies, VUR was resolved in 65% and improved in 23%, while hydronephrosis and bladder deformity were resolved in 90% and 81%, respectively. On urodynamic studies, mean bladder compliance significantly improved (29.0 to 51.5 mL/cmH_2O), while detrusor overactivity disappeared in 40% and was suppressed in 47%. Interestingly, DSD was resolved in 29% and reduced in 52%. Postoperative urinary incontinence developed in one patient. No groups other than Koyanagi's group have reported outcomes of radical TURP in SCI patients.

3.5.2.2. Cerebrovascular disease

One study (254) using claims data from Taiwan's National Health Insurance Research database compared outcomes of TURP between cerebrovascular and non-cerebrovascular disease patients. Compared with non-cerebrovascular disease patients, cerebrovascular disease patients showed significantly more postoperative UTI (odds ratio 1.37), postoperative urinary retention (odds ratio 1.89), in-hospital mortality from 1 month to 12 months (odds ratio 8.27), and worse medication-free survival rates (hazard ratio 1.24). In addition, significantly more cerebrovascular disease patients used α-blockers at 3 months (odds ratio 1.41) and bethanechol until 12 months (odds ratio: ～1.39−1.55), compared with non-cerebrovascular disease patients. Interestingly, the use of anticholinergics showed no significant difference between the two groups.

Lum et al. (255) and Moisey et al. (256) reported outcomes of TURP or open prostatectomy in patients who had a prior history of cerebrovascular disease. Preoperatively, 56% and 73% of their patients, respectively, suffered from urinary retention.

Lum et al. (255) showed that 50% of the patients had satisfactory results (urinary continence with good flow) that were associated with the site of cerebrovascular disease (85% of left-side lesions, 31% of right-side lesions, 0% of bilateral lesions, and 50% of brain stem lesion), time from cerebrovascular disease (77% of cerebrovascular disease >12 months), and neurological deficit (67% of grade 1 patients, 53% of grade 2, and 17% of grade 3).

Moisey et al. (256) reported that 73% of the 28 patients regained normal micturition, while six cases who continued abnormal micturition had poor recovery from cerebrovascular disease and additional neurological co-morbidities.

3.5.2.3. Parkinson's disease (PD)

Staskin et al. (251) and Roth et. al. (257) retrospectively reviewed outcomes of TURP in patients with PD, while Chandiramani et al. (258) reported clinical characteristics and therapeutic outcomes in patients with PD and multiple system atrophy (MSA), which included patients with PD (n=11) and MSA (n=5) undergoing TURP.

Staskin et al.(251) reported that in 36 patients with PD, the rate of urinary incontinence increased from 17% preoperatively to 28% postoperatively. Moreover, de novo urinary incontinence developed in 20%. Voluntary regulation of the external urethral sphincter evaluated by concentric needle electromyography was strongly associated with the postoperative continence status: of 26 patients with normal external urethral sphincter control, 25 patients were continent postoperatively, while of 10 patients with abnormal external urethral sphincter control, only one patient was continence postoperatively.

Roth et al. (257) reported that 16 of 23 (70%) patients improved after TURP. Significant improvement was demonstrated in median IPSS (19 to 7), median IPSS QOL (4 to 2), maximum flow rate (5 to15 mL/s), and median voided volume (110 to 330 mL). Ten patients had urgency urinary incontinence preoperatively, which resolved in 5 and improved in 3. No patient developed de novo urinary incontinence. Age, Hoehn and Yahr scale, and time from onset of PD were not significantly associated with the clinical outcomes of TURP. Roth et al. (257) speculated that the patients who showed de novo urinary incontinence in Staskin's study probably suffered from MSA, not PD. Therefore, Roth et al. (257) concluded that "PD should no longer be considered a contraindication for TURP provided that preoperative investigations including urodynamic assessment indicate prostatic bladder outlet obstruction. For these patients we strongly recommend urethral or anal sphincter electromyography. This is a robust investigation for supporting the diagnosis of MSA as selective atrophy of the anterior horn cells that innervate the urethral and anal sphincter is a characteristic feature of MSA but not of PD."

The results of the study reported by Chandiramani et al. (258) were almost in line with the previous studies described above. TURP brought about good results in 3 of 5 patients with PD, while of 11 patients with MSA, urinary incontinence was exaggerated in 9 patients and urinary incontinence was temporarily improved in the remaining two patients, but recurred within one year postoperatively. Eventually, no patients with MSA regained urinary continence.

3.5.2.4. Diabetes mellitus

Two studies compared outcomes of TURP between diabetic and non-diabetic patients, but neither study mentioned the presence or absence of diabetic cystopathy (259, 260).

Soleimani et al. (260) showed that the decrease in IPSS was insignificantly larger in non-diabetic compared to diabetic patients. The rates of perioperative complications also did not differ significantly.

Lin et al. (259) used Taiwan's National Health Insurance Research database and showed that postoperatively, diabetic patients had significantly less UTI (odds ratio 0.78), higher urinary retention (odds ratio 1.35), and worse medication-free survival (hazard ratio 1.14) compared with non-diabetic patients. In addition, significantly more diabetic patients used anticholinergics within three months (odds ratio 1.23) and α-blockers from three to 12 months (odds ratio 1.18), compared with non-diabetic patients.

3.6. Bulking agents

Despite early positive results with urethral bulking agents, a relative early loss of continence is reported in patients with neuro-urological disorders (4, 261).

3.7. Urethral slings

3.7.1. Autologous sling procedures

In women with NLUTD, the use of an autologous fascial sling (usually close to the bladder neck) has been widely used to treat stress urinary incontinence. The aim of the procedure is to compress the urethra and to elevate it to an intraabdominal position to create resistance and thus increase the passive bladder outlet resistance and leak point pressure. In men, the sling can be placed just distal to the prostatic urethra or a the bladder neck (262).

The tissue more frequently harvested, especially when concomitant bladder augmentation is considered, is the rectus fascia, but *fascia lata* and bladder pedicles are also used (262, 263). It is common to perform the sling procedure in conjunction with other procedures such as bladder augmentation; long-term series have shown that, when the patients only underwent the sling, 12-30% of them developed afterwards increases in detrusor pressure and/or uninhibited contractions leading to review of anticholinergic therapy or augmentation (264-266). The most extended approach is open surgery, although robot-assisted surgical series have been described when bladder neck procedures with bladder neck sling and appendicovesicostomy are performed (267).

In a systematic review performed by the EAU Guidelines on Neuro-Urology group, it has been shown that reporting on stress urinary incontinence surgeries in neuro-urological patients is heterogeneous, identifying 16 different outcome parameters and nine definitions of cure, mainly using subjective outcome parameters (268). Table 5 summarizes the results of published case series. Complete continence is observed in 57 to 89% of the patients (LE 3). Some series suggest that girls have better outcomes than boys (263, 269-271). It should be emphasized that many patients will be dependent on bladder emptying using intermittent catheterisation or suprapubic catheterisation, because the patient's neurological dysfunction may preclude voluntary voiding and because the sling is usually inserted under tension in order to compress the urethra, correcting neurogenic intrinsic sphincter deficiency. All the series report a low morbidity rate from the procedure, including urethral erosion.

3.7.2. Suburethral synthetic slings

Midurethral synthetic slings have taken a major role in the management of stress urinary incontinence in the non-neuro-urological population, but limited evidence is available regarding neurogenic stress incontinence; concerns about the risk of urethral erosion due to the high tension needed to compress the urethra have been raised (272) (LE 3). Furthermore, intrinsic sphincter deficiency represents the usual pathophysiology in neurogenic stress urinary incontinence, contrasting with urethral hypermobility in non-neurological women.

Data on the efficacy of midurethral tension-free tape operations in adult women with NLUTD is scarce. Both the retropubic and the transobturator route have been used, including single-incision mini-slings (273). Table 6 summarizes the available evidence on the topic; studies with less than 12 months of follow-up and in which mi-

durethral slings were performed concomitantly to other procedures have been excluded. Continence rates range from 50 to 83.3%, and urethral erosion or other complications are rare. Hamid et al. have published two studies reporting on the results of 12 women with neurogenic stress urinary incontinence due to different spinal lesions (traumatic, stenosis and lumbar surgery) undergoing a retropubic midurethral sling with a median follow up of 2.3 (274) and 10 years (275). Although 3 patients were lost from follow-up in the second study, continence rate was acceptably maintained (83.3 and 77.8, respectively).

El-Azab *et al.* (276) reported a prospective, non-randomised study in 40 adult women with spinal pathology at or below S2 and neurogenic stress urinary incontinence comparing pubovaginal slings (n=20) with synthetic midurethral slings (n=20); inclusion in either group depended on the preference of the patient and surgeon. Cure rates were 80% for the midurethral and 85 % for the pubovaginal sling group; one patient had mesh erosion. Both groups showed significant reductions in UDI-6 and IIQ-7 scores after surgery.

The role of male synthetic slings in post-prostatectomy incontinence is well defined, but little evidence is available for patients with neurogenic stress urinary incontinence. Table 6 summarizes the available evidence. Initial experiences with small case series on MMC and SCI patients report a dry rate of 45-56% (277-279). Attention should be paid to possible infection of the sling and abscess formation. The use of synthetic male slings should be very cautious until further data emerge from clinical trials (LE 4).

Table 5: Results of bladder neck sling procedures in patients with NLUTD

	n	LE	Number of patients	Mean age (years)	Male/Female	Bladder augmentation surgery (%)	Appendico-vesicos-tomy / other continent stoma (%)	Follow-up (years)	Continence rate (%)
Rectus fascia / aponeurotic sling									
Athanasopoulos et al. 2012 (280)	33	3	33/33	37	0/33	42% cysto-plasty 9% myomec-tomy	-	4.3	78% dry 91% ≤ 1 pad
Karsenty et al. 2008 (270)	11*	3	11/11	42	0/11	100	100	3.6	72
Snodgrass et al. 2007 (269)	30	3	30/30	8.6	18/12	0	100	1.9	57% dry 83% ≤ 2 pads
Castellan et al. 2005 (271)	58	3	58/58	11.4	15/43	100	84	4.2	88 (dry 4-6 h)
Barthold et al. 1999 (282)	27	3	27/27	NS	2/8	80	63	2.1	28 (sling)
					5/13	78		3.6	50 (wrap)
Gosalbez et al. 1998 (283)	30	3	28/30	10	6/24	97	60	3.1	93 (dry 4-6 h)
Kakizaki et al. 1995 (262)	13**	3	11/13	13	10/3	69	-	3	69% dry 92% dry + damp
Gormley et al. 1994 (284)	15	3	15/15	NS	0/15	13	20	0.5-8.5	85% dry 92% ≤ 1 pad
Elder et al. 1990 (285)	14	3	14/14	12.6	4/10	93	-	1	86
Bladder pedicle									
Albouy et al. 2007 (263)	14	3	14/14	14	7/7	100	36	5	79% dry for 4 h 93% dry for 3 h

**** 11 women in the study, but one did not undergo fascial sling placement.***

***** Rectus fascia in 8 patients and fascia lata in 5 patients.***

LE: level of evidence

Table 6: Results of suburethral synthetic sling procedures in patients with NLUTD

	LE	Type of surgery	n	Neurological disorder	Mean age (years)	Cath. pre (%)	Cath. post (%)	De novo UUI (%)	Follow-up (years)	Continence rate (%)
Women										
Sakalis et al. 2018 (273)	3	RP-MUS	21	SCI	55.8	89.5	NR	14.3	3.9	52.4 dry 61.9 improved
		TO-MUS	12					16.7		50 dry 75 improved
		Minisling	5					-		60 dry 80 improved
Losco et al. 2015 (286)	3	TO-MUS	27	SCI	56	81.5	88.9	7.4	5.2	81.5 dry 85.2 improved
El-Azab et al. 2015 (276)	2	PVS	20	SCI, MMC, LD surgery	36	55	100	10	NR	85
		RP-MUS	20	SCI, SCT, MMC	34	25	60	30		80
Abdul-Rahman et al. 2010 (275)	3	RP-MUS	12	SCI, LD surgery, spinal stenosis	53	75	75	8.3	10*	77.8 cured* 100 improved*
Hamid et al. 2003 (274)	3					75	75	8.3	2.3	83.3 dry 91.6 improved
Men										
Pannek et al. 2017 (279)	3	I-Stop®	13	SCI	53.5	81.3	81.3	-	NR	69.2 dry 76.9 improved
		Remeex®	3							0 cured 0 improved
Vainrib et al. 2015 (278)	3	InVance®	8	3 MMC 11 SCI	31	NS	21	-	2.1	29 dry
		AdVance®	5							
		Virtue®	1							
Groen et al. 2012 (277)	3	Advance®	20	"12 MMC 8 SCI"	23	95	95	-	1	40 dry 65 improved

**** 1 patient died and 2 patients were lost from follow-up; results are from the remaining 9 patients.***

LD: lumbar disc; LE: level of evidence; MMC: myelomeningocele; NR: not reported; NS: not specified; PVS: pubovaginal sling; RP-MUS: retropubic midurethral sling; SCI: spinal cord injury; SCT: spinal cord tumour; TO-MUS: transobturator midurethral sling; UUI urgency urinary incontinence.

3.8. Artificial urinary sphincter (AUS)

The AUS is recognized as one of the most effective treatments for stress urinary incontinence. It has the inherent advantage that it provides an adequate urethral closure pressure during the urine storage phase of the micturition cycle but then allows voiding to take place in the face of a low bladder outlet resistance. In patients with stress urinary incontinence, it can provide either complete or "social" continence in 75% to 87% with satisfaction rates ranging between 85% and 95%. These rates are provided by published case series that mostly include patients with post-prostatectomy stress urinary incontinence, along with some neurological patients. However, outcomes are probably similar for patients with neurogenic stress urinary incontinence and a low-pressure bladder reservoir (LE 4) (287). It should be noted that most of the published data on the use of the AUS in neurogenic stress urinary incontinence relates to men, although the device is also used in female patients with neurological disease in few case series (LE 3) (288-291).

Before using the AUS in neurogenic stress urinary incontinence, several factors must be considered:

- The risk of implant infection and erosion is probably higher than in the post-prostatectomy stress urinary incontinence population. It is generally recommended that patients undergo pre-operative urine culture and sterilization of the urine before surgery (292) (LE 4). A recent study has evaluated the risk AUS and/or penile prosthesis infection in patients with untreated asymptomatic bacteriuria and patients with negative urine culture and found no difference in infection rate between both groups over 15 months follow up and only 7% of the infected devices showed the same organism as in pre-operative urine culture (LE 3) (293).
- Manual dexterity must be sufficient to allow the patient to use the AUS pump - either to open the cuff to urinate, or to allow intermittent catheterisation (287). They must also accept the need for intermittent catheterisation should the bladder have reduced contractility. However, some studies seem to indicate that the cycling activation of the pump could be avoided in patients performing intermittent catheterisation (LE 3) (294, 295). Bersch et al. (294) have described a modified technique.
- The cuff implantation site in adult patients with NLUTD is debated. The cuff can be implanted via a retropubic approach at the level of the bladder neck or around the prostatic apex. Alternatively, the cuff can be implanted around the bulbar urethra using a perineal incision. Proponents of the retropubic approach argue that perineal incisions may cause healing problems for patients in wheelchairs. Moreover, traumatic catheterization is a well-known risk factor of urethral erosion in the non-neurological population undergoing an AUS (296) (1 to 5.5% in contemporary series), although it is recognised that intermittent catheterisation is possible in AUS implanted patients (297), the risk of traumatic catheterisation and subsequent cuff erosion might be higher when the bulbar urethral site is used. Recent study looked at the difference between a cohort of patients who underwent bladder neck or peri-bulbar cuff implantation that have found no difference in risk of erosion in univariate or multivariate analysis between bladder neck or peribulbar cuff site. The only factor that has been associated with reduced device survival was the use of intermittent catheterisation (LE 3) (298). Bladder neck cuffs are usually larger, which might allow the passage of large bore rigid cystoscopes if needed for treatment of bladder stones for instance (LE 4) (299). On the other hand, inserting an AUS cuff around the bladder neck is technically more difficult in adults in comparison with peri-bulbar implantation (LE 4). Laparoscopic approach has been used for bladder neck sphincter implantation (LE 3) (289, 300-306). The use of robot assisted approach have described in men but mostly in women (290, 291, 307, 308) with acceptable short term follow up results in experienced centres (LE 3). One study has compared robotic female AUS implantation to open approach and found comparable continence rate and lower peri-operative complications in robotic group (LE 3) (309). Challenges in robotic approach have been described. Inadequate measurement of the cuff size due to loss of tactile sensation might lead to oversizing of the cuff and failure of the procedure which will require cuff revision (LE 4) (310).
- It is necessary to know the ejaculatory status of males in order to discuss the possible impact of the device on ejaculatory function. Cuff implantation around the bladder neck may allow patients to achieve antegrade ejaculation (311) (LE 4).

A thorough urodynamic evaluation of the bladder is mandatory in order to evaluate the potential impact of bladder compliance following AUS implantation. This has been reported in several retrospective series (LE 3) (262, 283, 294, 296, 312-323). The reasons for this change in bladder behaviour are not known, and it has been observed particularly in populations of patients with MMC (316, 318-320, 322). In the event of any doubt about the quality of the bladder reservoir, bladder augmentation should be performed. The main results of published series are summarized in Table 7. The continence rate is high, especially when a bladder augmentation has been performed (59 to 100% of the patients). The risk of infection when bladder augmentation is done simultaneously was found to be similar if it was done staged and similar to the risk of infection if no augmentation is done (LE 3) (303, 323), but earlier infection was noted in patients with simultaneous AUS and augmentation in one study (LE 3) (324).

The oldest series include some patients with the previous version of the AMS 800 (AMS 792); Therefore, it is possible that the long-term outcomes for patients being implanted today may be better than those seen in the past as a result of technical modifications of the device. Device infection, cuff erosion into the urethra and loss of fluid from the implant are the main causes of loss of an AUS. Infection and erosion typically occur in the early months after implant but late erosions are seen (315) (LE 3). The majority of the authors consider AUS to be the "gold standard" procedure to treat neurogenic stress urinary incontinence in men (LE 3).

In a systematic review of 30 case series, comparing outcomes of various treatment options for stress urinary incontinence in neurological patients, bulking agents were found inferior to AUS (77+/-16% versus 27+/-20%, P = 0.002) but not with sling procedure (58 +/- 25%). The overall continence rate of AUS was lower in neurological patients (77%) than reported in the literature in non-neurological patients (approaching 100%). The overall complications (AUS 32 +/- 27%, slings 14 +/- 14%, bulking agents 4 +/- 6%) and reoperation (AUS 51 +/-25%, slings 7 +/- 9%, bulking agents 12 +/- 14 %) were higher in AUS in comparison to urethral bulking agents and urethral sling procedures (LE 3) (325).

Few case series have evaluated the use of AUS in women with and without NLUTD by open, laparoscopic and robot assisted approaches around the bladder neck (LE 3) (288-291, 309, 326, 327). The overall continence, complication, and reoperations are comparable to male AUS cases in intermediate to long term in expert centres (LE 3), which might limit the generalisation of these results. There are no randomised studies comparing the female AUS to other treatment options in female neurogenic stress urinary incontinence such as fascial slings and spiral slings.

To conclude we have to knowledge the good performance of AUS in neurological and non-neurological patients and the relative du-

rability of the device if we accept minor revisions (such as pressure balloon change) as part of the normal life of an AUS. Recent long term follow- up articles are encouraging but emphasise the need to keep these complex surgeries in the hands of specialised centres (328-332).

Table 7: Results of AUS in patients with NLUTD

	n	LE	Number of patients	Age (years)	Male/ female	Bladder augmentation surgery (%)	Follow-up (years)	Continence rate (%)	Cuff Implantation Site	Complication/revision rate (%)
Tricard et al. 2020 (289)	23	3	23	54	0/23	0	11.6	69.6% continent, 17.4% improved, 13% unchanged incontinence	Bladder neck 19/23 Open 4/23 Laparoscopic	Complications 8/23 Revision: 69.9% Explantation 8/23 (34.8%)
Gondran-Tellier et al. 2019 (290)	8	4	2/8	64	0/8	0	1	67.5% Continent 0 Pads 0gm/24/hours 37.5% Improved 1 pad 8-15 gm/24 hr pad test	Bladder neck Robot assisted laparoscopic approach	37.5% urinary retention in post operative period
Peyronnet et al. 2019 (291)	49	3	5/49	70.5	0/49	0	18.5 months (1.5 years)	81.6% continent 12.2% improved continence 6.1% Unchanged continence	Bladder neck Robot assisted laparoscopic approach	Explantation due to vaginal erosion 2% 3/49 revision (1/49 due to bladder neck atrophy, 1/49 due to mechanical failure, 1/49 due to difficulty in handling the pump due to proximal location)

	n	LE	Number of patients	Age (years)	Male/ female	Bladder augmentation surgery (%)	Follow-up (years)	Continence rate (%)	Cuff Implantation Site	Complication/revision rate (%)
Khene et al. 2018 (298)	65	3	65/65	23 Peribulbar cuff 19 Bladder neck cuff	65/0	0	21 years (peribulbar) 16 years (Bladder neck)	Peribulbar cuff (83% continent) Bladder neck cuff (75% continent) P=(0.75)	Peribulbar 59% Bladder neck 41%	Early complications: Peribulbar (20%) vs bladder neck (19%) Mechanical failure: Peribulbar (42%) vs bladder neck (50%) Erosion: Peribulbar (15%) vs Bladder neck (11%) Infection: Peribulbar 16% vs bladder neck 8% Equal device survival between bladder neck and peribulbar location Only variable associated with reduced survivals was use of intermittent catheterization
Guillot et al. 2018 (328)	14	3	14/14	27.3	14/0	0	18.3 years	50%	4/14 Peribulbar 10/14 Periprostatic	3/14 explantation due to erosion or infection 8/14 revision 7.1% revision free at 20 years
Chartier-Kastler et al. 2011 (329)	51	3	51/51	35	51/0	6/51 pre-AUS Augmentation 11/51 concomitant Augmentation 3/51 Subsequent Augmentation	6.9 years	74% had complete or partial incontinence	Bladder neck	9.8% erosion 9.8% infection 26% Required Revision over 10 years
Yates et al. 2013 (307)	6	4	6/6	51.5	6/0	0	1.1 year	100%	Robot assisted laparoscopic approach bladder neck	0% erosion 0% revision 0% infection

	n	LE	Number of patients	Age (years)	Male/ female	Bladder augmentation surgery (%)	Follow-up (years)	Continence rate (%)	Cuff Implantation Site	Complication/revision rate (%)
Costa et al. 2013 (326)	344	3	54/344	57.2	0/344	7/54	9.6 years	Complete continence 85.6% Social continence 8.8%	Bladder neck	Infection 4.8% Vaginal erosion 3.2% Urethral erosion 1.9% Skin erosion 1.9% Bladder erosion 1.1% Mechanical failure requiring revision: 13.6% Mean mechanical survival: 13.5 years in non-neurogenic vs. 9.9 years in neurogenic (p<0.001)
Phe et al. 2017 (288)	26	3	26	49.2	0/26	0	7.5	58%	Bladder neck	9/35
Shen et al. 2011 (330)	19	4	4/19	50.7	19/0	0	4.16	64% overall 57.1% neurogenic	Peri-bulbar	Overall: Infection 32%, Mechanical failure 8% Neurogenic: infection 42.9%, Mechanical failure 14.3%
Thomas et al. 2002 (327)	68	3	34/68	20	0/68	0	7	82% overall 90% neurogenic	Bladder neck	Overall: Mechanical failure required replacement 17%, infection/erosion required removal: 46% Neurogenic: Mechanical failure required replacement 21%, infection/erosion required removal: 50%.
Venn et al. 2000 (331)	100	3	59/100	35	Overall: 70/30 Neurogenic:42/17	0	11	Overall: 84% Neurogenic:86% Male peri-bulbar cuff: 92% Male bladder neck cuff: 84% Female bladder neck: 73	Male peri-bulbar cuff: 39 Male bladder neck: 31 Female bladder neck: 30	Overall: Mechanical failure required replacement 27% Infection/erosion required removal 37% Higher female infection/erosion 56% versus 28.6%
Bersch et al. 2009 (294)	51	3	51/51	38.7	37/14	19.6 (sacral root surgery)	8	70.6% (total) /90.2% (social continence)	Bladder neck	7.8/35.3
Lai et al. 2007 (296)	218	3	11/218	46.3	215/3	NP	2.4	69	Peri-bulbar	18.2/36.4
Lopez Pereira et al. 2006 (320)	35	3	35/35	14.4	22/13	20/35	5.5	91.4	Bladder neck	11.4/20

	n	LE	Number of patients	Age (years)	Male/ female	Bladder augmentation surgery (%)	Follow-up (years)	Continence rate (%)	Cuff Implantation Site	Complication/revision rate (%)
Patki et al. 2006 (321)	9	4	9/9	38.2	9/0	NP	5,9	77	Peri-bulbar	22/43
Murphy et al. 2003 (332)	30	3	13/30	54	29/1	NP	NP	23	Peri-bulbar	33/70
Herndon et al. 2003 (317)	134	3	107/134	10	94/41	85/134	7.5	86	Bladder neck (122), peri-bulbar (12)	16/41
Castera et al. 2001 (313)	49	3	38/49	14	39/10	9/49	7.5	67	Bladder neck (37), peri-bulbar (12)	20/12
Shankar et al. 2001 (333)	45	4	NP	11	45/0	NP	7	89	Bladder neck	4.4/6.7
Kryger et al. 2001 (318)	32	3	28/32	6.7/14.5	25/7	9/32	15.4	100	Bladder neck	41/95
Elliott et al. 1998 (314)	323	3	10/323	Global: 60.4	313/10	NP	5.7	NP	Bladder neck/ peri-bulbar	Global: 26.2/28.6
Fulford et al. 1997 (315)	61	3	34/61	26	43/18	7/34	10 to 15	88	Bladder neck (female)/peri-bulbar (male)	29.4/91.2
Levesque et al. 1996 (319)	54	3	49/54	10/12	34/20	23/54	NS (>10)	59.3	Bladder neck	24/67
Singh et al. 1996 (323)	90	3	90/90	26	75/15		4	92	Bladder neck/ peri-bulbar	16.7/28
Simeoni et al. 1996 (322)	107	3	107/107	13.7	74/33	22/107	5	76.6	Bladder neck(98)/ peri-bulbar(9)	22.3/19.6
Gonzales et al. 1995 (316)	19	3	19/19	8.4	19/0	7/19	8	84.2	Bladder neck	5/100
Belloli et al. 1992 (312)	37	3	37/37	13-19	35/2	2/37	4.5	59	Bladder neck(33)/ peri-bulbar(4)	10.8/38

**** AUS modified***

*****AUS modified and two groups of patients depending of their age at AUS***

3.9. Adjustable continence devices

Options beyond AUS comprise autologous bulbar and pubo-cervical slings, alloplastic static sub-urethral slings (transobturator or retropubic), adjustable periurethral balloons, bulking agents, and re-adjustable sling type devices such as ATOMS®, Virtue®, transobturator adjustable slings and retropubic like REMEEX®.

Rudimentary perineal urethral compressions were abandoned before 1980 due to ineffectiveness, the difficulty of dissection and the poor results (287). Grégoir (334) in 1956 had already proposed the use of urethral suspension for the management of stress urinary incontinence, and he specified the use of fascia bands in contact with the membranous urethra with strong tension. This Grégoir principle has resurfaced and given way to the use of tension-free vaginal tapes. Autologous slings in the overall male neurological population present a complete continence rate of 58 +/- 25% and a failure rate of 22 +/- 22%. The complication and re-operation rate are 14 +/- 14% 7 +/- 9 %, respectively (325).

Studies on synthetic sub-urethral slings are scarce in this subset of patients. Bulbourethral slings were described in patients after radical post-prostatectomy stress urinary incontinence by Schaeffer et al. with a total or partial success rate of 75%, reoperation erosion and infection of 27%, 6% and 3%, respectively (335). While there is a growing interest in the minimally invasive management of neurogenic stress urinary incontinence in men, the evidence is still very limited.

There are retrospective studies in patients with SCI or MMD and neurogenic stress urinary incontinence that are low-level evidence from small samples and retrospective design. In a 2001 study, Comiter reported the use of a polypropylene sling anchored to the pubic bone in 21 male patients with stress urinary incontinence of which only 1 had a neurological aetiology (MMC) with neurogenic overactive detrusor. The continence rate in this study was 76% including the patient with MMC, with no infection and no erosion of the tape (336). The only reported series on the use of the male readjustable system MRS II REMEEX® in neurological patients showed not very promising outcomes. Pannek et al. (279) presented a retrospective series of 16 SCI patients with neurogenic stress urinary incontinence showing the results of the use of re-adjustable sling REMEEX® (n=3) and non-adjustable male alloplastic transobturator tape sling (n=13). None of the patients managed with REMEEX® improved, i.e. none achieved continence. In addition, one patient required removal of the tape because of infection and in another a perineal abscess with urethral erosion occurred that required urethral sealing and permanent derivation with suprapubic tube. Ammirate et al. reported initial experience using the adjustable transobturator male sling (ATOMS®) in 8 males with stress urinary incontinence due to MMC and cauda equina syndrome. During a 12 months follow-up, they reported complete continence in all of the patients and a low complication rate (2 grade 1 complications according to the Clavien-Dindo system) (279).

The use of adjustable devices in neurogenic stress urinary incontinence is underreported. Fears regarding infection and urethral complications such as erosion precludes its use in patients who catheterize their bladders transurethrally. Since small case series is the only actual evidence concerning efficacy and safety of REMEEX® or ATOMS® in the neurological population and the outcomes were unfortunate, with 2 relevant infectious and no efficacy for the REMEEX ® and too short follow-up for ATOMS®.

Adjustable continence therapy has surge as an option in male and female neurogenic stress urinary incontinence. It consists of two silicone balloons attached to a titanium port each one though a tube. Retrospective, small series including SCI patients demonstrate a 44% continence rate per patient and 41% per device, with 19% rate of erosion, 6% infection, 31% explantation, none of them requiring subsequent AUS (337).

At a long term of 48 months of follow up in a neurogenic population (males and females) 92% of whom performed clean intermittent catheterization, 55% indicated more than 50% improvement of incontinence of whom 39% were fully continent (338).

Rate of migration is lower in patients with upper motor neuron lesion compared to those with lower motor neuron lesion.

A recent study specifically assessing ProACT device in female neurological versus non-neurological population found no significant continence difference, 39% versus 36% respectively (p=0.69, improvement rate 31% and 34% or overall complications (24% versus 35%) or explantation rate (20% versus 19%) (339).

3.10. Bladder neck and urethral reconstruction / closure

Complete bladder neck or urethral closure of the bladder outlet may be required if alternative approaches to manage refractory stress urinary incontinence or incontinence associated to urinary fistulae were inappropriate or have failed. This procedure can be considered especially in SCI patients with untreatable osteomyelitis due to urinary fistulae draining through the scars (340). In women, bladder neck closure can be achieved either via a vaginal or an abdominal approach. In men we use an abdominal approach. In some cases without severe perineum lesions the urethra can be closed through a vaginal incision in women or períneal incision in men (341). More recently, a robotic approach has been used with success to perform surgeries in the bladder neck including its closure (267). Bladder drainage is maintained using a continent catheterisable abdominal conduit (Mitrofanoff or Monti procedure using large or small bowel), a suprapubic catheter or an ileo-vesicostomy (342). In a single surgeon series in 35 patients with 4-13 years follow-up, bladder neck closure was done simultaneously with suprapubic catheter diversion. Indications for bladder neck closure included severe urethral erosion in 80%, decubitus ulcer exacerbated by urinary incontinence in 34%, urethrocutaneous fistula in 11%, and other indications in 9%. The overall complication rate was 17%. All but two patients were continent at follow-up (343).

In a retrospective series, suprapubic catheters seemed to be associated with fewer complications and emergency rooms admissions than Mitrofanoff or ileo-vesicostomy procedures (344). Bladder neck or urethral closure can be technically difficult and a secondary operation to close a persistent fistula may be needed in some cases (345). Interposing vascularised tissue between the bladder neck suture line and the urethral or vaginal closure is a well-described aid to the avoidance of closure failure; a flap of rectus abdominis can be used for this purpose. Bladder neck closure has also been used in children where other means of correcting SUI have failed or are felt to have a limited chance of success. The published series of cases provided some reassurance that children with closed bladder necks do not suffer from excessive complications in the form of renal deterioration, bladder rupture or stone formation. As a general principle, urethral closure should not be undertaken in cases where it is possible to maintain urethral patency using alternative approaches to treat stress urinary incontinence. For example, patients with NLUTD are at high risk of stone formation in the bladder or upper tracts and it is desirable to maintain easy endoscopic access to the bladder in order to allow potential endoscopic treatment. Finally, preserving the natural urethra may constitute a

safety measure if high bladder storage pressures are present or in the event of any complication with bladder access via a continent catheterisable abdominal conduit or suprapubic catheter (346).

The last guidelines of European Society for Pediatric Urology (ESPU) and European Urological Association (EAU) reviewing the period 2000-2017 postulated that the creation of a continent catheterisable stoma in association with bladder neck closure is an option for the treatment of complex cases of incontinence in children and adolescent patients (347). However due to the high incidence of metabolic and surgical complication close follow-up is mandatory to detect and treat consequences early.

In selected patients urethral closure may represent a simpler alternative to complete closure of the bladder neck in neurological patients with severe incontinence or urinary fistulae. In a retrospective series including 12 (four males and 8 females) patients, 9 with SCI and 3 with progressive MS, the authors achieved urinary continence in all but one patient in a 20 months follow-up. All patients had a urinary diversion, either an ileo-vesicostomy, or an augmentation cystoplasty and construction of a neourethra. Four patients had one additional procedure to gain continence, but five patients required 3.8 procedures/patient to achieve continence. Closure of the male urethra was more easily accomplished than closure of an extensively damaged eroded female urethra (341).

4. BLADDER COVERED BY STRIATED MUSCLE

Voiding function for an acontractile bladder can be restored when the bladder is covered by striated muscle that can be stimulated electrically, or that can be contracted voluntarily. The rectus abdominis (348) and latissimus dorsi (349) were used in patients with NLUTD (350, 351). However, this technique is not suitable for smaller bladders, and intermittent catheterisation may still be needed due to persistent PVR (352).

5. BLADDER AUGMENTATION

Bladder augmentation or augmentation cystoplasty is a generally accepted therapy for a small-volume, high-pressure bladder. The purpose of bladder augmentation is to increase bladder storage capacity, decrease bladder pressure, improve bladder compliance, protect upper urinary tract function, provide urinary continence, resist infection, and offer a convenient method of voluntary and complete bladder emptying. The technique has been in existence for >100 years, and has recently been performed laparoscopically or robotically. Currently, the bladder augmentation techniques available in clinical practice include autoaugmentation (vesicomyotomy), intestinal cystoplasty (ileum), colocystoplasty (sigmoid), gastrocystoplasty (stomach), ureterocystoplasty, seromuscular augmentation, and tissue engineering cystoplasty (353).

The aim of auto-augmentation is to reduce detrusor overactivity or increase low bladder compliance. The advantages include low surgical burden, low rate of long-term adverse effects, positive effect on QOL, and it does not preclude further interventions (354-357). Bladder auto-augmentation with rectus muscle backing may become an alternative surgical technique for carefully selected patients to improve bladder capacity and compliance. However, this technique is indicated only in cases without anterior abdominal wall anomalies (352).

Replacing or expanding the bladder by intestine or other passive expandable coverage will improve bladder compliance and at least reduce the pressure of detrusor overactivity (358, 359). In patients with severely thick and fibrotic bladder wall, bladder substitution with bowel after performing a supratrigonal cystectomy (359) to create a low-pressure reservoir is indicated. To improve NLUTD and protect kidneys from damage, augmentation uretero-enterocystoplasty can be performed as reported by Liao et al (353, 360). It refers to the procedure that combines bladder augmentation with simultaneous ureteral anti-reflux implantation and ureteroplasty. The ureteral anti-reflux implantation can be performed with ureteroplasties (ureterolysis and tailoring/shortening) because of megaureter, severe tortuous ureter, and constricting ureteric stenosis. Ureterolysis refers to mobilization and straightening of the ureter. Tailoring refers to shortening the length of the ureter, and reducing the diameter only for megaureters (353, 360). The augmentation uretero-enterocystoplasty may be beneficial for patients with low-pressure or high-grade VUR, ureterovesical junction obstruction or ureter tortuosity and adhesions, and/or severe upper urinary tract damage, especially for those patients with a long medical history (359-361). In a study of 173 patients who underwent bladder augmentation, Wang and Liao showed that concomitant ureteral reimplantation (160 patients) could be beneficial for the following indications: VUR grade III or greater, VUR at low pressures (less than 10 cm H2O), upper urinary tract dilatation grade III or greater, and ureterovesical junction stenosis. After surgery, only one patient (0.6%) had persistent VUR, though 14 patients (8.1%) developed ureteral stricture (360). Improved QOL and stable renal function have been reported during long-term follow-up, even though intermittent catheterisation may become necessary after this procedure, which is more prevalent in neuro-urological population (362). Long-term complications included bladder perforation (2%), mucus production (13%), metabolic abnormalities (3%), bowel dysfunction (15%), and stone formation (10%) (362). Though more research is needed to better evaluate the morbidity of different surgical techniques and the indications for concomitant surgeries, enterocystoplasty associated with supratrigonal cystectomy remains the gold standard for bladder augmentation (363).

The long-term scientific evidence shows that bladder augmentation is a highly successful procedure that stabilises renal function and prevents anatomical deterioration; however, lifelong follow-up is essential in this patient group given the significant morbidity associated with this procedure (362). Special attention should be paid to patients with pre-operative renal scars since metabolic acidosis can develop (364). Poor compliance with intermittent catheterisation can increase the risk of chronic renal failure (363). Patients with lower baseline renal function may be at higher risk for developing chronic renal failure following bladder augmentation than patients with a normal preoperative creatinine clearance (363). For better evaluation of both lower and upper urinary tract dysfunction, a new comprehensive classification system has been proposed by Liao (353, 365-367), using magnetic resonance urography in combination with video-urodynamics. The appearance of calyces and dilation of the renal pelvis, tortuous and dilation of the ureter, and thinning of the renal parenchyma are key factors in the magnetic resonance urography upper urinary tract dysfunction grading system. This new system better discriminates among grade changes in upper urinary tract function, allowing for better informed clinical decision-making and long-term follow-ups (353).

Experimental methods of bladder augmentation with tissue engineering are a promising area for further investigation. Small intestinal submucosa had been applied as a scaffold for rebuilding a functional bladder with partial long-term success rate in patients with

NLUTD. With regard to the pilot clinical experience with 8 cases in 2014, assertion had been arisen on the limited ability of small intestinal submucosa grafted surface for bladder expansion (368). Liao's group is encouraged to continue the bladder augmentation with small intestinal submucosa and prospectively followed this cohort to determine if the mid-term results are maintained. They reported the ongoing clinical experience with small intestinal submucosa mediated bladder reconstruction based on the long-term follow-up data in 2019 (369). A total of 15 patients with poor bladder capacity and compliance underwent small intestinal submucosa BA. The duration of follow-up ranged from 4.5 to 8.3 years (mean: 6.3 years). A total of 9 patients showed stable improvement, leading to the overall success rate of 60%. Four patients experienced gradual decrease in incontinence episodes. Two patients had no symptomatic benefit. Compared with the pre-operative status, the results indicated significant increases in bladder capacity and significant decreases in the detrusor pressure profile at 1, 2–3, and 4–5 years postoperatively. In addition, bladder compliance significantly increased at 2–3 years postoperatively. The results of patients with successful and unsuccessful procedures were reported separately. There were no significant differences between groups with successful and unsuccessful procedures in preoperative video-urodynamic parameters. Macroscopic examination showed that the regenerated bladder wall was not distinguishable from the native bladder based on ultrasound, cystogram, and endoscopy. Histologic examination showed a complete conversion of small intestinal submucosa, leaving the bladder wall containing smooth muscle, vessels, and relatively thick connective tissue. This technique helps increase bladder volume, alleviate upper urinary tract dilation, and offer some patients with relatively safe conditions for intermittent catheterisation during long-term follow-up. Despite known complications and a relatively low success rate, small intestinal submucosa bladder augmentation has the advantage of a simpler surgical procedure and avoidance of bowel-based complications compared with enterocystoplasty. However, this procedure cannot be recommended as a substitute for enterocystoplasty, especially in patients with seriously damaged bladder, high-grade VUR, severe upper urinary tract deterioration, and/or detrusor fibrosis. Careful patient selection remains of the utmost importance, and patients need to be motivated to perform regular intermittent catheterisation (368, 369). In addition, the combination of 3D bioprinting technology and in situ in vivo bioprinting may be the main research direction in the future (370).

6. URINARY DIVERSION

When no other therapy is successful, urinary diversion must be considered for the protection of the upper urinary tract and for the patient's QOL.

6.1. Incontinent urinary diversion

Incontinent diversion with a urine-collecting device is indicated, if catheterisation is impossible. It could be considered in patients who are wheelchair bound or bed-ridden with intractable and untreatable incontinence, in patients with lower urinary tract destruction, when the upper urinary tract is severely compromised, and in patients who refuse other therapy. An ileal segment is used for the deviation in most cases (371-374). Compared with the ileal conduit, it was suggested that the colonic conduit has fewer complications (347). Patients gain better functional status and QOL after surgery (375).

To avoid pyocystitis and to prevent bladder cancer, a cystectomy is usually performed at the same time.

6.2. Continent urinary diversion

This should be the first choice for urinary diversion. The creation of a continent catheterisable channel should be offered to patients with difficulties performing transurethral intermittent catheterisation. Patients with limited dexterity, particularly those with relapsing-remitting disease and/or degenerative neurological condition, may prefer a stoma instead of using the urethra for catheterization (376-378). A high revision rate needs to be considered (347). The literatures concluded that continent catheterizable tubes/stomas are an effective treatment option in neuro-urological patients unable to perform intermittent catheterisation through the urethra (379). For cosmetic reasons, the umbilicus is often used for the stoma site (380-385). However, the complication rates were significant with the post-operative events requiring re-operation (379).

6.3. Undiversion

Long-standing diversions may be successfully undiverted or an incontinent diversion changed to a continent one with the emergence of new and better techniques for control of detrusor pressure and incontinence. The patient must be carefully counselled and must comply meticulously with the instructions (386). Successful undiversion can then be performed (387).

IV. CONCLUSIONS

In surgery for neurological urinary incontinence, the LE is limited and varies widely from LE 1 to 4 (LE is mostly 3).

1. RECOMMENDATIONS FOR PRACTICE

Botulinum toxin injections into detrusor / external urethral sphincter

- Intradetrusor onabotulinumtoxinA injections are effective and safe if antimuscarinics failed. Generally, 100-300 units are used having a duration of effectiveness of 6-14 months. Abobotulinumtoxin A is not yet licensed although the outcomes are promising.
  (LE 1; GR A)

- Intrasphincteric botulinum toxin injections may be effective and safe to treat DSD but are not yet licensed. The optimal dose and mode of injection is unclear and the duration of effectiveness is about 3 months.
  (LE 2; GR B)

Invasive neuromodulation / neurostimulation

- Sacral anterior root stimulation combined with sacral deafferentation (dorsal rhizotomy) is a valuable therapeutic option in carefully selected patients with complete SCI.
  (LE 3; GR C)

- Sacral neuromodulation may be effective and safe but there is a lack of RCTs in the neurological population and it is unclear which neurological patients would be most suitable.
  (LE 2; GR B)

Urethral, prostatic, and bladder neck surgery

- Urethral / prostatic stents are rarely indicated. Adverse events are relevant and stent removal is a challenge.
  (LE 3; GR C)

- Sphincterotomy may be considered in carefully selected male patients. The recurrence rate is high and the decrease of intravesical pressure often unsatisfactory.
  (LE 3; GR C)

- Urethrotomy is indicated in the case of urethral strictures hindering urethral catheterisation.
  (LE 3; GR C)

- Urethroplasty is a challenging procedure and a patient-tailored stepwise approach is crucial.
  (LE 3; GR C)

- TURBN / TUIBN is performed in the case of relevant PVR due to a fibrotic bladder neck. TURP is an option in pure PD patients with urodynamic prostatic obstraction (exclude MSA!).
  (LE 3; GR C)

- Treatment with bulking agents is minimally invasive but outcomes are mostly disappointing in the medium- and long-term.
  (LE 3; GR C)

- Autologous (preferable) and synthetic urethral slings can be used for treating neurogenic stress urinary incontinence. Preoperatively, relevant detrusor overactivity and VUR has to be excluded / treated. Patients have to be informed about the risk for postoperative de novo urinary urgency (incontinence).
  (LE 3; GR C)

- AUS is still the gold standard for treating neurogenic stress urinary incontinence. However, relevant complications and redo surgeries are common. The laparoscopic approach is promising.
  (LE 3; GR C)

- Adjustable continence devices are mainly used in post-prostatectomy stress urinary incontinence and the experience in neurological patients is very limited.
  (LE 3; GR C)

- Bladder neck / urethral reconstruction / closure is rarely indicated and combined with suprapubic catheter or urinary diversion.
  (LE 3; GR C)

Bladder covered by striated muscle

- Voiding function of an acontractile detrusor can be restored when the bladder is covered by striated muscle (rectus abdominis or latissimus dorsi) that can be stimulated electrically or contracted voluntarily. However, the evidence is very limited.
  (LE 4; GR D)

Bladder augmentation

- Bladder augmentation improves bladder compliance and decreases intravesical pressure. It is considered in patients after failed botulinum toxin treatment or in those not willing / not suitable to undergo regular intradetrusor botulinum toxin injections. Careful patient selection is of utmost importance and adherence to intermittent catheterisation is required.
  (LE 3; GR C)

Urinary diversion

- Incontinent diversion preferably with an ileal segment is indicated if intermittent catheterisation is not possible or in the case of severely impaired renal function.
  (LE 3; GR C)

- Continent urinary diversion is the first choice, but relevant complications and redo surgeries are common. In the case of limited manual dexterity or spasticity a catheterisable stoma through the umbilicus (instead of catheterisation through the urethra) should be considered.
  (LE 3; GR C)

- Undiversion is rarely indicated. It has to be meticulously planned and patients have to be carefully informed.
  (LE 4; GR D)

2. RECOMMENDATIONS FOR RESEARCH

Considering the limited LE, well-designed, adequately powered and sampled prospective studies are urgently needed in surgery for neurological urinary incontinence. However, while awaiting high-level evidence studies, current best clinical practice management is justified.

FIGURES

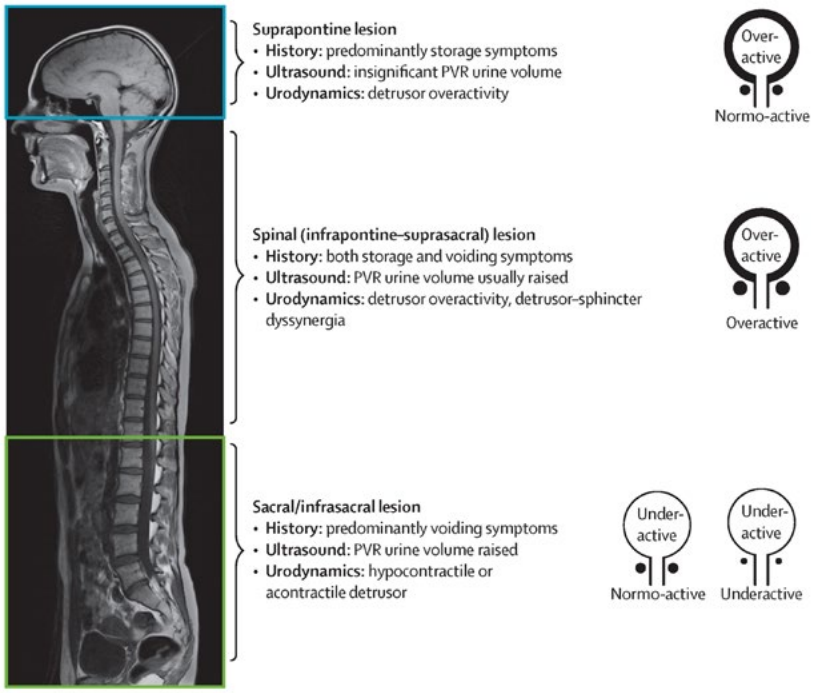

Figure 1. Patterns of lower urinary tract dysfunction following neurological disease (with permission from (1)).

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COMMITTEE 13

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Chair
de Ridder, Dirk. Chair (Belgium)

Members
Goh, Judith (Australia)
Greenwell, Tamsin (United Kingdom)
Mourad, Sherif (Egypt)
Vaze, Ajit (India)

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I. GENERAL INTRODUCTION

Fistulae are usually complications of obstructed labour or of pelvic surgery or radiotherapy, although congenital and fistulae with rare aetiologies also occur. The vast experience of high volume surgeons in large fistula centers in the developing world and the more advanced techniques used by surgeons in the developed world to repair fistulae, is in sharp contrast with the limited amount of high quality publications on this topic. There is a clear need for prospective randomized studies.

Because of the nature of the literature on fistulae, not only systematic reviews and meta-analyses and randomized controlled trials are reported, but also cohort studies and even relevant case studies. We hope that this chapter will inspire people to setup and run future trials on fistula prevention, treatment and complication management.

II. EPIDEMIOLOGY

1. VESICOVAGINAL FISTULAE

1.1. Obstetric fistulae

Epidemiological studies on obstetric fistulae (OF) are difficult to manage, given the local circumstances in developing countries. Many of them are based on retrospective case series from a single fistula centre (hospital –based) or use questionnaire based approaches (community –based). A questionnaire-based study in Pakistan in 9134 women, showed that the region of origin (e.g. Punjab), delivery by caesarean section or women reporting complications during the pregnancy were more likely to develop OF (OR = 1.96, 95%CI = 1.19-3.16).[1] A population-based cross-sectional study in India of 3939 women showed an incidence of 0.3%. [2] A systematic review by Adler et al. found 19 studies that could be evaluated.[3] The studies included data from West Africa, Bangladesh, Turkey, Jordan, Ethiopia, Egypt and India. The number of new fistulae ranged from 0.09 per 1000 recently pregnant women in community-based studies to 0.66 per 1000 pregnancies in hospital-based studies. A study in Mozambique on a selected cohort of recently delivered women, found a fistula incidence of 1.1 per 1000. [4] The WHO has suggested that over two million women, mostly from sub-Saharan African and Asian countries, have fistulae. Given an estimated population of 645 million women of reproductive age in sub-Saharan Africa and South Asia in 2010 (http://esa.un.org/wpp/unpp/p2k0data.asp), this would suggest that 3 per 1000 women of reproductive age have a fistula, which is considerably higher than other estimates. They estimated the pooled prevalence from population studies at 0.29/1000 pregnancies. For Sub-Saharan Africa this number rises to 1.6/1000 and for South Asia to 1.2/1000. The incidence was estimated at 0.009/1000 recent pregnancies. Rural areas probably under report the real prevalence. [5]. Cowgill et al. performed another systematic review, also looking at the association of stillbirth and fistula.[6] They included 62 studies. Incidence estimates ranged from 0 to 4.09 OF cases per 1000 deliveries, while prevalence estimates were judged more prone to bias and ranged from 0 to 81.0 OF cases per 1000 women. Reported frequency of still birth (SB) associated with OF ranged from 32.3 % to 100 %, with estimates from the largest studies around 92 %. The major risk factors appear to be young age at first marriage, short stature, pregnancy with a male child rather than a female child, failure to attend ante-natal care, low socio-economic status, low social class, lack of employment and illiteracy. Misconceptions regarding the cause of OF persist, mostly in rural areas and most in men. Misuse of family planning, intercourse during the menstruation, curses by relatives, sexually transmitted diseases (STD) and rape or gender-based violence are still seen as potential causes.[7] Education programs should be directed against these misconceptions. Health system causes such as poor quality obstetric care, staff unaccountability, late referral, poor nursing standards are very prevalent in sub-Saharan Africa and rural areas of Pakistan and other parts of Asia. [8, 9, 10]

The systematic review by Swain et al. calculated that the prevalence of OF is 1/1000 in low and middle income countries and 1.57/1000 if only sub-Saharan Africa and South-Asia data are taken into account.[2, 11]

Author	Year	Region	Incidence	Prevalence
Adler et al. [3]	2016	Africa, South Asia	0,29% (95%CI: 0,00-1,07)	5,68% (95%CI: 5,04-6,40)
Swain et al. [2]	2020	developing countries	not studied	1/1000 to 1.57/1000
Cowgill et al. [6]	2015	Africa, South Asia	0-4.09/1000	0-81/1000

The consequences of OF include divorce (16-92%), social isolation, worsening poverty, malnutrition, sexual dysfunction and mental illness (including anxiety/depression), insomnia, general ill health and thoughts of worthlessness and suicide. [12, 13]

There are few detailed reports documenting these women's obstructed labours. The time of onset of labour is rarely recorded and reports from delivery locations may disregard the fact that the woman has laboured at home for days prior to attending the delivery location. The reason for the woman not receiving help rarely differentiates between the absence of health-seeking behaviour and the lack of services. A study in Mali and Niger looked at the pathway these patients followed. The mean duration of the fistula was 4 years and the entire care process took up to 2.7 years, of which 7 months were spent at the repair centre.[14, 15] Treatment seeking behaviour is poorly understood. A study in sub-Saharan Africa showed that only 60.3% of women experiencing fistula related symptoms actually sought treatment and that only 28.5% underwent surgical treatment. The leading reasons for not seeking treatment were: unaware that it can be repaired (21.4%), do not know where to get the treatment (17.4%), economic constraints (11.9%), the fistula healed by itself (11.9%) and feeling of embarrassment (7.9%). The regression analysis indicated, teenagers as compared to adults 35 years or older [16]; and women without formal education compared to women with formal education [16], had reduced odds of treatment-seeking.[16]

Recommendations

Community-based epidemiological studies using standardised and validated collection tools with acceptable sensitivity and specificity are highly recommended.	A
Observational and longitudinal studies are needed, utilising advanced epidemiological analyses for risk factors (multivariate analysis controlling potential biases), the impacts and consequences of vesicovaginal fistula (VVF) and for factors determining health-seeking behaviour.	A
Community health workers play a major role in detecting and managing women at risk of OF. Training and resources should be invested to allow for early detection and referral programs.	A

1.2. Iatrogenic Fistulae

While in the developing world poor obstetric care is usually at the origin of VVF, gynaecological or pelvic surgery is the main causes of VVF in the industrialised world. In some developing countries, as caesarean sections and gynaecological procedures to treat benign and malignant conditions of the female reproductive tract are more commonly performed, the rate of iatrogenic fistulae is increasing (e.g. Pakistan, Bangladesh). [17, 18]

1.2.1. Post-gynaecological surgery

A recent study by Dallas et al. on nearly 300000 women undergoing hysterectomy for benign indications, there were 2,817 (1.0%) ureteric injuries, 2,058 (0.7%) bladder injuries and 834 (0.3%) genitourinary fistulae (80/834 of which developed after an injury repair). Diagnosis was delayed in 18.6% and 5.5% of ureteral and bladder injuries, respectively. Subsequent genitourinary fistula development was lower if the injury was identified immediately (compared with delayed) for both ureteric (0.7% vs 3.4% odds ratio [19] 0.28; 95% CI 0.14–0.57) and bladder injuries (2.5% vs 6.5% OR 0.37; 95% CI 0.16–0.83). Indwelling ureteral stent placement alone was more successful in decreasing the risk of a second ureteral repair for immediately recognized ureteric injuries (99.0% vs 39.8% for delayed injuries). With multivariate adjustment, prolapse repair (OR 1.44, 95% CI 1.30–1.58), an incontinence procedure (OR 1.40, 95% CI 1.21–1.61), mesh augmented prolapse repair (OR 1.55, 95% CI 1.31–1.83), diagnosis of endometriosis (OR 1.46, 95% CI 1.36–1.56), and surgery at a facility in the bottom quartile of hysterectomy volume (OR 1.37, 95% CI 1.01–1.89) were all associated with an increased likelihood of a genitourinary injury. An exclusively vaginal (OR 0.56, 95% CI 0.53–0.64) or laparoscopic (OR 0.80, 95% CI 0.75–0.86) approach was associated with lower risk of a genitourinary injury as compared with an abdominal approach. [20] They concluded that genitourinary injury occurs in 1.8% of hysterectomies for benign indications and that immediate identification and repair is associated with a reduced risk of subsequent genitourinary fistula formation.

The types of fistulae associated with gynaecological procedures may include communication between any reproductive organ (uterus, cervix, Fallopian tube, vagina), intestinal tract (colon, rectum), genitourinary organ (bladder, ureter, urethra), and cutaneous system (abdominal wall, perineum). In general, VVF are the most common type. The most common causes of VVF as a consequence of surgery, in developed countries is an injury to the urinary tract during hysterectomy for benign conditions (60-75%), followed by hysterectomy for malignant conditions (30%), caesarean section (6%), and obstetric injuries (1%). [21] [22] Overall, the risk of pelvic organ fistula following hysterectomy has been reported to be between 0.1 and 4%. [23]. It is important to recognise that most urinary tract injuries do not result in a fistula.

The prevalence of genitourinary injury and fistulae vary slightly from centre to centre. In one US retrospective study from the Mayo clinic, gynaecological surgery was responsible for 82% of the fistulae, obstetric procedures for 8%, and various forms of irradiation for 6%, and trauma or fulguration for 4%. The majority of fistulae followed treatment for benign conditions. [24] The relative proportions of the types of urinary fistula have changed with urethral fistulae having increased from 6 to 13%, while ureteric, bladder and/ or urethral fistulae having dropped from 20 to 16 and 11 to 7%. (2)

Given the various indications for, and types of hysterectomies, it is important to have an understanding of the type of hysterectomy since genitourinary or colonic fistula is reported with all of these procedures. The overall incidence of hysterectomy complications is estimated to be <2%, with bladder injury (1.3%) and ureteric injury (<1%) being most commonly reported. [25] Traditionally, the most common route used to remove the uterus for benign and malignant gynaecological conditions is abdominal (open incision, laparotomy); referred to commonly as total abdominal hysterectomy (TAH). The types of hysterectomies also include total vaginal (TVH), laparoscopically-assisted vaginal (LAVH), total laparoscopic (TLH), and subtotal or supracervical abdominal (SCH) or laparoscopic (LSH). Laparoscopic procedures may be done using traditional laparoscopic techniques, robotic assistance, and more recently, the single-site umbilical technique or through Vaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES). [26]

Benign and malignant conditions confined to the uterus are usually treated with a simple hysterectomy using any of the methods mentioned above. More advanced malignant conditions are usually treated with a radical hysterectomy in which parametrial and/ or vaginal dissection and removal may be involved. In rarer cases, exenterative procedures to remove the bladder or colon may be required if malignant extension to these organs is found. In some centres, robotic radical hysterectomies have been more commonly employed to treat gynaecological malignancies. The rate of urogenital fistula associated with simple abdominal hysterectomy for

benign disease is often reported as being of the order of 1 in 1000. In a national study from Sweden the rate of women undergoing any fistula surgery was reported as 0.26% in women having had a hysterectomy compared to 0.0007% in those not exposed to hysterectomy, with the 'number needed to harm' being estimated at 5700.[27] From Finland the rate of VVF was reported to be 1 in 1250 after all hysterectomies, 1 in 455 after laparoscopic, 1 in 1000 after total abdominal, and 1 in 5000 after vaginal hysterectomy.[28] The publicly available tables from the national hospital database in England give similar figures of 1 in 600 after total abdominal hysterectomy, and 1 in 5000 after vaginal hysterectomy.[29, 30] More detailed longitudinal analysis of patient-level information from the same dataset suggests a rate of 1 in 788 for all types of hysterectomy, 1 in 540 for abdominal hysterectomy for benign disease, 1 in 896 following vaginal hysterectomy for benign disease (excluding prolapse), and 1 in 3861 following vaginal hysterectomy for prolapse.[31]

Caesarean hysterectomy is a recognised cause of fistula, [32] and, with the increase in the number of caesarean deliveries there have been more fistulae related to obstetric surgical trauma.

The degree of bladder injury appears to be a major factor in iatrogenic fistula formation. In one study, 1,317 benign hysterectomies were reviewed (46% abdominal, 48% vaginal, and 6% laparoscopically assisted vaginal) with reference to risk factors for VVF following intraoperative injury to the urinary tract. In all, 34 cystotomies occurred with 4 (11.7%) developing a VVF. Patients who developed a VVF were more likely to have a large cystotomy and these individuals trended toward greater tobacco use, larger uterine size, and more operative blood loss. [33] Another study involving 3,076 vaginal hysterectomies with or without additional gynaecological procedures, one ureteric injury and 54 bladder lacerations were noted yielding a total of 4 VVF. The bladder lacerations occurred during the hysterectomy portion of the surgery in 61% of cases and during the additional procedures in 39%. [34] Also in developing countries iatrogenic fistulae occur. Raassen et al. found 805 iatrogenic fistulae in a series of 5959 (13.5%) patients in 11 countries. Most fistulae occurred as a consequence of caesarean section, intervention or hysterectomy for ruptured uterus.[35]

VVFs associated with hysterectomy may require ureteric reimplantation in as many as one-third of the cases. [36] Ureteric trauma should be considered in any hysterectomy or operative obstetric procedure regardless of the difficulty but certainly in more difficult cases.[37] Iatrogenic ureteric injury may occur after less common procedures such as ureteroscopy, lumbar sympathectomy, abdominal trauma, and iliac vessel ligation. [38]

1.2.2. Oncological fistulae

The literature relating to fistulae of oncological aetiology is limited both in quantity and quality. Seventy-six papers of possible relevance were identified, of which only 52 contained any relevant material. Only one randomised trial was directly identified from the literature searches,[39] although one non-systematic review of relevance,[40] and two systematic reviews were found;[41, 42] each of the latter contained only one further randomised trial. One national cohort study, and one non-randomised cohort study, are included,[31, 43] but all other identified material comprised case series or case reports, and represent level 3 or lower evidence. Two cases of duplicate publication (*i.e.* the same paper in two journals) were found.

In the oncological context, fistulae may occur as a result of primary or recurrent malignancy, or as a consequence of cancer treatment by surgery, radiotherapy, chemotherapy, or a combination of therapies.

In one study, 536 women underwent a radical hysterectomy for invasive cervical cancer. More advanced stage of disease, obesity, diabetes, and postoperative surgical infection were predisposing factors to urinary tract complications. In this study, ureteric injury occurred in 1.32%, bladder injury in 1.49% with VVF forming in 2.61% and ureterovaginal fistulae in 2.43% of cases, respectively. [44] In a similar report, 1,092 women with cervical cancer underwent a radical hysterectomy with obligatory pelvic lymphadenectomy. A VVF occurred in 0.3% and a ureterovaginal fistula occurred in 1.4%. [45] The rate of GU injury likely varies between centres. For example, in one report of 479 women undergoing different methods of radical hysterectomy for cervical cancer over a 15 year period, 52 (10.8 per cent) had urological complications (17 bladder and ureter injuries, 35 fistulae and strictures). [46] In contrast, one institution reported that , with modifications and careful dissection, ureteric and bladder injury have almost been eliminated.[47]

In two recently published case series, one of fistulae specifically associated with gynaecological cancers,[40] and one of urogenital fistula from all causes,[30] those relating directly to primary cancer were uncommon, (2/20=10%)[40] and (2/348=0.6% - *2/66=3% of the oncological cases in this series*),[30] respectively. Fistulae associated with cancer surgery (3/20=15% and 30/348=8.6% - *30/66=45% of the oncological cases in this series*) or radiotherapy (15/20=75% and 34/348=9.8% - *34/66=52% of the oncological cases in this series*) made up a much larger proportion of both series.

Immune-deficiency may be a further contributory factor, and enterovesical fistula has previously been reported in association with non-Hodgkin's lymphoma in HIV-AIDS,[48] and VVF has been seen in association with classical Hodgkin's affecting the vagina in a long-term pessary user.[49]

1.2.2.1. Cancer surgery

It is likely that all operations carried out in the pelvis can be complicated by genital tract fistula in some circumstances.[30] Operations carried out with the intention of curing malignant disease will inevitably carry a higher risk of subsequent fistula formation, as compared to those undertaken with less radical intent.

Following radical hysterectomy for cervical cancer (Wertheim-Meigs procedure) the rate of fistula formation reported from case series is between 0.6% and 4.4%.[44, 50, 51, 52, 53, 54, 55] It should be noted that these data are very heterogeneous, some reporting all types of fistula together. Where they are reported separately, the rates of vesicovaginal and ureterovaginal fistula appear to be of the same magnitude with both being reported in between 0.9% and 2.5%. of cases [44, 56, 57] The data from UK cited above suggest a urogenital fistula rate of 1 in 95 following radical abdominal hysterectomy in women with malignant disease as compared to 1 in 540 for TAH for benign disease, and one in 2041 for TVH for all benign disease (including prolapse).[31] Overall, the rate of urogenital fistula appears to be approximately 9 times higher following radical hysterectomy in women with malignant disease as compared to that following simple hysterectomy (abdominal or vaginal) in women with benign conditions.[31]

The risk of visceral injury or subsequent fistula formation following radical hysterectomy undertaken in pregnancy, or immediately following Caesarean section is not obviously increased over those carried out electively in non-pregnant individuals; Monk & Montz described inadvertent cystotomy followed by vesicovaginal fistula

in one of 21 women operated on during or immediately after pregnancy.[58]

Several modifications to the conventional Wertheim-Meig's procedure of radical hysterectomy have been described in an effort to reduce the associated morbidity. None of them seems to offer a benefit regarding fistula formation. [46, 50, 59]

Given the increased risk associated with radical surgery for malignancy, it is intuitive that the risks would increase with the stage of disease and with the extent of the surgery undertaken. There are few published reports of fistula following exenterative surgery. One study noted a 16% VVF rate in 19 women following exenteration for vulval carcinoma;[60] while another describes a 15% bowel fistula rate and an 8% urinary fistula rate from a series of 75 exenterations for recurrent cervical cancer.[61] In contrast, Ungar et al. describe only one ureterovaginal fistula and one pouch–vaginal fistula in 212 women undergoing exenteration out of a total of 2540 women treated for cervix cancer in one centre over a 13 year period (0.9%).[62]

Bladder sparing techniques during pelvic exenteration can carry a risk for fistula formation.[63] Also when the bladder has been removed and a neo-bladder has been constructed, fistulae between the neo-bladder and the vagina may occur.[64, 65]

The introduction of laparoscopic surgery within oncology is seen to have considerable advantages in terms of patient recovery; the risk of operative injury to bowel and the urinary tract, and subsequent fistula formation may however remain a concern in such cases. Although some studies, both case series and non-randomised cohorts, describe similar rates of injury to those described following open radical surgery,[43, 56, 57, 66, 67] others have reported injury or fistula rates several times higher following laparoscopic radical hysterectomy.[51, 68]

The risk of urinary tract injury from minor surgical interventions is in general low, although the use of repeat procedures may confer a significant increase in risk. VVF has been reported following repeated use of CO_2 laser for vaporisation of vaginal condylomata,[69] and following cone biopsy of the cervix.[70] In one personal series of 370 urogenital fistulae, 4 were associated with large loop excision of the transformation zone (LLETZ) of cervix, 3 of which followed a second LLETZ procedure (*Hilton, personal communication*).

Rarely, localised malignancies have been associated with VVF. One example is a primary mixed mullerian vaginal tumour reported in a 48-year female. [71] The mechanism for fistula formation is likely to be direct invasion into the bladder.

Genitourinary injuries during colorectal surgery are rare. Eswara et al. described 75 GU injuries in 42570 colorectal surgeries: cystotomy (35%), incomplete ureteric transection (29%), ureteric injuries (15%). Pre-operative external beam radiotherapy or chemotherapy and delayed repair were associated with worse outcome.[72]

1.2.2.2. Radiation fistulae

Pelvic irradiation can be delivered by external beam as well as locally (intracavitary/brachytherapy). Fistula formation appears to be slightly higher for postoperative external radiation (1.9%) compared to intravaginal brachytherapy (0.8%). [73] It does not appear that pre-treatment factors accurately predict those who will develop fistula related to radiotherapy. [74]

The literature in this area is particularly heterogeneous in nature, with wide variation in (and some lack of clarity over) the tumour type and stage being treated, the form of radiation and the site and dose delivered. In a series of urogenital fistulae from the UK, 34/348 or 9.8% were associated with previous radiotherapy; of those related to gynaecological cancer, 34/66 or 52% had undergone radiotherapy.[30] In a further series of cases specifically related to gynaecological malignancy, 15/20 or 75% had undergone previous radiotherapy.[40] In both series most cases followed radiation used for the treatment of cervical cancer, although, 5/34 or 15% followed treatment of endometrial cancer, and 1/34 or 3% followed treatment of a multifocal gynaecological cancer in one series.[30] Amongst a series of 216 radiation-induced fistulae, the time to diagnosis of the fistula was made between 3 months and 10 years (mean 21 months) following radiation.[75] In other series fistulae have been reported to develop or present up to 30 years after the 'causative' influence.[30, 76] (Figure 1a and 1b)

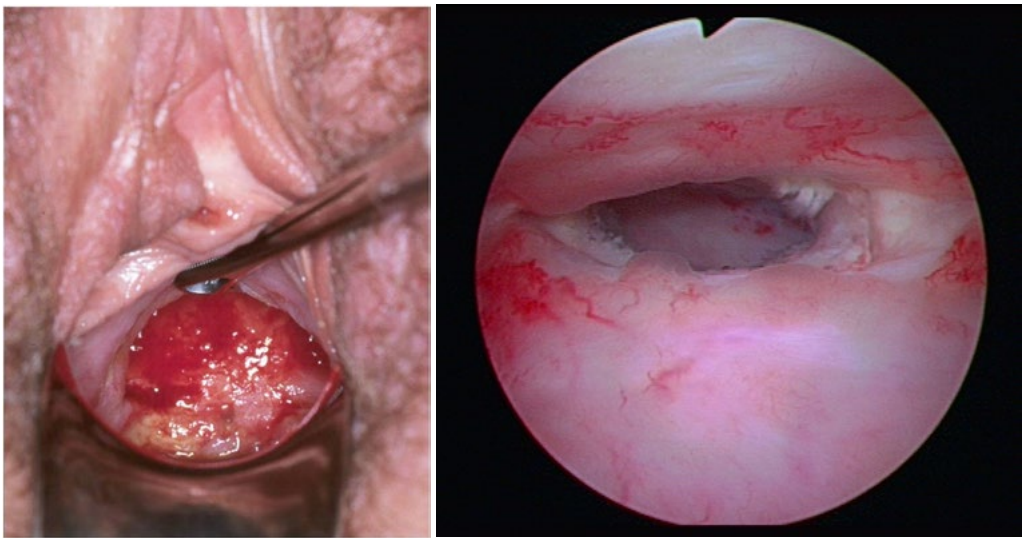


Figure 1a. Left: Acute radiation fistula; Right: fistula 20 years after radiotherapy, both for cervixcarcinoma

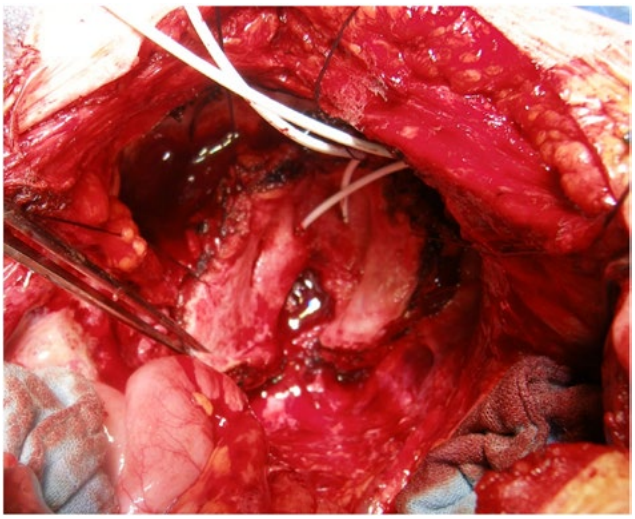


Fig 1b.Supratrigonal vesico-perineal radiation fistula in a small contracted bladder that occurred 22 years after cobalt irradiation for a gynaecological tumour.

The incidence of any deleterious clinical impact on the gastrointestinal and urinary tracts following radiation varies in the literature between 1% and 12%,[42, 77, 78, 79, 80, 81, 82, 83] with fistula rates of 1% to 5%.[40, 84]. In a retrospective review of 2096 patients treated for cervical cancer over a 10-year period using unspecified regimen/s of radiotherapy, 38 patients (1.8%) were found to have developed fistulae, all of whom had stage IIIa/b or IV disease at presentation.[80] Of these cases, approximately 3/4 involved the rectum, with 1/3 being combined rectovaginal and VVF; 1/4 were vesicovaginal only.[80]

Following a clearly defined regimen of external beam radiation plus brachytherapy for the treatment of primary squamous cell carcinoma of vagina in 91 women, de Crevoisier et al. reported 10.0% grade 2-3 urinary tract toxicity (using the Franco-Italian glossary) [85] and 12.1% grade 2-3 gastrointestinal toxicity.[78] Unsurprisingly, they found anterior tumour location to be correlated with increased risk of bladder toxicity and decreased rectal toxicity. Two women in this series developed rectovaginal fistulae (2%), and one ureterovaginal fistula (1%).[78]

In a series of 10,709 women treated by telebrachytherapy (67.5 Gy) for a range of gynaecological cancers in one centre over a 22 year period, 133 (1.2%) developed urological complications of which 35 (0.3%) developed fistulae.[82]

In a series of 28 women treated by brachytherapy for recurrent corpus or cervix cancer, four patients developed chronic morbidities related to treatment. Three fistulae were reported in two patients (7.1%): one combined rectovaginal and VVF and one ureterointestinal fistula; a further patient developed a ureteric stricture and small bowel obstruction requiring resection.[83]

These data tend to suggest a higher rate of fistulae formation following the application of radiotherapy in locally recurrent disease than in primary disease. From a small series of urological complications following radiotherapy for gynaecological cancers, 14 had developed vesicovaginal fistula; of these 4 (29%) had evidence of tumour recurrence.[81] In the series reported by Jones at al. 326/1161 (28%) developed urological complications over a 20 year period; 46 developed fistulae (4%), of whom 33 (72%) had evidence of active malignant disease.[53]

In prostate cancer patients, recto-urethral fistula are described after cryotherapy (0.1-4%)[86], HIFU (0.7%)[87], brachytherapy (2%) [88].

When a fistula occurs after radiotherapy, it is considered good clinical practice to exclude tumour recurrence before attempting a fistula closure. Feddock et al. found 27 fistula in 325 patients after post-radiation biopsies for cervical cancer.[89] The fistula were toxicity related in 51.9%, a consequence of primary disease in 22.2% and of recurrent disease in 25.9%. The residual or recurrent cancer found in the biopsies was only 31.5%. Elevated radiotherapy doses to the rectum, advanced tumour stage and post-radiotherapy biopsy were considered risk factors for fistula formation.

1.2.2.3. Chemotherapy

There are few reports of fistula formation in association with the use of chemotherapy. One case report described a patient who developed a VVF having undergone TAH for atypical endometrial hyperplasia whilst taking *tamoxifen* following a previous modified radical mastectomy. Surgical repair of the fistula was initially unsuccessful, although after discontinuing the *tamoxifen* and continued bladder drainage, healing occurred.[90] It was hypothesised that the impaired healing was a result of the administration of the hormone therapy.

1.2.2.4. Combination therapies

Adjuvant or neoadjuvant therapies are used to increase the efficacy of the primary treatment, compared to its use in isolation. It might be anticipated that this would also increase the range and magnitude of adverse effects.

In a case control study examining the urinary tract complications of radical hysterectomy only a single VVF was seen in 50 patients (2%) – in a patient receiving preoperative irradiation (45-50 Gy). [91] A small case series found 2/20 or a 20% rate of urinary fistulae following preoperative irradiation and radical hysterectomy in a heterogeneous group of 'high risk' cervix cancers.[92] A further case series described the impact of combined external whole pelvic irradiation (50 Gy) and intravaginal cone boost (20-26 Gy) following radical hysterectomy in 108 women. The overall rate of fistula formation was 3.7%, 2.2% following 'prophylactic' radiation, and 10.5% in 'salvage' cases where recurrent disease was present.[93]

Modarress et al. reported a randomised comparison of preoperative combined chemoradiation (cisplatin plus external beam therapy) and neoadjuvant chemotherapy (cisplatin plus vincristine) followed by radical hysterectomy in stage IB-IIB bulky cervical cancer.[39] Four patients developed hydronephrosis (3 in the chemoradiation group – 13.3%) and two vesicovaginal fistula (both in the chemoradiation group – 6.7%).[39] Two further case series reported 2/36 or a 5.6% rate of fistulae following preoperative chemoradiation (cisplatin plus brachytherapy) followed by radical hysterectomy,[94] and 4/46 or 8.7% rate of fistulae following the use of neoadjuvant and postoperative chemotherapy using irinotecan, cisplatin and nedaplatin.[95]

1.3. Rare causes of VVF

Foreign bodies such as pessaries, sex toys, herbs, cups etc… can be a cause of VVF. [96, 97, 98, 99] Often the presentation is delayed (up to 15 months). Also ketamine abuse can not only lead to severe changes in the bladder wall structure, but also to fistu-

la formation, as was shown in 14.8% of 27 patients undergoing a CT-urography. [100]

2. UTEROVESICAL FISTULAE

Uterovesical fistulae classically present as a triad of cyclical hematuria and amenorrhea without urinary incontinence. This clinical entity was first described in the literature by Burkland in 1949 and by Nourse in 1953 but is referred to as Youssef's syndrome since his publication in 1957[101, 102, 103]. Menouria and amenorrhea are the most common symptoms.

Uterovesical fistulae can have several causes. The mechanism through which the abnormal connection between bladder and uterine cavity arises can be acute (e.g. traumatic during caesarean section), progressive (e.g. migration of foreign body) or congenital. [104]

The most common cause is an iatrogenic injury during caesarean section (83-93% of cases) [105]An increased number of caesarean sections leads to an increase in abnormally invasive placentae. Placenta praevia and percreta can lead to dramatic obstetric situations, necessitating an emergency caesarean section. The uterovesical fistulae can form afterwards when the bladder and the uterus and the bladder are not well separated or sutured. [106]

In a study by Rao on 14 patient's, an emergency caesarean section was at the origin of the fistula and in 58% the fistula was formed after the second caesarean section.[107] The mean duration between the caesarean and the diagnosis of the uterovesical fistula was 7 months. These findings have also been confirmed by Washington et al. looking at 34 patient's with cervicovesical or uterovesical fistulae of whom 29% had caesarean section compared to 9% who delivered vaginally.[108]

Congenital forms of uterovesical fistulae – often associated to more complex urogenital malformations -have been described as well, but are very rare.[109]

The diagnosis can be made clinically or by performing cystoscopy during the episodes of menouria. Hysterography, ultrasound, CT scan and MRI scan can be helpful in establishing the location and the size of the fistula. Early detection of abnormally invasive placentas by ultrasound has a good diagnostic accuracy (overall sensitivity of 100% (95% CI 96.5-100) and overall specificity of 61.9 (95% CI 51.9-71.2) for all types of abnormally invasive placenta.[Cali, 2018, Diagnostic accuracy of ultrasound in detecting the depth of invasion in women at risk of abnormally invasive placenta: A prospective longitudinal study] There is a correlation between the ultrasound staging of the placenta accreta spectrum and the peri-operative complications. This is important for counseling patients and for optimizing the care at the time of the delivery.[110]

The treatment is surgical, although there is one case report of a successful conservative treatment as well.[111] Classically a trans-peritoneum approach will be used, where the plane between bladder and uterus will be developed, the fistula closed and eventually interposition material will be used. Laparoscopic and robotic approaches (even early after caesarean section) have been described.[19, 112] The outcome of the surgery is very good. A multidisciplinary approach is advocated to prevent infertility.[113]

3. URETERIC FISTULAE

The real incidence and prevalence of ureteric fistulae is difficult to assess, because the literature only consists of retrospective case series. Studies on large databases suffer from the lack of detail on the type of ureteric fistulae, studies on smaller, mostly institutional, databases suffer from selection bias. However, some of the more recent studies shed some light on the occurrence of ureteric fistulae and the impact of the fistulae on some of the outcomes.

Post gynecological surgery

Genitourinary tract fistulae have an occurrence rate of approximately 1–2% for all major gynecological surgeries. [114] Among these injuries, 75% occur during hysterectomy, which leads to an average of 5,000 injuries annually in the United States. [115]

Blackwell et al. performed a study on 223872 patients, undergoing a hysterectomy between 2007 and 2011, using the Healthcare Cost and Utilization Project California State Inpatient Database. They made a distinction between ureteric injuries that were recognized and diagnosed during the surgery and those that were not recognized and thus repaired in a secondary surgery. Ureteric injury occurred in 1,753 of 223,872 patients (0.78%) and it was unrecognized in 1,094 (62.4%). The 90-day readmission rate increased from a baseline of 5.7% to 13.4% and 67.3% after recognized and unrecognized injury, respectively. Nephrostomy tubes were required in 2.3% of recognized and 23.4% of unrecognized ureteral injury cases. Recognized and unrecognized ureteric injuries independently increased the risk of sepsis (aOR 2.0, 95% CI 1.2e3.5 and 11.9, 95% CI 9.9e14.3) and urinary fistula (aOR 5.9, 95% CI 2.2e16 and 124, 95% CI 95.7e160, respectively). During follow up unrecognized ureteral injury increased the odds of acute renal insufficiency (aOR 23.8, 95% CI 20.1e28.2) and death (1.4, 95% CI 1.03e1.9, p ¼ 0032).[116]

Hwang et al. performed a meta-analysis comparing the risk for urological complications between laparoscopic radical hysterectomy (LRH) and abdominal radical hysterectomy(ARH).[117] The odd ratios (OR) of LRH for the risk of intraoperative urological complications compared to abdominal radical hysterectomy (ARH) was 1.40 [95% confidence interval (CI) 1.05-1.87]. The OR of LRH for postoperative complication risk compared to ARH was 1.35 [95% CI 1.01-1.80]. The incidence of bladder injury was statistically higher than that of ureter injury (p = 0.001). In subgroup analysis, obesity and laparoscopic assisted vaginal radical hysterectomy were associated with intraoperative urologic complications

The urinary bladder is often injured when the prevesical plane is dissected, especially during formation of a bladder flap during abdominal or laparoscopic hysterectomy. These injuries tend to be noticed at the time of surgery except for serosal injuries that do not create a full-thickness defect in the bladder wall, which can lead to delayed cystotomy and vesicovaginal fistula formation during the postoperative period. Factors that increase the risk of cystotomy during hysterectomy include cesarean delivery, endometriosis, pelvic adhesions disease, and cancer.[118] Ureteric injuries tend to be less frequent than bladder injuries, but possibly because their incidence is grossly underestimated. Studies demonstrate that about 66% of ureteric injuries go unrecognized at the time of surgery. Injuries tend to occur during dissection along the pelvic sidewall, especially when dissecting along the infundibular-pelvic ligament. Less common sites of injury include the lower uterine segment during ligation of the uterine vessels and the base of the bladder during ligation of the cardinal and uterosacral ligaments.[114] Several factors predispose the patient to ureteric injury and these include

former pelvic surgeries, hemorrhage, endometriosis, cancer, and compromised exposure secondary to large pelvic masses (leiomyomas) or obesity. [115]

Prevention of genitourinary tract injury. It is vital to identify the bladder and ureters accurately during dissection to preclude injury to these structures during a hysterectomy. Clarke-Pearson and Geller (2013) recommend insertion of a Foley catheter at the start of the case, and confirming drainage will reduce the rate of bladder injury regardless of the surgical route taken. As with the urinary bladder, identification principles help to prevent injury to the ureters. The ureters pass over the bifurcation of the common iliac vessels before coursing below the uterine artery and passing anterior and lateral to the cervix. It is important to pinpoint the ureter on the medial aspect of the broad ligament when operating in the pelvis. Using a retroperitoneal approach by opening the pararectal space can help to identify the ureter in this region. If hemorrhage obscures the surgical field, it is vital to apply pressure rather than clamping and ligating. There is no evidence that preoperative ureteral stenting decreases the rate of ureteric injury during hysterectomy, but intraoperative stenting in cases in which the ureters cannot otherwise be identified can help (Clarke-Pearson and Geller, 2013).

Wallis et al. performed a retrospective cohort study of patients undergoing hysterectomy for benign disease from 2010 to 2014 using the American College of Surgeons National Surgical Quality Improvement Program.[119] They identified 101,021 patients treated with hysterectomy for benign disease: 18,610 (18.4%), 27,427(27.2%), and 54,984 (54.4%) underwent vaginal, open, and laparoscopic hysterectomy, respectively. Cystoscopy was performed in 16,493 cases (16.3%). There were 2427 patients (2.4%) who underwent a concomitant urological intervention. Patients undergoing laparoscopic hysterectomy had increased occurrence of urological intervention, excluding cystoscopy (adjusted odds ratio 1.47, 95% confidence interval 1.29-1.69), compared to vaginal hysterectomy; no differences were found between open and vaginal hysterectomy or laparoscopic and open hysterectomy. Larger uteri, a postoperative diagnosis of endometriosis, increasing comorbidity, and African American race were associated with increased odds of urological intervention whereas concomitant cystoscopy was associated with a decreased chance

Among the whole cohort, 2427 patients (2.4%) underwent a concomitant urologic procedure other than cystoscopy: 1447(1.4%) had endoscopic stent insertion, 375 (0.4%) had a ureteric repair, 717 (0.7%) had a bladder repair, 6 (0.01%)underwent total cystectomy, and 1 underwent urinary diversion without cystectomy.

Sometimes the ureteric injury can be associated to a vesicovaginal fistula. Seth, Jimenez=Romero et al. reviewed their case series of 116 patients retrospectively and found that 3.4% of their patients had an associated ureteric injury. [120]

Prevention

As mentioned above, two thirds of the ureteric injuries are not recognized during surgery. Therefor prevention is very important. The use of cystoscopy is advocated by some authors, while others doubt about the added value. Barber et al. (2019) did retrospective study on 39529 women undergoing a hysterectomy and looked at the rate of delayed 30-day lower urinary tract injury. There was no difference in delayed lower genitourinary tract injury between patients who underwent cystoscopy at time of hysterectomy compared with those who did not undergo cystoscopy (0.27% vs 0.24%, P=.64). Patients who underwent cystoscopy were more likely to be diagnosed with a urinary tract infection (2.6% vs 2.0%, RR 1.27 95% CI 1.09-1.47). Median operative time was increased by 17 minutes in cases where cystoscopy was performed (132 vs 115 minutes, P<.001). [121]

Patton et al. (2019) performed an RCT comparing the use of 10mg Furosemide to saline intravenously during cystoscopy to confirm ureteral patency.[122] Furosemide 10 mg in a routine cystoscopy resulted in a shorter time to confirmation compared with the administration of the placebo (86.5 seconds, IQR 55.0-137.0 vs 165.0 seconds, IQR 77.0-280.0; P<.05). Furthermore, at any given time period, patients receiving intravenous administration of furosemide 10 mg were 2.3 times more likely to have ureteric patency confirmed compared with patients receiving normal saline (95% CI 1.59-3.23). There were no adverse events related to administration of intravenous furosemide and no delayed diagnoses of ureteric injury. Espiallat-Rijo and collegues (2019) also performed a randomized controlled trial comparing saline, 10% dextrose solutio, oral phenazopyridine or intravenous sodium fluorescein. Compared with saline, 10% dextrose and sodium fluorescein resulted in improved visibility and provided significantly more satisfaction in the evaluation for ureteric patency with no considerable increase in operative time or morbidity.[123]Oliveira et al. (2019) used CO2 cystoscopy and could visualise ureteric jetting at 145 seconds (range, 80-300 seconds).[124]

Although the beneficial effects of PUC on IUI incidence remain controversial, when a ureteric injury occurs during pelvic surgery, the presence of prophylactic ureteric catheters can significantly reduce both diagnostic delay and postoperative morbidity. By promoting an immediate repair, ureteric catheterization reduces need for further diagnostics and secondary interventions. [125]

Uretero-arterial fistulae

The obvious symptom of an arterial-ureteric fistula is gross haematuria, that can be pulsatile. Most of the time it is intermittent haematuria. Some predisposing factors have been described: inflammation after ureteric surgery, retroperitoneal fibrosis after (mostly vascular) surgery or radiotherapy. Most of the fistulae occur after placement of ureteric stents. The time to fistulae from the initial stent can be between 1-8 years. [126] This type of fistula also has been found after endovascular repair of a ruptured abdominal aortic aneurysm (rEVAR) [127] The mortality rate has decreased from 69% in 1980 to 7-23% in 2018. [128]

In case of gross hematuria during ureteric stent change in female patients with history of previous pelvic surgery and radiation, UIAF must be suspected and immediately treated, since it represents a urological emergency. Angiography can be useful to confirm the diagnosis and endovascular treatment with vascular endoprosthesis is the best therapeutic option.[129]

Uretero-Cutaneous And Uretero-Intestinal Fistulae

Ureterocutaneous fistulae have been described as complications of obstructed uteric stones, [130] colorectal surgery, [131] and as complication of an arterial iliac graft. [132] Uretero intestinal fistulae can present as ureterocolic or uretero-ileal fistulae. [133, 134]

4. URETHRO-VAGINAL FISTULAE

An obstetric urethrovaginal fistula may occur as a result of obstructed labour with or without associated VVF. It is more common when the obstructed labour occurs in primiparous rather than multiparous women.[135] In high resource communities urethrovaginal fistula in adults are mostly iatrogenic.

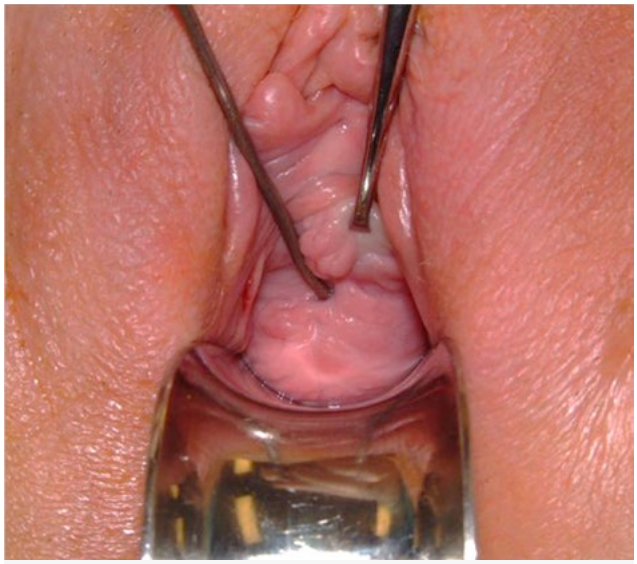


Fig 2: Urethro-vaginal fistula following mid-urethral tape procedure for SUI

In feminising genital reconstructions in children with disorders of sexual differentiation and surgical repairs of cloacal malformations, urethrovaginal fistulae can occur as early or late complications. [136] [137, 138] [139, 140] Urethrovaginal fistulae have been reported in gender reassignment procedures. [141, 142]

In the surgical treatment of stress incontinence in women with bulking agents [143, 144]or synthetic slings several cases of urethrovaginal fistulae have been reported.[145, 146, 147, 148] [149, 150, 151, 152] (see Fig. 2) Even conservative treatment of prolapse with pessaries can lead to the formation of fistulae, if these pessaries are neglected for an extended period of time, although fistula formation after only 2 weeks of pessary use has been described.[31, 153]

Trauma – including inappropriate catheterisation- and foreign bodies are obvious cause of fistulae. [154, 155, 156, 157, 158, 159, 160] Urethral diverticula and their surgical repair may also lead to urethrovaginal fistulae.[161, 162, 163]

Urethrovaginal fistula have also been described in some Behçet patients with vasculitis and local necrosis of the urethrovaginal septum. [164, 165] Irradiation complications can also result in the formation of urethrovaginal fistula.[166]

5. FISTULAE INVOLVING THE GI TRACT

The literature relating to non-obstetric fistulae involving the gastro-intestinal tract is sparse and of poor quality. It should be recognised that, whilst in most papers the term 'enterovesical' is used to describe fistulae between small bowel and bladder, and 'colo/recto-vesical/vaginal' to describe those between large bowel and bladder/vagina, in some reports 'enterovesical' appears to be employed generically to include all fistulae involving the gastrointestinal tract. In this chapter, the term 'intestino-vesical' will be used in circumstances where the generic term is clearly more appropriate.

Whilst occasionally reported congenitally,[167] the most common non-obstetric causes of fistula involving the gastro-intestinal tract are diverticular disease, Crohn's disease, and malignant disease or its treatment. There are few data on the incidence of fistula formation in these conditions, although published estimates are in the range 2-6% in Crohn's disease,[168, 169, 170] and 20% in diverticular disease.[171]

Intestinal fistulae in Crohn's disease most typically involve the small bowel, although communication with urinary tract and large bowel are also found; involvement of the bladder was reported in 27% and of the colon in 14% in one series.[172] Two large series examining the urological complications in association with Crohn's disease reported that whilst a majority of patients were female, the most serious complications were seen in males; most significantly, 13/14 or 93% of the ileo-vesical fistulae described in these series were in men.[168, 173]

Whilst clearly diverticular disease involves the large bowel primarily in all cases, diverticular fistulae have been reported to communicate with the bladder in 65% of cases, the vagina or uterus in 28% and small bowel in 7%.[171] Diverticular disease is the most common cause of colovesical fistulae in most reports, accounting for up to 75% of cases,[174, 175, 176, 177, 178, 179, 180, 181] with colon cancer, bladder cancer, radiotherapy and Crohn's disease accounting for the remainder.

Although there are no direct comparisons between racial groups, the distribution of these causes may vary between populations. Malignancy and/or previous radiotherapy account for 53-93% of cases of colovesical fistula reported from China,[182, 183] presumably reflecting the previously low prevalence of inflammatory bowel disease.[184]

Previous hysterectomy appears to be a significant factor in the incidence of fistulae associated with diverticular disease.[185] In a national case controlled study from Sweden, involving a total of 783,245 women over a 30 year period, the risk of undergoing fistula surgery increased four-fold in hysterectomised women without diverticulitis (hazard ratio (HR) 4.0 (95% confidence interval (CI) 3.5 to 4.7)), seven-fold in women with diverticulitis without hysterectomy (HR 7.6 (95% CI 4.8 to 12.1)) and 25-fold in hysterectomised women with diverticulitis (HR 25.2 (95% CI 15.5 to 41.2)). [186] Another study described previous hysterectomy in 50% of colovesical and 83% of colovaginal fistulae associated with diverticular disease.[171]

6. EVIDENCE STATEMENTS

The risk of injury to the bowel or urinary tract and of subsequent fistula formation is higher in women with malignant disease undergoing radical surgery than in women with benign disease undergoing simple surgical procedures	2
Several modifications to conventional radical hysterectomy have been described, although they have not consistently been shown to mitigate the risk of urinary fistula postoperatively.	3
Data on exenterative surgery are inconsistent, although the risk of fistula formation may be higher following exenteration for recurrent disease as compared to that following radical hysterectomy for the primary treatment of malignancy	3

The rate of visceral injury and fistula formation is inconsistently reported following laparoscopically assisted radical hysterectomy, but may be somewhat higher than following open surgery	3
Local ablative treatments applied in gynaecological oncology, whilst apparently relatively low risk as single treatments, may carry considerable risk for fistula formation when repeated.	3
The rate of fistula formation following radiotherapy for gynaecological cancer appears to be of the same order as that following surgical treatment	4
The risk of fistula formation following radiotherapy for locally recurrent malignancy is higher than following its use in primary disease	2
The use of neoadjuvant or adjuvant therapies is likely to be associated with a greater risk of fistula development than the primary treatment alone	2
The most common non-obstetric causes of fistula involving the gastro-intestinal tract are diverticular disease, Crohn's disease, malignancy and radiotherapy.	2
The causative factors may vary in different populations, with malignancy being more commonly reported in association with enterovesical fistula in China than in other countries	3

7. RECOMMENDATIONS

The development of fistula following radiotherapy for primary treatment should trigger a search for evidence of tumour recurrence	D
Vaginal urinary leakage after pelvic surgery, local ablative treatments or radiotherapy should trigger an investigation for the eventual presence of a fistula	B

III. CLASSIFICATION OF FISTULAE

The Consultation believes that fistula audit research is considerably hampered by the plethora of VVF classification systems, of which we believe there are 32. The Consultation feels that the fistula system that is able to relate its classification to outcome is the classification that should be used in the next few years. The Waaldijk and Goh classifications are the only ones that have been used to document sufficient numbers of patients from diagnosis to follow-up (Fig 2). The Goh Classication has also shown inter – and intra-observer concordance. [187]Figure 2 shows the Waaldijk Classification assessing mainly the extent of the urethral involvement and whether the injury to the urethra is circumferential or not. Fistulae are classified into types I (distance between the distal edge of the fistula and the urethral meatus > 4cm with no involvement of the urethral closure mechanism), II (distance between the distal edge of the fistula and the urethral meatus 1-4cm (type IIA) or 0.5-1cm (type IIB) with involvement of the urethral closing mechanism at the bladder neck and mid-urethral level)and III. Type III fistulae are those fistulae other than vesico-vaginal fistulae and include recto-vaginal fistulae and uretero-vaginal fistulae.

Similarly, the Goh classification included three of the four proven variables known to affect the outcome for obstetric fistula repair. These are the location of the fistula (assessing the extent of urethral involvement), the size of the fistula and the amount of scarring (including whether or not it is circumferential).[188, 189, 190] Also

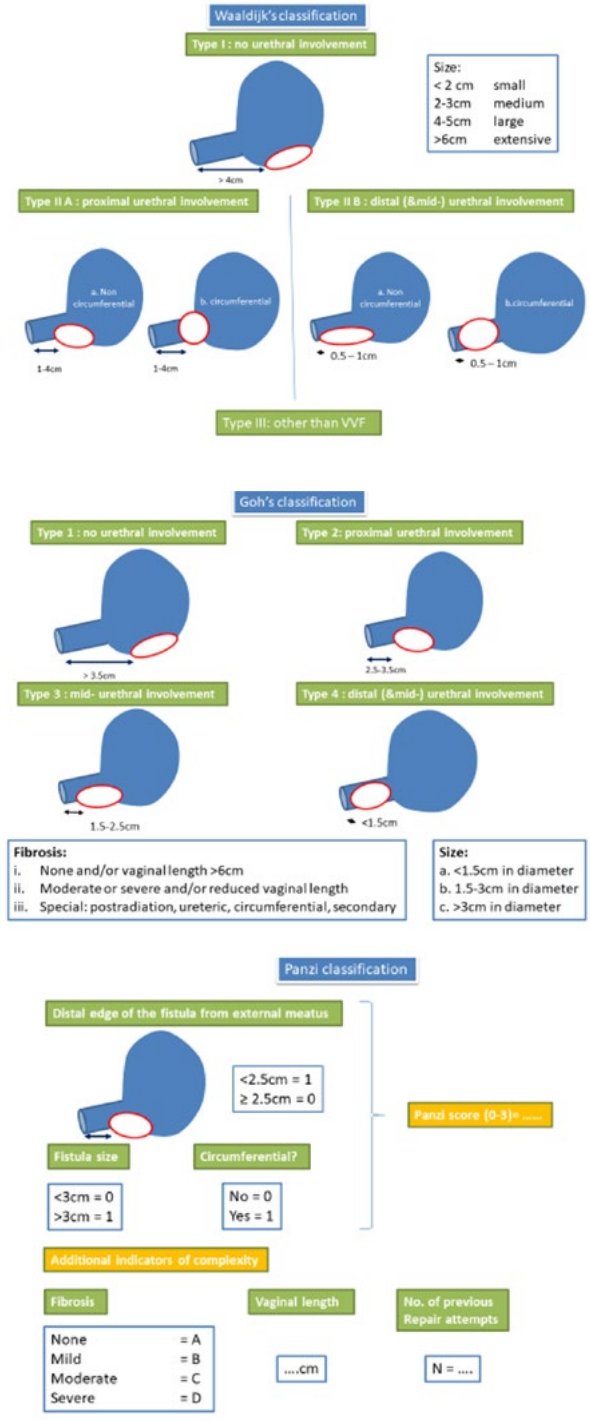


Fig. 3. Classification systems according to Waaldijk, Goh and Mukwege

bladder capacity or size is known to affect outcome, but since this is difficult or even impossible to measure pre-operatively, it has not been included in the Goh classification. (Fig 3)

There has been one comparative study showing that the Goh system is superior to the Waaldijk in terms of predicting closure. [191] Frajzyngier et al, in a prospective cohort study compared the classification systems of Lawson, Tafesse, Goh, Waaldijk and the

WHO.[192] They included 1274 patients in 11 centres. The predictive accuracy for fistula closure was 0.63 for the WHO score, 0.62 for Goh and 0.60 for the Tafesse score. The Waaldijk and Lawson systems fared worse. They propose a new empirical and simplified scoring system. They also suggested including other items in a prognostic scoring systems such as HIV status, malnutrition, malaria and genital cutting. A more recent study demonstrated that the Tafesse system has low predictive value for fistula closure. [193]

The Panzi score was developed following a retrospective analysis of features associated with surgical failure utilising the Goh and Waaldijk systems. [194] The fistula characteristics utilised in the score are location of the fistula, size of fistula and whether or not the fistula was circumferential in nature.

Classification systems have been developed for an obstetric fistula population. (Fig. 3) For iatrogenic fistula the classification is highly variable. The OF classification systems are not always applicable for iatrogenic fistulae. [195]

1. RECOMMENDATIONS

The use of a classification system is recommended. The Goh classification has shown good inter- and intraobserver reliability and is predictive for fistula surgery outcome.	A
Long-term follow up of fistula patients is recommended in order to study the outcome of both conservative and surgical management and, in particular, to determine its effect on quality of life.	C
When reporting the outcome after fistula repair, authors should make a clear distinction between fistula closure rates and post-operative incontinence rates, specifying the time at which follow-up was carried out.	B
A routine post-operative assessment of obstetric fistula needs to be developed to accurately determine the incidence and severity of any ongoing incontinence.	B

IV. DIAGNOSIS OF FISTULAE

1. CLINICAL DIAGNOSIS

Leakage of stool, urine, or possibly both is the hallmark sign of a fistula. The leakage is usually painless, may be intermittent if it is position dependent, or may be constant. Unfortunately, intraoperative diagnosis of a GU or GI injury is made in only about half of the cases that result in fistula. [196]In one study, 36% of VVF presented within one week of a laparoscopic hysterectomy and 50% in the second week. Most of the patients after TAH had leakage in the second week (90%). [197] As discussed above, more extensive dissection is a factor when lower urinary tract injury results in a fistula. However, other than a frank injury such as ureteric transection, not all injuries result in the formation of a fistula. With laparoscopic or abdominal dissection, ureteric injury may occur anywhere along the retroperitoneal ureter usually below the pelvic brim. Since the injury may not be recognised during surgery, post-operative pain is a key symptom.

The cause of VVF after hysterectomy varies with the extent of surgery and the amount of injury that has occurred. Several risk factors for bladder injury during surgery have been documented including the presence of endometriosis, pelvic adhesions, distended bladder and infection[198]. When there are adhesions in the uterovesical pouch, blunt dissection may tear the bladder and/or devascularise the area. The commonest sites for ureteric injuries during gynaecological surgeries are at the level of the uterine artery and at the pelvic brim. Ureteric injuries may result from crush or thermal injury, transection and devascularisation. Common presenting symptoms of post-operative ureteric injuries include abdominal pain, ileus, peritonitis, fever, haematuria, flank pain and raised white blood cell count. The time from surgery to diagnosis of ureteric injury is usually within 7 days post-operatively.

The clinical course observed in many of the patients with VVF suggests that the patient has an unrecognised or recognised injury to the bladder resulting in urinary extravasation. [199] It may be possible to abort the development of many VVF by early recognition and treatment of an unsuspected bladder injury. It is suggested that patients with severe abdominal pain, distension, paralytic ileus, haematuria or symptoms of severe irritability of the bladder after TAH should be investigated early for a possible genitourinary injury.

Another possible aetiology of VVF in the setting of laparoscopic procedures is trocar insertion injury. To prevent this the bladder should be emptied by intermittent or continuous bladder drainage prior to inserting the abdominal and pelvic trocars. During the laparoscopic procedure, gaseous distention of the urinary drainage bag may become evident indicating a hole in the bladder.This intraoperative sign however, has not been associated with fistula formation. [200]

The diagnosis of VVF is almost always made on clinical examination with or without an office dye test[142]. Imaging is required to

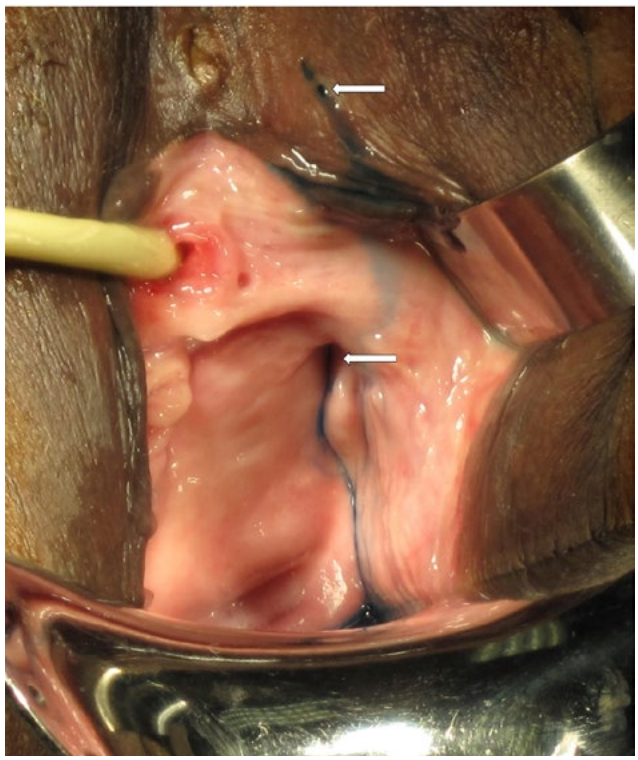


Fig. 4. Methylene blue introduced intravesically, demonstrating complex vesico-vagino-vulval fistula following pelvic fracture (arrows indicate external openings)

diagnose a ureteric fistula. Imaging has been demonstrated to have a high false negative rates for the diagnosis of VVF. Inspection of the vagina via a speculum usually reveals a defect in the anterior vaginal wall but a very small fistula may be more difficult to locate. The dye test for VVF involves retrograde filling of the bladder with dilute dye fluid (such as methylene blue) via a catheter inserted into the bladder. Ensure that the bladder is adequately filled. A speculum into the vagina is usually used and the dye test is positive when dye is observed leaking in the vagina. (Fig. 4) Alternatively, a tampon or swabs may be inserted into the vagina and the woman is asked to mobilise. If there is blue seen on the tampon/swab, the dye test is considered positive. Be careful that the tampon/swab is not positive due to leakage per urethram during the test. If there is urine in the vagina or tampon is wet but is not coloured (dye), then a ureteric fistula needs to be excluded.

A number of studies have investigated the role of routine cystoscopy in avoiding/detecting urinary tract injury at pelvic surgery; Indraratna et al. have recently reviewed these.[201]

Gilmour et al. undertook a systematic review of urinary tract injuries at benign gynaecological surgery including all studies of >500 patients reported between 1966 and 1998. [202] The overall rate of ureteric injury from 17 studies where cystoscopy was not undertaken (mostly hysterectomy) was 168⁄107,068=0.16%. In 10 studies where cystoscopy was undertaken routinely (mainly colposuspension or pelvic floor reconstruction), the rate of ureteric injury was 20/3235=0.62%. The corresponding rates of bladder injury were 0.26% (without cystoscopy) and 1.04% (with cystoscopy). Although the rates of detected urinary tract injury were approximately fourfold higher in those studies where cystoscopy was undertaken as a routine, it should be noted that none of these studies was randomised, and routine cystoscopy was undertaken predominantly during those procedures with intuitively the highest risk of injury.

Cystourethroscopy may provide direct visualisation of the fistula and its location relative to the ureteric orifices. In several series using cystoscopy (mostly with IV indigo-carmine) the sensitivity and specificity in detecting ureteric injury intra-operatively were >95%.

Urine may extravasate externally or internally. Creatinine levels in the urine are higher than serum levels. Therefore, in the setting of a suspected fisula, testing the creatinine level in either the extravasated fluid or the accumulated ascites and comparing this value to the the serum creatinine levels will confirm urinary leakage but not the location of the fistula. Likewise, testing potassium levels will show higher levels compared to serum levels. [203]

A recent trend to use a flexible scope in the vagina, vaginoscopy, can provide magnification, and direct visualisation with minimal discomfort to the patient, particulary in high fistulae.

2. IMAGING

Depending upon availability, radiological studies (cystography, urography, intravenous urography, and CT urography) may be useful. Ultrasonography and colour Doppler have been used by some, although their use in routine practice remains to be established. [204] [205] Imaging has been found to be associated with a high false negative rate for the diagnosis of VVF [142]. An unstructured review by Narayanan et al. suggested that magnetic resonance imaging, particularly with T2 weighting, provided optimal diagnostic information regarding fistula associated with pelvic malignancy, with contrast-enhanced CT with late excretory phase an acceptable alternative.[206] These newer modalities were considered to be superior to other X-ray contrast techniques and ultrasound. Ureteroenteric fistula have been diagnosed using 99mTc-DTPA renal scans.[207]

3. DIAGNOSIS OF GI FISTULAE

Pneumaturia, dysuria and/or recurrent UTI's are symptoms of a colovesical fistula but may be due to other causes as well. Accepting the limitations of small case series in this regard, a number of studies have investigated the value of a range of investigative techniques in the detection and evaluation of enterovesical or colovesical fistulae.[176, 178, 179, 183, 208, 209, 210, 211, 212] No test was shown to have consistent reliability; excluding those investigations for which only a single report was identified, CT (53%), cystoscopy (48%), and in the case of colovesical fistula, barium enema (38%) were perhaps the most useful; intravenous urography and sigmoidoscopy or colonoscopy appear to have limited utility in the diagnosis of GI fistula.

4. RECOMMENDATIONS

CT and cystoscopy appear more consistent in the confirmation and location of possible intestino-vesical fistulae, than other investigations	C
Level 3 evidence indicates that the routine use of cystoscopy with dye testing at gynaecological surgery has high sensitivity, specificity and negative predictive value in the detection of ureteric injury, although false positive tests do occur. The clinical and cost-effectiveness of routine cystoscopy remains to be established	C

V. MANAGEMENT OF VESICOVAGINAL FISTULAE

1. CONSERVATIVE MANAGEMENT

1.1. Immediate management by catheterisation

The goal of conservative management of VVF is rapid cessation of urinary leakage with return of normal urinary and genital function. The following are the indications listed below:

- Fistula onset is less than 3 weeks
- Progressively decreasing urine leakage with bladder drainage
- Fistula tract is long and narrow
- Width of fistula less than 1 cm
- Patient is compliant, co-operative and understanding
- Some of the contra-indications to conservative treatment are:
- Radiation induced VVF
- Scarring around fistula site
- Fistula onset is more than 6 weeks
- Fistula size more than 3 cm

Conservative management involves catheter drainage, anti-muscarinic and antibiotic therapy. In addition, it is wise to do a cystogram before removal of the catheter. The duration of catheter is debatable (2 weeks to 12 weeks). Bazi (2007) reported a non-systematic review of papers including information on the spontaneous fistula closure of vesicovaginal fistulae; whilst the data quality of all was poor, he identified 30 studies from which 12 could be included; these included cases that were almost exclusively of surgical etiol-

ogy; it should be noted that in 9 of these 12 studies the sample size was less than 5 patients.[213]

The time of fistula formation and the start of catheterization varies widely, most of them were less than 3 weeks duration. The success rates also vary from 0-100%. In obstetric fistula, spontaneous healing of fistula is reported to be 28% by Waaldijk in 1994, 1997 and 2004. [214, 215] Hilton reported a 6.9% spontaneous closure rate. [216] Oakley in 2014 reported 60 of 226 patients were treated conservatively with catheter drainage, antimuscarinic and antibiotics for 12 weeks. Only 11.7% resolved spontaneously.[217]

Davits et al. reported in 1991, 4 cases of VVF (2 post abdominal hysterectomy and 2 post vaginal hysterectomy for benign indication) between 40-48 years of age. All of them underwent catheter drainage, antimuscarinic and antibiotics for a duration of 18 to 54 days and had longterm follow up for 14 years.[218]

Elkins et al. reported 6 cases of conservative treatment in benign condition. 2 out of 6 were successful (unpredictable result with success rate of 12-80%).[219]

De Ridder et al. reported 13% success rate. The principle was introduction of catheter before epithelization is complete leading to healing of abnormal passage by urinary diversion. [220]

Zimmern PE et al. reported closure of VVF with success rate of 10.8% by catheterization alone. [221]

A systematic review by Hillary et al. described 6 studies on conservative treatment (2 in low resource and 4 in well-resourced countries). Duration of catheterization varied from 3 to 12 weeks. The inference derived was conservative management is likely to be successful, provided fistula was less than 3 mm, non-oblique tract, non-radiation induced or malignant fistula. The success rates were less than 13%. [222]

In 264 of 1716 cases, success rate of 15.4% was reported by Waaldijk.[223] In a more recent update, Waaldijk reported on catheter treatment in 1962 fresh OF. 1332 of them or 68% healed by catheter treatment only (minimum 4 weeks of catheterization). [224] (Fig. 5)

A success rate of 11% was reported by Taylor and Smith in 4 of 35 cases of obstetric fistula.[225]

A rare case of endoscopic closure of a radiation fistula was reported by Tatsuo with conservative management aided by endoscopic fibrin glue.[226] Bodner-Adler et al. reported conservative management in 239 out of 1430 cases (16%) of VVF with a success rate of 8% (12/239).[227]

1.2. Minimally invasive treatment

Due to the unpredictable result of only catheter drainage, minimally invasive techniques are used in an attempt to achieve better results. Several studies (mostly case series) describe non-surgical strategies as the sole treatment option consisting of: Transvaginal injection of fibrin sealant, Nd:YAG laser welding, Cystoscopic electrofulguration followed by fibrin sealant, Endo-vaginal cyanoacrylate glue , Platelet Rich Plasma with or without fibrin glue , Curettage of fistula tract and Rubber/ metal ball placement. The success rates were definitely high from 67-100%, but most fistula were small (<1cm). [228, 229, 230, 231, 232, 233, 234, 235, 236, 237]

Marin Sanchez described 2 cases, where after embolization in PPH, partial bladder necrosis with VVF were treated conservatively with good results.[238]

Cystoscopic fulguration using a small cautery electrode is possible by pushing it fully inside the VVF until the edges are blanched. In patients with fistula less than 3.5mm, the treatment was successful in 11 out of 15 cases.[232]

Dogra and Saini tried laser welding of VVF for less than 3 mm fistulae, however if more than 6mm, this method failed.[228]

In patients with thin VVF septum, large VVF and non-oblique tract, fulguration may be more damaging. Devascularisation of tissue will ultimately lead to a bigger and more complex fistula.

Fibrin sealant (fibrinogen + thrombin) can be injected directly into the fistula tract, after fulguration, followed by prolonged bladder drainage. It facilitates healing by recruiting macrophages and providing a semisolid support structure rich in growth and angiogenic factors which supports the fibroblast to connective tissue transition. [229, 239, 240, 241]

1.3. Pharmacotherapy to assist fistula closure

No medical therapy is available for the management of vesicovaginal and ureterovaginal fistulae. However, multiple therapies are used along with the management to assist and expedite fistula closure and improve closure rates.

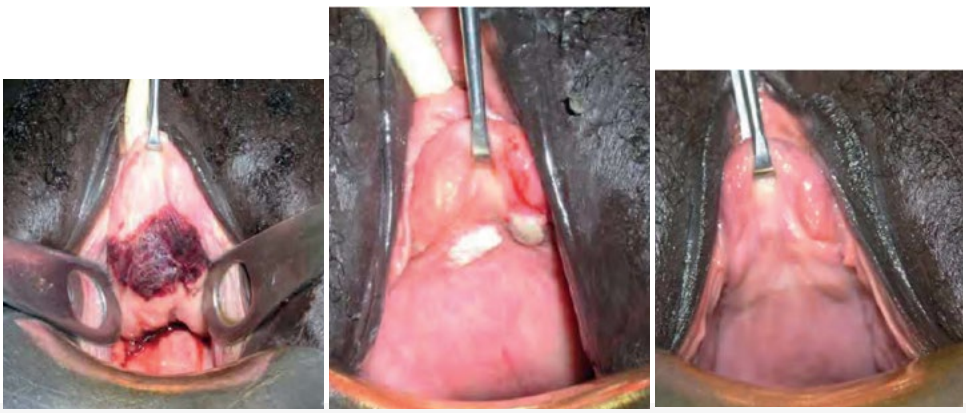


Figure 5: Spontaneous healing of a postpartal fistula by catheter drainage (Courtesy of. K. Waaldijk 2022) [1]

Pre-operative: During the waiting period, indwelling catheters were discouraged, and vaginal estrogen therapy can be used in post-menopausal women. A 4- to 6-week treatment regimen prior to surgery is commonly recommended. It may be used alone or in combination with oral HRT/ERT.[242]

Acidification of urine to diminish risks of cystitis, mucus production, and formation of bladder calculi may be a consideration, particularly in the interval between the diagnosis and surgical repair of VVF. Vitamin C at 500 mg orally 3 times per day may be used to acidify urine. Alternatively, methenamine mandelate at 550 mg plus sodium acid phosphate at 500 mg 1-4 times per day also can be administered to achieve urine acidification.[243]

Intra-operative: Antibiotic prophylaxis for VVF repair was studied in a paper from the Benin Republic by Tomlinson and Thorton. In their series of 79 patients who underwent repair of a VVF by a single surgeon, they found intraoperative ampicillin did not reduce the odds of failed repair. However, patients given prophylactic antibiotic therapy did have fewer urinary infections and required less antibiotic therapy postoperatively.[244]

Anticholinergic drugs are used to prevent early suture tension by causing a relaxation of detrusor smooth muscle hence preventing bladder spasms.[243] Urised which is a combination of antiseptics (methenamine, methylene blue, phenyl salicylate, and benzoic acid) and parasympatholytic (atropine sulfate, and hyoscyamine sulfate) can be used if available. Other antimuscarinics such as oxybutynin, solifenacin, darifenacin, tolterodin, fesoterodine etc.. can be used as well, although no specific data exist on fistula.

The use of antibiotic therapy postoperatively is controversial. Many physicians administer oral antibiotic prophylaxis to patients with VVF postoperatively until the Foley catheter is discontinued. Others check closely for the development of a urinary tract infection and administer antibiotic therapy when urine cultures are positive for bacterial growth. Close follow-up and prompt evaluation for any urinary tract infections and antibiotic therapy, when indicated, are mandatory.

Other measures include minimizing an increase in abdominal pressure, the use of laxatives and a high fiber diet, minimal pelvic examination, and pelvic rest (by avoiding using tampons, or coitus) for 6 weeks.

1.4. Palliation and skin care

This is essential as there is always a waiting period between diagnosis and therapy. Incontinence pads, help to reduce odor, reduce social stigma, and help the patient to continue routine work and allows them to be socially active.

Ammoniacal dermatitis, is a devastating complication characterized by local rashes, skin excoriation around the vulva and the medial side of the thigh due to the continuously wet environment. Silicon barrier creams and zinc oxide ointments have been shown to be effective to some extent. Other conservative measures viz. washing with water, avoiding irritants, drying thoroughly, avoiding rubbing with dry toilet paper, moisture barrier creams, talcum powder or cornstarch and wearing loose clothing and cotton underwear with frequent change of wet pads can be advised with proper counseling and assistance if needed.

Local estrogen cream is only useful in fistulae in post menopausal women (some OF may be diagnosed only at that age) . It increases the vascularity, helps vaginal tissues become softer and more pliable for the subsequent repair in terms of tissue healing.[242]

For personal hygiene and skin care, sit baths with a solution of permanganate or baking soda douches may be helpful. Keeping the perineum and vulva as dry as possible is comfortable for the patient. Inventive collection systems have been described for this purpose.[245] Hyperbaric oxygen treatment has also been described as an adjuvant treatment in radiation-induced fistulae.[246]

The evidence for all of the above 3 is level 3B.

1.5. Nutrition

Malnutirtion is common in surgical patients and is often unrecognized, untreated and worsens in hospital. A 1994 study reported that 40% of 500 patients sequentially admitted across five sub-specialties (including general and orthopedic surgery) were at least mildly undernourished (body mass index < 20, TSF or MAMC < 15th percentile). [247]There are clear prospective associations between inadequate nutritional status and the risk of poorer outcomes for surgical patients, including infection, complications and length of stay. Positive outcomes depend heavily on adequate immune defense and wound healing. Both rely on enhanced synthesis of new proteins, which is significantly limited by negative nitrogen and energy balance. Those patients who received 1,500–2,000 calories per day had a lower mortality rate and a higher fistula closure rate compared with the patients who received <1,000 calories per day. [248]

There is little evidence that parenteral is more effective than enteral nutrition, but it is certainly costlier and associated with higher risks of serious complications, particularly infection. There is evidence that early (within 24 hours) enteral feeding has significant benefits over late enteral and parenteral feeding.[249] Also Early Recovery programs have been shown to be beneficial, although they have not been studied for fistula repair specifically.[250]

1.6. Role of physiotherapy

Pre- and post-surgical VVF and physiotherapy is multifaceted. Most of the women need general rehabilitation, based upon obstructed labor and its subsequent care. All affected women benefit from pelvic floor assessment, education and muscle exercise to optimize the outcome of surgery.

A multi-disciplinary team, including an active physiotherapy team should become an integral part of best care in fistula management. [251]

The Paula exercise method (PEM) has been tested in post-VVF repair management and showed beneficial effects in reducing urine leakage, improving pelvic floor muscles strength, quality of life and sexual function. [252, 253, 254]

2. SURGICAL MANAGEMENT

Fistula surgery is not easy. One of the most important aspects of the unmet needs in fistula surgery training has been the lack of standardization A global competency-based fistula surgical training manual has been created by the International Federation for Gynaecology and Obstetrics (FIGO) with International Society of Fistula Surgeons (ISOFS). The purpose of this manual is to enable health care providers to acquire the required knowledge, skill and professionalism to prevent fistula and provide holistic care to fistula patients that includes medical, psychosocial and surgical care. A

multi-disciplinary team-based approach is encouraged in the training of each doctor and his/her team nurses, physiotherapists and other health professionals. The course is structured at three levels: standard, advanced and expert levels of fistula training.[255]

In the developed world, fistula incidence is much lower. Most results of fistula repair in literature are extremely positive. Since there is no systematic reporting of fistulae and the complications or outcome of the repairs, underreporting, selection bias can be possible confounding factors leading to these positive reports.

If catheter drainage fails, then fistula repair will be necessary. There are certain surgical principles to observe during fistula repair:
- Necrotic tissue must be removed prior to fistula repair.
- Fistula repair must only be undertaken by a properly trained surgeons.
- Adequate post-operative care is essential.
- Proper follow-up should be arranged.

2.1. Timing of surgery

The most appropriate timing for repair of vesico-vaginal fistulae remains one of the more contentious issues in this area. The debate continues between the advocates of early intervention, in order to minimise the distress to the patient from continuousurinary leakage, vs. those in favour of delaying intervention until local inflammatory change has resolved, necrotic tissues have sloughed, and the patient's recovery from the causative event completed, so as to optimise results.

There is no consensus in the literature regarding the definition of 'early' in this context, with different studies either failing to specify at all, or giving a broad range of definitions. Although some studies have used the terms 'immediate',[256] 'less than two weeks',[257] or 'less than 30 days',[258] most reports have considered either less than 6 weeks,[259, 260, 261] or less than 3 months,[257, 262, 263, 264] as their definition of early intervention. Giusti et al. reported a 100% success rate in 16 patients who were treated at a mean of 9d (4-17d) after a hysterectomy for a laparoscopic transperitoneal extravesical fistula repair with Tachosil™ interposition. [265] Although relatively few studies have reported their outcomes for both early and late approaches to management, overall the results do not appear to be significantly different. The overall results for early management are estimated at 91%±6% and for later management (where provided) 90%±27% (p=1.00; Fisher's Exact test).

2.2. Surgical approaches

2.2.1. Vaginal procedures

There are two main types of closure technique applied to the repair of urinary fistulae, the classical saucerisation technique described by Sims,[266] and subsequently modified as a partial colpocleisis by Latzko,[267] and the more commonly used dissection and repair in layers or 'flap-splitting' technique (variously attributed to Hayward, Collis & Lawson Tait).[268] Individual surgeons inevitably employ these techniques somewhat variably, and in different situations, and there are no data comparing their outcomes.

The conventional dissection and repair in layers is entirely appropriate for the majority of post-surgical fistulae, although modifications may be necessary in specific circumstances. In juxta-cervical fistulae in the anterior fornix, vaginal repair may be feasible if the cervix can be drawn down to provide access. Dissection should include mobilisation of the bladder from the cervix, and the repair should usually be undertaken in such a manner (usually transversely) to reconstruct the underlying trigone and prevent distortion of the ureteric orifices.

Vault fistulae, particularly those following hysterectomy, can again usually be managed vaginally. The vault is incised transversely and mobilisation of the fistula is often aided by deliberate opening of the Pouch of Douglas.[269] The peritoneal opening does not need to be closed separately, but is incorporated into the vaginal closure.

Where there is substantial urethral loss, reconstruction may be undertaken using the method described by Chassar Moir[270] or Hamlin & Nicholson.[271] A strip of anterior vaginal wall is constructed into a tube over a catheter. Plication behind the bladder neck is probably important if any prospect for continence is to be achieved. The interposition of a labial fat or muscle graft not only fills up the potential dead space, but may also provide additional bladder neck support and improves continence by reducing scarring between bladder neck and vagina. These are technically demanding procedures and outcomes of such complex repairs using robust measures regarding continence or sexual function are lacking.

With very large fistulae extending from bladder neck to vault, the extensive dissection required may produce considerable bleeding. The main surgical difficulty is to avoid injuring the ureters. They are usually situated close to the supero-lateral angles of the fistula, and if they can be identified endoscopically, they should be catheterised. Straight ureteric catheters passed transurethrally, or double pigtail catheters may both be useful in directing the intramural portion of the ureters internally; nevertheless great care must be taken during dissection. In such cases where the ureters cannot be visualised cystoscopically, interventional radiological techniques may be utilised to place antegrade ureteric stents from a percutaneous nephrostomy access tract.

2.2.2. Abdominal procedures

Repair by the abdominal route is indicated when high fistulae are fixed in the vault and are inaccessible through the vagina; most typically this might be following hysterectomy in nulliparous women, in endometriosis, or in those who have not delivered vaginally. Other indications for transabdominal repair are the need for simultaneous augmentation cystoplasty, or in the setting of a ureteric injury requiring reimplantation or simultaneous VVF and ureterovaginal fistula.

A transvesical repair has the advantage of being entirely extraperitoneal. It is often helpful to elevate the fistula site by a vaginal pack. The ureters should be catheterised under direct vision either endoscopically prior to skin incision, or following opening of the bladder. The technique of closure is similar to that of the transvaginal flap-splitting repair except that for purposes of haemostasis the bladder urothelium is usually closed with a continuous suture.

A simple transperitoneal repair is relatively uncommonly employed (although this technique does seem to be favoured by some using the laparoscopic approach – see below), although a combined transperitoneal and transvesical procedure is favoured by many urologists and is particularly useful for fistula repair following Caesarean section. A midline incision is made in the vault of the bladder; this is extended downwards in a racquet shape around the fistula. The fistulous track is excised and the vaginal or cervical defect closed in a single layer. The bladder is then closed in two layers.

There are no randomised studies comparing abdominal and vaginal approaches; given that those surgeons undertaking both routes for repair would usually see specific indications for the two such

a comparison is most unlikely ever to be seen as feasible, ethical or appropriate. Nine non-randomised cohort studies reporting results from both abdominal and vaginal procedures were identified in the current review.[22, 30, 261, 272, 273, 274, 275, 276, 277] In all, these series included 388 vaginal repairs and 345 abdominal repairs with overall closure rates at first operation of 89% and 87% respectively (p=0.367; Fisher's exact test). The same reports included 255 transvesical repairs with a 93% cure rate, and 399 transperitoneal repairs with an 89% success rate (p=0.130; Fisher's exact test).

Although repeat operations are certainly justified, the success rate decreases progressively with increasing numbers of previously unsuccessful procedures. In a series of 2484 largely obstetric fistulae, the success rate fell from 81% for first procedures to 65% for those requiring two or more procedures.[278] Series of surgical cases are rarely large enough for this effect to be evident, although the series published by Hilton found successful fistula closure was significantly more likely in the women who had not had attempts at closure before referral (98.2%) than in those who had one or more previous unsuccessful procedures (88.2%) (p=0.003; Fisher's exact test).[30]

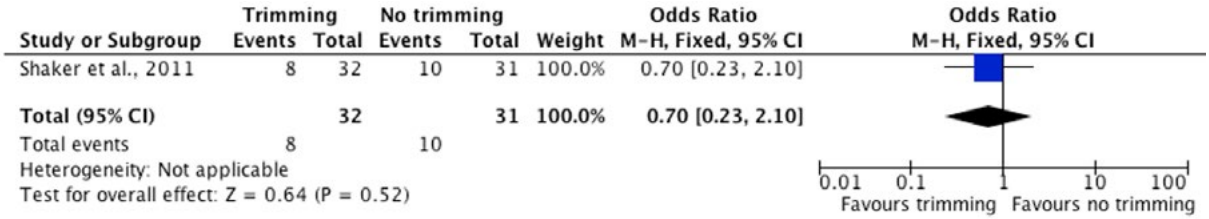
There is only a single randomised trial comparing aspects of surgical technique; Shaker et al. report an RCT comparing trimming of the fistula edge with no trimming.[279] Although there was no statistical difference in success rates between the two groups, in those cases where repair was unsuccessful and trimming had been undertaken, the fistula tended to become larger, whereas those where there was no trimming were more likely to be smaller upon recurrence (figure 6).[279]

2.2.2.1. Laparoscopic

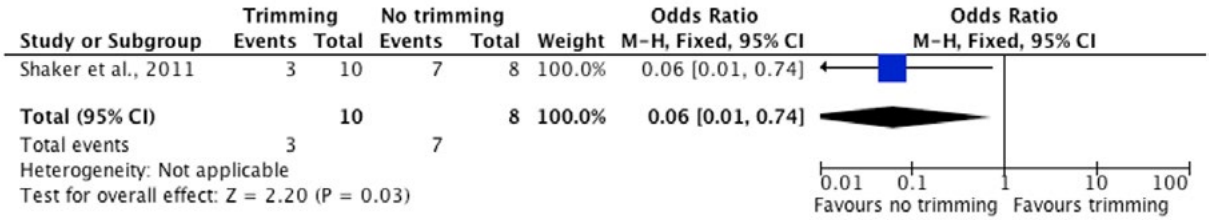
Laparoscopic repair of a VVF was first reported by Nezat et al., in 1994.[280] Fifteen series were identified in the current review,[256, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293] (plus an additional series in which 2 laparoscopic procedures were undertaken amongst a small series of vaginal and open abdominal operations).[277] All reported series are quite small (1-25 cases, median 6 cases), and in total only 119 patients were included, with an overall cure rate of 92% (confidence interval 4%) (See table 4). It is not clear from these series whether they include all fistula repairs undertaken in the reporting centres, or whether they were selected in some way; if the latter, it is not clear what selection criteria were used. It is possible that there may be both selection and reporting biases that make it difficult to fully evaluate laparoscopic procedures against alternative surgical approaches.

A combined vesicoscopic, laparoscopic and vaginal approach has been used successfully by some groups, but the experience remains limited.[294, 295]

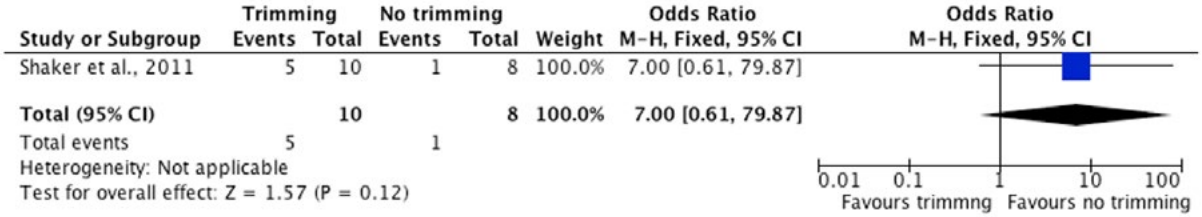
What about the veiscoscopic approach?



(i) Forest plot of comparison: 1 Trimming vs. no trimming of fistula edge, outcome: 1.1 Failure of fistula closure



(ii) Forest plot of comparison: 1 Trimming vs. no trimming of fistula edge, outcome: 1.2 Recurrence smaller than original



(iii) Forest plot of comparison: 1 Trimming vs. no trimming of fistula edge, outcome: 1.3 Recurrence larger than original

Figure 6: Forest plots relating trimming of edges at fistula surgery

2.2.2.2. Robotic

The first report of a robotically-assisted repair of vesico-vaginal fistula was from Melamud et al. in 2005.[296] Since that time four additional reports have been identified,[297, 298, 299, 300] including a total of 17 cases (see table 4). The reported cure rate is 100% in all series, although the same comments as above, in relation to possible selection and reporting biases, apply equally here. At this stage, whilst one could state that fistula repair with robotic-assistance appears to be feasible, it is not possible to indicate what its place or potential advantages are over alternative approaches.

Some of advantages to the robotic technique include three-dimensional visualisation, increased dexterity with wristed instrumentation improving on the severe angulation required for laparoscopic or open VVF repair, and easier intracorporeal knot tying. The retrovesical approach through the vagina can reduce the time for bladder healing significantly and allow the procedure to be done as a single day procedure. Currently, there are no direct comparisons between the classical transabdominal VVF repair, transvaginal VVF repair, and the minimally invasive robotic/laparoscopic techniques

Miklos JR et al. performed a systematic review on laparoscopic and robotic fistula repairs. They included 44 studies: 9 articles of robotic-assisted approach, 3 laparoscopic single-site surgeries, and 32 conventional laparoscopic approaches. A literature review revealed a balanced number of reports for both transvesical and extravesical approaches. The overall success rate of laparoscopic VVF repair was 80% to 100% with a follow-up period of 1 to 74 months. The success rate of transvesical and extravesical techniques were 95.89% and 98.04% (relative risk, .98; 95% confidence interval, .94-1.02). There was no statistical difference in success rates of VVF repair with different number of layers in the fistula closure or with use of interposition flaps, but there was a small increase in success in the cases that documented intraoperative bladder filling to test the integrity of the bladder closure. In conclusion, transperitoneal extravesical VVF repair has cure rates similar to the traditional transvesical approach. Laparoscopic extravesical VVF repair is a safe, effective, minimally invasive technique with excellent cure rates similar to those of the conventional transvesical approach in experienced surgeons' hands.[301]

Sharma et al. reviewed 15 studies on 75 patients who were treated robotically with a 90% successrate. [302]

Gellhaus PP et al. published a series of robotic repair either concomitantly with gynaecological surgery or as a salvage procedure after an previous attempted repair, showing good results for both approaches. [303]

2.2.2.3. Fibrin glue

The use of fibrin glue in urological indications was reviewed by Shekarriz and Stoller;[304] they identified nine reports (eight in human subjects) of the use of fibrin glue in fistula repair, including a total of 16 patients.[226, 305, 306, 307, 308, 309, 310, 311] A further six more recent reports were identified in the current review, where fibrin glue was used either by endoscopic injection or direct application, making a total of now 53 patients with fistulae of various aetiologies.[226, 229, 312, 313, 314, 315, 316] Several of these publications were individual case reports, although there was also one randomised trial comparing fibrin glue (20 patients) with a Martius graft (20 patients) in obstetric fistula patients.[315] All of the case reports described successful repair (1/1=100% cure); the RCT reported 13/20=65% cure; the overall success rate therefore for the 53 reported patients was 77.4% (confidence interval 7.3%) (See table 5). In one case successful closure of a radiation induced fistula was reported from the combined use of bovine collagen and fibrin glue.[226] Overall, the indications for, and optimal patient selection for this approach are not defined.

2.2.2.4. Endoscopic repair

Mackay described a technique for transurethral endoscopic suture repair of vesico-vaginal fistula in 1997.[317]; there have been three further papers using a similar technique on between one and four patients (total 10 cases).[273, 317, 318, 319] Although in three of these series the reported cure rate was 100%, overall, fistula closure was found in 80% (confidence interval 24%).

2.2.2.5. Adjuvant Techniques in the Repair of VVF: Tissue Interposition

Tissue flaps are often added as an additional layer of repair during VVF surgery. [320, 321, 322, 323, 324] Most commonly, such flaps are utilised in the setting of recurrence after a prior attempt at repair, for VVF related to previous radiotherapy (described later), ischemic or obstetrical fistula, large fistula, and finally those associated with a difficult or tenuous closure due to poor tissue quality. However, there is no high level evidence for the use of such flaps in any of these situations. Furthermore, there is no high level evidence that the use of such flaps improves outcomes in the setting of an uncomplicated VVF.

For those VVF repaired transvaginally, a labial fat pad (Martius flap) or a peritoneal flap can easily be mobilised. From a transabdominal approach, greater omentum can be used as an interposition flap.

A variety of other flaps including gracilis muscle flaps, labial myocutaneous flaps, seromuscular intestinal flaps, and rectus abdominis flaps as well as free grafts of bladder urothelium have been utilized as adjunctive measures in the repair of complex VVF.[325, 326, 327, 328, 329, 330, 331, 332]

There is no evidence that a Martius or any other interposition graft improves the outcome in primary fistula repair.

3. POST-OPERATIVE MANAGEMENT

3.1. Catheter type

No studies were identified comparing different catheter types or duration of drainage following fistula repair. Most reports do not describe their catheterisation practices in any detail; in those that do, the majority have employed urethral catheterisation, with a small number preferring suprapubic drainage or a combination of both. The reason for catheterisation is to ensure free urine drainage until such time as the repair is soundly healed; for this reason some have advocated both suprapubic and urethral drainage, arguing that whilst one catheter might easily become blocked, two are unlikely to do so simultaneously.[30] Bladder spasm are very common and could have a negative effect on the repair. [333]

3.2. Duration

There appears to be no consensus over the duration of catheterisation recommended following fistula repair of various types and aetiologies. In a retrospective study of obstetric fistula patients in Ethiopia, approximately equal numbers of patients were catheterised for 10, 12 or 14 days. There was no significant difference in outcome in terms of the rate of repair breakdown, and the authors therefore suggested that postoperative catheterisation for 10 days

may be sufficient in the management of less complicated obstetric VVF.[334]

In a recent review of practices amongst obstetric fistula surgeons, Arrowsmith reported a considerable range of practice. For 'simple' fistulae, the average duration of bladder drainage used was 12 days (range 5-21 days); for 'large' fistula the average was 17 days (range 0-30 days); and for 'difficult' fistulae, the average was 21 days (range 14-42 days).[335]

Torloni et al. reported on 2 non-inferiority trials including 684 patients, that showed no difference between short and longterm (> 10d) catetherisation regarding length of stay, fistula repair, incontince or the occurrence of UTI.[336]

The WHO published new guidelines for catheterisation after simple fistula repair and concluded that short term catheterisation defined as 7 tot 10 days, was sufficient for simple fistula repairs. [337]

Studies of non-obstetric fistula management are no more consistent in their description of duration of catheterisation. Most report periods of between seven and 21 days drainage; most typically 10-14 days for surgical fistulae and 14-21 days for radiotherapy-associated fistulae. There is no more than level 3/4 evidence to support any particular practice in these aspects of fistula management.

The summary of the surgical management of VVF can be found in Figure 7-9.

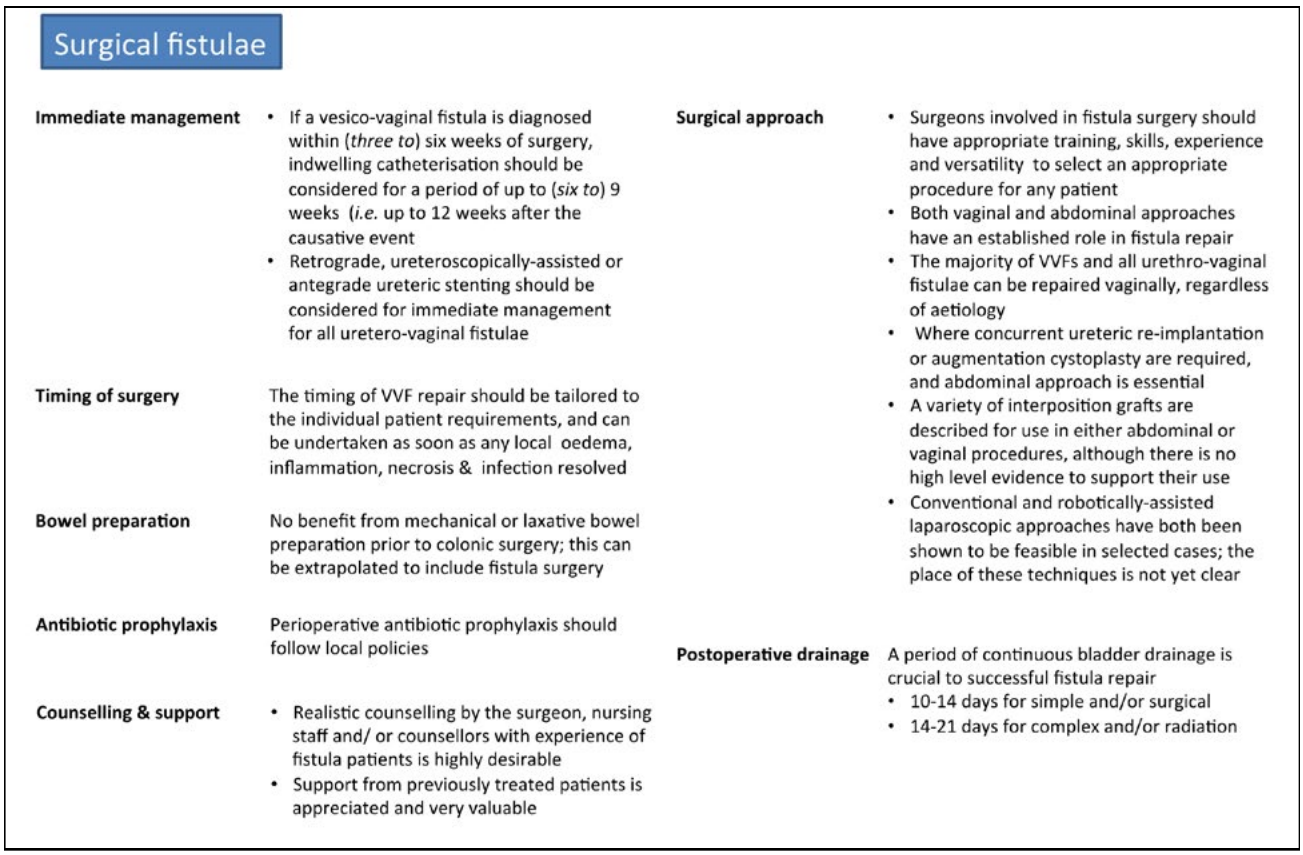


Figure 7. Treatment recommendations for vesicovaginal fistula

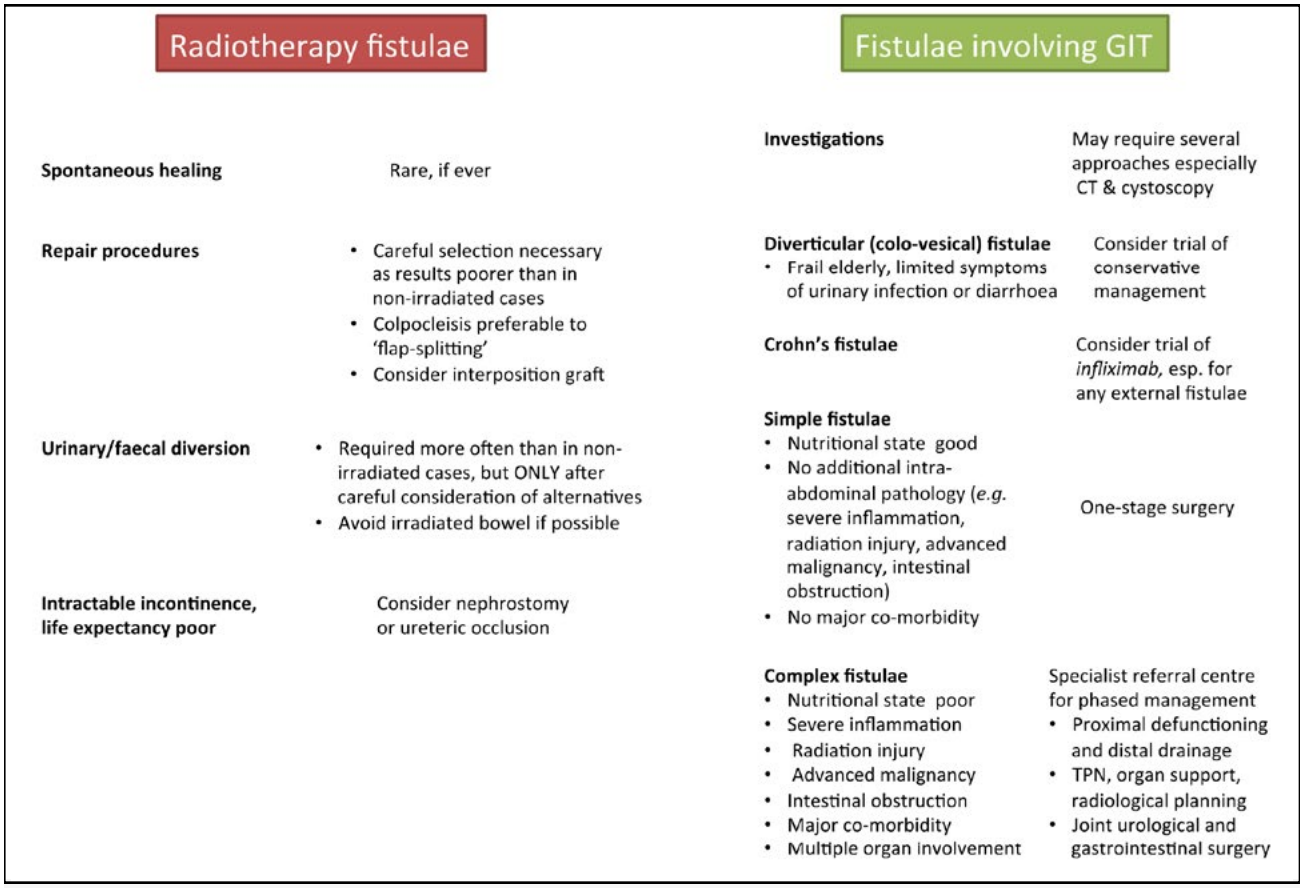


Fig 8. Treatment recommendations for radiation fistula and fistula involving the gastro-intestinal tract

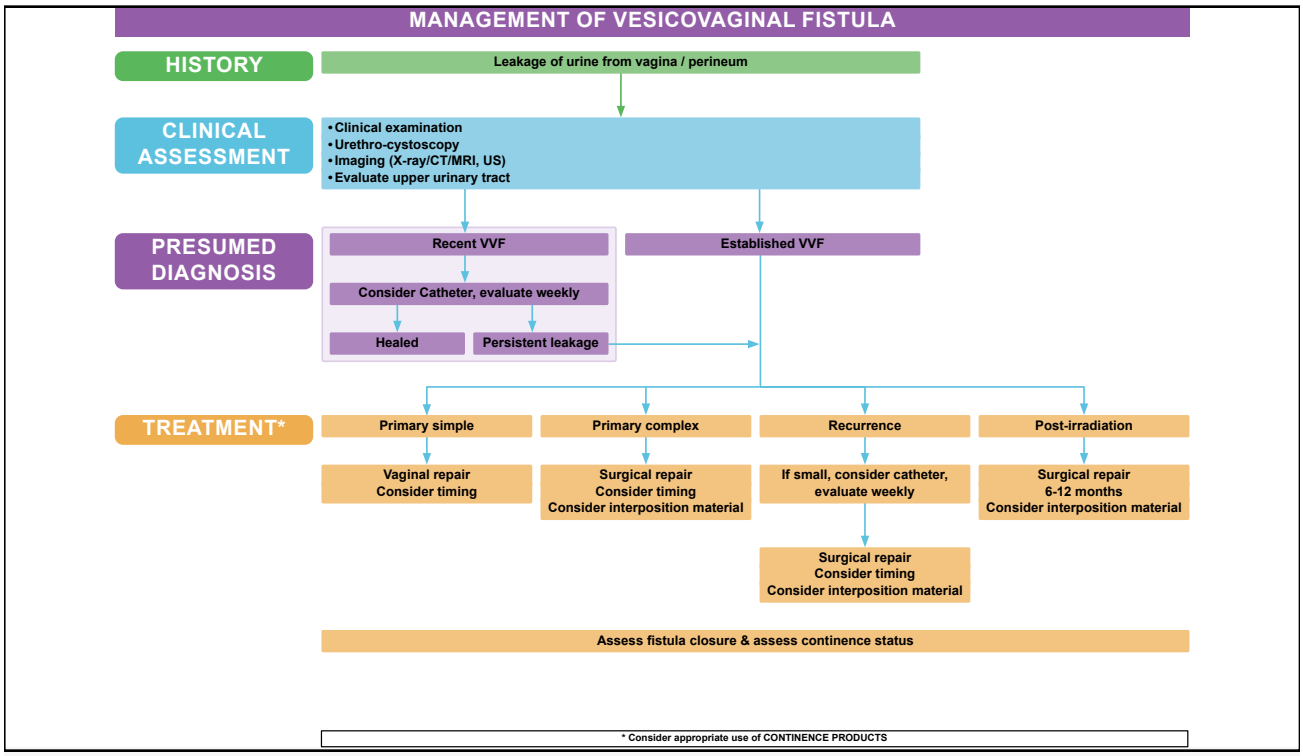


Figure 9. Algorithm for iatrogenic vesicovaginal fistula

4. OUTCOMES FROM TREATMENT AND FOLLOW-UP

In the developing world longterm follow-up of patients is difficult to organise, so most papers only report on shortterm outcomes. But also in the developed world data on longterm outcome of fistula repair are scarce Comparing the outcomes of treatment between different reports and different methods is made difficult by the inconsistent and relatively inefficient outcome measures used. These have ranged from the apparent achievement of a water-tight repair based on dye-testing in the operating theatre, to patient reported symptoms at the time of discharge from hospital. Follow-up in obstetric fistula patients is inevitably difficult in many developing world centres, but even amongst surgical or radiotherapy cases in the developed world, relatively few reports describe examination findings or symptoms at later postoperative review. Long-term outcomes and quality of life measures have only rarely been reported. [338, 339]

Reporting on fistula repair outcomes should always include the fistula closure rate, urethral continence status and sexual function. Next to that attention needs to be given to aspects of social reintegration. [340, 341]

Bengston et al. published an incontinence prediction calculator based on age, the number of prior surgeries, the fistula size, the circumferential nature of the fistula, scarring and the urethral length. [342] A prospective validation of this tool is awaited. The assessment of post-repair continence can be done with a 1-hour pad test. A 1.5gr cut off will identiy 94% of women who will remain continent. [343]

5. MANAGEMENT OF COMPLICATIONS OF VVF

The complications of obstetric fistulae and/or the complications of fistula repair are many and these include:

- Recurrent Fistula:
  - Success rate of uncomplicated vesicovaginal fistula (VVF) 70-80%
  - Success rate of complicated VVF 50-60%
- Stress incontinence after successful fistula closure: 16_33%
- Infections: wound, urinary tract infections (UTI) and pyelonephritis and urosepsis
- Voiding Dysfunction (overactive bladder – incomplete micturition – dysuria)
- Ureteric obstruction (ligation – fibrosis – injury)
- Outlet obstruction (meatal stenosis, urethral stricture, bladder neck obstruction (BNO))
- Bladder contracture
- Vaginal stenosis (overcorrection – fibrosis)
- Sexual dysfunction (vaginismus – dysparunia)
- Rare complications (granulomas – diverticulum formation)
- Neurological complications (foot drop – neurogenic bladder)
- Complex neuropathic bladder dysfunction and urethral sphincter incompetency often result, even if the fistula can be repaired successfully
- Psychological trauma (social isolation – divorce)

While fistula complications might be more manageable in the developed world due to the availability of reconstructive surgery and a multidisciplinary approach, the same complications might have severe consequences for patients in developing countries due to the lack of the appropriate skills, experience or equipment. It is important to realise that HIV is not a prognostic factor for complications.[344]

VI. RECURRENT FISTULA (PERSISTENT INCONTINENCE)

Fistulae can be closed successfully in around 72% to 92% of cases. The definition of success, however, is often different when the perspectives of the patient and the surgeon are compared. “Success” to a fistula patient means complete restoration of urinary continence and control, whereas many surgeons define “success” as simply closing the fistula. [220]

It is essential to establish defined criteria that will allow meaningful comparison of treatment outcomes. The patient-oriented criterion of continence restoration should be the goal when the outcomes of various fistula treatments are compared. Persistent incontinence despite successful closure of the fistula has been termed “the continence gap”.[345]

A patient whose fistula is closed but who remains incontinent may be just as wet as a patient whose fistula closure operation failed. The estimates of persistent urinary incontinence after a successful closure of the fistula come from case series, ranging from 16.3% in a large retrospective review of patients by Wall et al. to 33% in a small series of complex fistulae in which the proximal urethra was lost.[346, 347] Adequate epidemiologic studies on the prevalence of fistulae and its sequelae are scarce, and because long-term data on surgical outcomes are difficult to obtain, the prevalence of persistent incontinence after surgery appears to be severely underestimated.

Persistent urinary incontinence in patients after fistula repair is due to multiple factors including scarring, location of the fistula/s and surgical experience of the operator as well as failure to perform a sling operation or urethral reconstruction at the time of repair in patients likely to require such intervention. The goal of fistula surgery should be restoration of continence and resumption of a full and active life on the part of the patient, not just closing the fistula.

1. PATHOPHYSIOLOGY OF PERSISTENT URINARY INCONTINENCE AFTER FISTULA REPAIR

Several possible etiological factors can be postulated in women who remain incontinent after successful fistula closure: loss of bladder tissues, massive damage to the mid-urethral continence mechanism, damage to attachments of the urethra, fibrosis and loss of compliance, neuropathy, etc. . . .

Loss of bladder tissue is one of the main reasons why obstetric fistula repair is technically difficult. The loss of bladder tissue from pelvic ischemia during obstructed labour affects both the technique needed for, as well as the functional outcome of, fistula repair.

Although there are as yet no basic histological studies of the tissue surrounding obstetric fistulae, it seems clear that these tissue have themselves sustained significant damage during obstructed labour. The fistula itself develops in an area which becomes necrotic; but the tissues surrounding the fistula have also suffered varying degrees of ischemia. In some cases pressure necrosis may destroy virtually the entire bladder, so that if the defect can be closed at all, the afflicted woman is left with a remarkably small (30 - 50 ml) bladder. Also the compliance may be altered by the extensive fibrotic changes that often take place. To date there have been few urodynamic studies reported on patients who have undergone successful fistula closure.[348]

In the study by Carey et al., of 22 women with severe urinary incontinence after fistula closure, 9 had urodynamic stress incontinence with normal bladder compliance, 3 had urodynamic stress incontinence with poor bladder compliance, 9 had mixed incontinence, and one had voiding difficulty with incomplete bladder emptying and overflow[202]. Limited data from urodynamic studies by Hilton and by Carey, Goh et al. suggest that detrusor overactivity and changes in bladder compliance are frequent causes of urinary incontinence in fistula patients with post-repair incontinence, in addition to the leakage resulting from successful closure but persistent intrinsic sphincter deficiency. [348, 349] There is a great need for further investigation of these issues; unfortunately, those hospitals most likely to see large numbers of patients with obstetric fistulae also usually lack the resources for more advanced urological investigation.

A number of patients with vesicovaginal fistulae develop vesical calculi. [350, 351] Often these bladder stones develop in association with a foreign body in the vagina. After stone removal, the bladder should be allowed to heal prior to attempted fistula closure. If this is not done, there is substantial risk of post-operative infection and breakdown of the repair.

The ischemic changes produced by obstructed labour often have a devastating impact on urethral function. Complete urethral loss occurs in about 5% of fistula patients, with about 30% of fistula patients sustaining partial urethral injury. Goh et al. found that up to 63% of fistula patient have sustained some injury to the urethra. [352]

Depending on the amount of tissue that is lost at the bladder base, the ureteric orifices can be found in bizarre locations, ranging from the lateral vaginal walls all the way up to the level of the vesico-urethral junction and the pubic arch. Aberrant ureteric locations of this kind can easily be missed on clinical examination and are one cause of persistent incontinence after otherwise “successful” fistula closure. Standard urological tools such as ureteric stents are usually not available in hospitals in the developing world, and most of the surgeons who work in such hospitals are not trained in “urological” techniques such as ureteric reimplantation.

The impaction of the fetal head is sometimes serious enough to cause ischemic injury to the bladder will also cause ischemic injury to the vagina, which is likewise trapped between the two bony surfaces. These injured areas heal with varying degrees of scarring. Adetiloye and Dare detected fibrotic changes in 32% of fistula patients and minor vaginal wall fibrosis in another 36% in their sonographic study of a small number of patients. [353]

The presence of vaginal scarring appears to be an important prognostic factor in determining the likelihood both of successful fistula closure, and also for the development of debilitating urinary stress incontinence after otherwise successful fistula repair. Kelly and Kwast reported worsening surgical outcome in fistula patients who have vaginal scarring. [354]

2. MANAGEMENT OF RECURRENT FISTULA

The most important concept is the recognition of the differences between simple and complex fistulae.

Vaginal surgery for small fistulae can be attempted under local anaesthesia. [355] Larger or more complex fistulae can be treated under spinal anaesthesia, which is preferred over epidural or general anaesthesia by many authors. [356]

Operating by the abdominal route increases the cost and time of the operation, but is still often performed for some high fistulae where surgical access is problematic. Experienced fistula surgeons may be able to repair such defects vaginally. A retrospective study by Chigbu compared the outcome of juxtacervical fistula through the vaginal or abdominal approach. [357] Both approaches had similar cure rates and hospital stays, but the abdominal route was associated with a significantly higher need for blood transfusion.

General anaesthesia is also more expensive, more complicated to administer, carries more risks, and should therefore be reserved for those patients who need an abdominal approach.

2.1. The Complex Fistula

A complex obstetric fistula can be described being larger than 3 cm, involving the urethra, and associated with reduced vaginal capacity from significant scarring and/or a reduced bladder volume. Sometimes the defect may be urethrovaginal, but more commonly both the urethra and bladder are involved and therefore the fistula is called an urethrovesicovaginal fistula.[188]

Most of authors with extensive experience in the management of obstetric fistulae comment on the great difficulty in achieving postoperative continence in patients who have had extensive damage to the urethra, even if the defect itself has been closed successfully. Rates of postoperative urethral incontinence range between 6-50%.[348, 354] Often the diagnosis of postoperative incontinence is given only if the patient suffers from severe incontinence while walking. If rigorous questioning is used to exclude any leakage with coughing or other exertion, the rate of postoperative incontinence increases dramatically.

The four risk factors that lead to a high rate of incontinence following fistula repair are:

- ***Urethral involvement***. Odds Ratio 8.4 for developing urethral incontinence post operatively.
- ***Large size of the fistula***. Odds ratio 1.34 for each cm increase in size of the defect.
- ***Severe vaginal scarring***. Odds Ratio 2.4 if the scarring is significant enough to prevent the introduction of a Sims speculum without relaxing episiotomies.
- ***Small bladder size***. Odds ratio 4.1 if the bladder capacity is less than 120 ml.[188]

In repairing complex obstetric fistulae, the principles for simple fistula repair still apply, but with the following additions:

Exposure is more difficult. In complex cases the fistula may be obscured from view due to the presence of severe vaginal scarring.

Such scaring often consists of a thick band of scar tissue on the posterior vaginal wall. Occasionally, the vagina has been completely occluded. Wide bilateral episiotomies may be required and where possible the scar should be released from the lateral pelvic sidewalls. This will enable the fistula to be seen more clearly.

The ureters should be identified and protected against possible injury, as in the case of a simple repair.

The bladder and urethra should again be carefully mobilized. The tissues are often thin, scarred, and fragile in such cases. The mobilization often has to be extended along the lateral pelvic side walls and even on to the posterior aspect of the pubic symphysis in order to free the lateral and anterior bladder.

The mobilization of tissues should be wide to ensure a tension-free closure.

The utility of tissue flaps remains controversial. In some cases the use of tissue transposition techniques such as the Martius graft and various forms of sling operations are the mainstays of treatment.

Using the fibrin glue could be useful in many cases especially the recurrent cases with tissue damage. The use of fibrin glue as an interpositioning layer during the vaginal anatomical repair of complicated vaginal fistulae appears to be of great value as an alternative to the use of Martius flaps interpositioning. Decreasing the operative time and adding simplicity to the already complicated procedure are additional values of using this procedure. [358]

Often destruction to the vagina has been so extensive that rotational skin or myocutaneous flaps are required in order to cover the defect. [359]

If these principles are applied, the success rate in fistula closure is high, but many women remain incontinent despite successful closure. In patients in whom all of the risk factors mentioned above are present, the postoperative incontinence rate may approach 100%. [360, 361]

In light of this dismal successrate, some surgeons now suggest that two further principles of repair be maintained:

Maintain the urethral length;
A shortened urethra has been noted in post-repair fistula patients returning for furthertreatment of persistent urinary incontinence. An unpublished series of72 patients with post fistula repair incontinence foundan average urethral length of 1.4 cm in these women. This suggests that continence might be improved if normal urethral length can be restored at the time of fistula closure. Vertical (as opposed to horizontal) repair of urethrovaginal fistulae has therefore been suggested. This appears to be possible in approximately 20% of such cases. In cases in which there is an urethrovesicovaginal defect, vertical repair of the urethral defect may improve success, while the vesical defect can be repaired either vertically or horizontally. [362]

Support the urethra;
For all urethral defects larger than 4 mm with a urethral remnant less than 2.5 cm, many fistula surgeons use an ‘anti-incontinence’ procedure during the initial repair. Currently there are two widely used procedures. The first sutures the urethra/bladder neck to the periosteum of the pubic ramus in a type of suspension operation. The fascia or muscle of the bladder is sutured on either side of the bladder neck area to the posterior aspect of the symphysis pubis or the arcus tendineus. [363]

The second procedure creates a sling of tissue to support the urethra. A pedicle of tissue is created on either side of the urethra from the lateral pelvic side wall. In theory this involves use of the pubococcygeus muscle, but more often it is simply a pedicle of fibromuscular tissue or scar that can be harvested. The pedicles created on either side are then sutured together in the midline. If either of these two extra steps are used, the incontinence rate after closure of complex fistulae can be reduced from 100% to 50%. [361]

Pope et al. compared the outcome of this type of pubococcygeal sling with refixation of the bladder neck in a retrospective series of 185 slings and 50 refixations and 32 combined cases. Approximately 49% of patients remained incontinent in all groups and no redommendation on a preferred technique could be made. [364, 365]

Various authors have described neourethral reconstruction using bladder flaps. All of these operations are based upon transabdominal techniques such as that described by Elkins et al.[366] In this technique, a neo-urethra is created by mobilizing a flap from the anterior bladder, which is then rolled into a tube. The anterior surface of the neourethra is then sutured in two layers and the posterior edge of the fistula is closed transversely, also in two layers. The neourethra is reattached to the posterior edge of the pubic symphysis, and a Martius graft is placed before reapproximating the vaginal epithelium. In 18 of 20 cases, this technique resulted in fistula closure, but four women had severe stress incontinence postoperatively. Other authors have described various urethral reconstruction techniques, used for various indications. Most series are small and follow-up is limited. [367, 368, 369]

It is not known how many had mild incontinence. Neither of these surgical methods is ideal. Although they may create an anatomical urethra, often that urethra does not function normally. A further option in such cases is to create a ‘tube’ using either technique and then attempt to render the patient continent with the use of a urethral plug. [370]

Advanced Surgical Techniques
A transabdominal approach could be used for large, supratrigonalvesicovaginal fistulae, associated ureterovaginalfistulae or if bladder augmentation and bladderneck reconstruction was required. The transvaginal route was preferred for small sub-trigonal fistulae. A combined abdominal and vaginal approach was used for large fistulae involving the trigone or the bladderneck. The surgical approach varied in each patient.

Interposition grafts or flaps were used when required. [371]The overall surgical failure rate was 4.3%. The average operative time for layered closure was 72 minutes (45-130 minutes) and that for graft or interposition tissue repair 100 minutes (90-165 minutes). The mean hospital stay was 9 days (6-17 days). There were no reported intra-operative complications. Postoperative complications were urinary tract infection, haematuria, wound infection and fever. None of the patients required blood transfusion. For the repair of small fistulae, surgeons did not use interpositional flaps but rather used the layered closure technique with a success rate of 97.1%. Complicated fistulae required repair by graft or tissue interposition and had a success rate of 94.8% which is similar to the experience of other Indian centres. [372] Risk factors for the failure of vesicovaginal surgery included previous failed repair, large-sized fistulae, fistulae involving the trigone or ureteric orifices, a small bladder capacity and unhealthy vesical aurothelium at the time of surgery.

The majority of the large-sized fistulae were successfully repaired using the transabdominal technique described by O'Connor, with interposition of an omental flap. This technique works well except when the fistula extends up to the bladder neck or when its transverse diameter is too large to allow tension-free approximation.

Combined abdominal and vaginal approach
This technique may be required in complicated fistulae involving the bladder neck. In cases where urethral continuity is disrupted due to a fistula, a combined approach may be preferable. The fistula is repaired by the abdominal route and continuity of the urethra is established by anastomosing the urethra through the vaginal route.

Urinary diversion
Urinary diversion in developing countries is usually not a viable option since stoma appliances and catheters (in the case of continent urinary diversions) are often unavailable or are too expensive. [373] In such cases performing a diversion procedure merely moves the fistula to another part of the body and the end result of such surgery may be more stigmatizing in the local culture than the original injury.

Uretero-sigmoidostomy has been used as a surgical option in developing countries for many years. Many data show that both short- and long-term complications will arise and that surgeons must face this and treat them. On the other hand a series of 9 Tanzanian patients undergoing diversion found that results were acceptable and that patients had a marked improvement in their quality of life. Even pregnancies after ureterosigmoidostomy have been described. [274, 374, 375, 376, 377]

Urinary diversion with the creation of a sigmoid or rectal pouch is feasible in selected patients. Longterm data on outcome are not yet available. The risk of complications is rather high and managing complications adequately often requires diagnostic capabilities that are absent in developing countries.

Recommendations:

A care programme for failed repairs with persisting incontinence after a successful repair, needs to be in place.	D
It is recommended that surgical treatment of post-operative stress incontinence should only be considered six months after fistula repair.	D
Autologous material should be used when a graft or sling is required and there is no place for synthetic sling material.	C
In recurrent identifiable fistula make sure of the size and number as this kind of fistula is better repaired by a well experienced fistula surgeon. It is important to use tissue interpositioning like a Martius flap or fibrin glue.	A

3. OVERACTIVE BLADDER AFTER VAGINAL FISTULA REPAIR

The successful repair of a vesicovaginal fistula can correct the anatomical defect, but it might not render the patient dry. Failure to store urine is another problem that may occur after vaginal fistula repair.

Although persistent incontinence after fistula repair tends to be blamed on urethral dysfunction, a few urodynamic studies suggest that bladder dysfunction may play a role. [254] [378]

In the Addis Ababa Fistula Hospital, 144 patients were urodynamically assessed post fistula claosure: Forty-nine percent had urodynamic stress incontinence only, 3 % had detrusor overactivity only and 43 % had both urodynamic stress incontinence and detrusor overactivity. Five percent of women had neither detrusor overactivity nor urodynamic stress incontinence. Seven percent had postvoid residual volume of 150 ml or more.[254]

There are no specific reports on the use of antimuscarinics in fistula patients. Oxybutinin is not always available in low resource setting.

In cases where there has been extensive loss of bladder tissue or marked reduction in bladder compliance due to fibrosis, augmentation cystoplasty can be performed, usually using by interposing a segment of bowel. In some case, urinary diversion may be indicated, but only after careful discussion of the issues involved with the patient.

Recommendations:
Patients complaining of persistent leakage due to urgency incontinence or those ended up with contracted bladder may try antimuscarinics, Botulinum A toxin injection or even augmentation cystoplasty in small poorly compliant bladders. (Grade C)

4. CONTRACTED BLADDER AS A COMPLICATION OF VVF REPAIR

Although contracted bladder is a recognized complication of vesico-vaginal fistula, there is very little if any mention of this of vesico-vaginal fistula in the literature. Nardos and colleagues mentioned that among 1045 who were subjected for repair of obstetric vesico-vaginal fistula, 17% suffered from small bladder capacity post-operatively. They also realized small bladder capacity is a risk factor for failure of repair of vesicovaginal fistula.[379]

It is wiser to post-pone treatment until successful repair of the fistula is achieved. Nevertheless, a group in India attempted to repair complex vesico-vaginal fistula and to augment bladder with ileum during the same procedure. Their repairs were successful in all the 4 cases they treated. [380]

It has to be mentioned that in 3 of these cases the origin of the fistula were obstetric and one secondary to genital tuberculosis. Eilber and colleagues suggested that abdominal approach to repair the fistula can be utilized if bladder augmentation is planned simultaneously. [381]

Treatment should follow the same principles and indications of treating contracted bladder of other etiologies. The only treatment option available is augmentation cystoplasty since pharmacological manipulation, detrusor botulinum toxin injection, and neuromodulationis unlikely to work since the problem is primarily myogenic.

Recommendations:

Contracted bladder is a recognized complication of vesico-vaginal fistula and it is a risk factor of repair failure.	EL4
Contracted bladder can be a cause persistent incontinence after successful closure of the fistula.	EL4
Augmentation cystoplasty may be the only reasonable option in extreme cases.	EL4
Every effort should be made during the repair of the fistula to preserve bladder tissue.	EL4
Diagnosis should rely on urodynamics.what are eyeball UDS?	EL4
Further research on this topic is required.	EL4

5. URINARY TRACT INFECTION

Urogenital fistulae may occur due to infective pathologies (e.g. lymphogranuloma venereum, schistosomiasis, tuberculosis, actinomycosis, measles or gangrene). [382]

Although urinary tract infection (UTI) is relatively uncommon in women with fistula, it may be seen as a complication of surgical repair of fistula or of the prolonged catheter drainage that usually follows such procedures.

No systematic reviews or meta-analyses were identified from the literature search. Only two randomised controlled trial (RCT) were identified.[244, 383] The majority of papers were uncontrolled retrospective case series, looking primarily at surgical techniques and outcomes in terms of continence.

Wondimeneh et al. reported gram negative bacteria to be the most prevalent cultured strains in north Ethiopian post fistula surgery women (Citrobacter 24.5% and E. Coli 11,3%). More worrying was the antibiotic resistance pattern: Enterobacter, E.coli and Proteus mirabilis were 100% resistant to tetracycline. Enterobacter, Proteus mirabilis, Klebsella pneumonia, Klebsella ozenae and Staphylococcus aureus were also 100% resistant to ceftriaxone.[384]

Concerning antibiotic prophylaxis, Muleta et al. showed that a single dose of Gentamycin (80 mg IV) given preoperatively at the administration of spinal anesthesia appears to be equally effective as the extended use of either of or combination of Amoxicillin, Chloramphenicol and Cotrimexazole.[383]

Ayed et al. reported on the basis of a multivariate analysis of a retrospective cohort that UTI prior to repair was an adverse prognostic factor for successful surgery (p=0.03); the OR however was not significant (OR 2.72; 95%CI 0.69, 12.1) making the conclusions of the study of limited significance. [272] In a small series of post-hysterectomy fistulae, managed by laparoscopic, open abdominal, or vaginal repair, Ou et al. reported only a single episode of UTI following a vaginal procedure (1 out of 6 cases), and none following the alternative approaches. [277]

Chigbu et al reported no difference in the rate of successful fistula closure, nor of postoperative UTI between abdominal and vaginal repair procedures in women with juxtacervical fistulae. [357] The numbers of patients included, and the methodology used in these reports makes conclusions on the relative rate of UTI following different repair procedures inappropriate.

Conclusions:
The literature on this topic is limited, and the majority is of inadequate scientific value to allow meaningful evidence statements and recommendations.

There is limited evidence from a single study that UTI prior to fistula repair may be a poor prognostic factor.	EL4
The use of intra-operative antibiotic prophylaxis has been shown to reduce the rate of UTI and of antibiotic use postoperatively following fistula repair, but has not been shown to influence the rate of successful fistula closure.	EL2
There is no evidence available to adequately determine whether the rate of UTI postoperatively varies between different surgical approaches nor non-surgical management techniques.	EL4

6. CONTRACTED VAGINA, DYSPAREUNIA & SEXUAL DYSFUNCTION

The extent of scarring has been considered an important predictor of surgical success and has been incorporated into fistula classification systems. [191, 192, 194] [385]

Muleta and colleagues reported severe vaginal scarring or obliteration in 14.9% of 14,373 women undergoing obstetric fistula repair in Ethiopia. [386]

It is common that some women report sexual symptoms following pelvic surgery; this is particularly problematic following vaginal surgery, including that for urinary incontinence and pelvic organ prolapse. In a study of quality of life after anatomically successful repair, both urinary and sexual symptoms were found to be common, and were reported with approximately twice the prevalence of the local population of comparable age.[387, 388] The persistent sexual symptoms were reported as ‘quite a problem’ or ‘a serious problem’ by 27%. No comparable prevalence data for sexual dysfunction in obstetric fistula patients has been identified from the literature.

The literature searches identified 5488 papers related to urogenital fistula, 1961 of which related to surgery; 272,261 related to dyspareunia, sexual dysfunction, vaginal constriction, scarring, cicatrisation, or obliteration, of which only 88 related to these problems following fistula surgery, after removal of duplicates. Additional hand searching of 2010 journals and conference abstracts identified a further 25 studies of which only 2 were of relevance. Overall, only 7 references were identified which contained any information of any relevance to the topic of this review; of these none were RCTs and only one included any comparative data.

Both systematic reviews identified interventions for the physical aspects of sexual dysfunction in women following pelvic radiotherapy.[42, 389] Only 7 useful studies were identified in these reviews, investigating the effects of vaginal dilators (or stents or specula), [390, 391, 392, 393] (390-393) (390-393) [387, 388, 389, 390] [385, 386, 387, 388] [384, 385, 386, 387] intravaginal estrogen, and benzydamine douches. The latter compound is an anti-inflammatory, which acts directly on inflamed tissues by stabilising cells and lys-

osomal membranes and by inhibiting the synthesis of prostaglandins.

It is used topically and is well absorbed through the vaginal skin reaching higher concentrations in the underlying inflamed tissue than after oral administration; it also has analgesic, local anaesthetic and antimicrobial effects. Each of these interventions might therefore be of potential value in the face of sexual dysfunction following fistula repair surgery.

Two studies (both from the same unit) investigated the effects of a programme of psychoeducational support along with the use of vaginal dilators.[391, 394] Both reported an increase in compliance with the use of dilators (see figure 5), although no difference in sexual function scores was found. [391] Two RCTs investigated the use of benzydamine, and one intravaginal estrogen to reduce vaginal symptoms and sexual dysfunction following radiotherapy. [395, 396, 397] Each of these reports found improvements in vaginal symptoms, although both were underpowered, and of limited quality.

Secondary amenorrhea is commonly seen in obstetric fistula patients. Whether this reflects the tissue loss within the pelvis or a hypothalamic influence as a result of the physical and emotional effects of a traumatic labor, stillbirth and fistula development is not clear. The live-birth rate has been reported to be no more than 10% in obstetric fistula patients, so estrogen deficiency as a result of lactation is unlikely to be a significant factor. [386]

Conclusions:

Vaginal scarring is a common finding in obstetric fistula patients, and has been commonly (but inconsistently) linked to poor prognosis for surgical outcome.	EL3
There is no evidence on the use of vaginal dilators in the management of scarring associated with obstetric vesicovaginal fistula. Extrapolated data from post-radiotherapy vaginal stenosis may or may not be appropriate. Compliance is likely to be a problem with this approach to management, although there is evidence that additional psychoeducational support may improve compliance; data on effectiveness are inconsistent.	EL3
Persistent symptoms of sexual dysfunction are common following fistula repair surgery, and have a significant impact of the quality of a significant number of women.	EL3
Data on alternative non-surgical modalities of treatment for vaginal and sexual symptoms following obstetric fistula repair are also limited. Extrapolation from post-radiotherapy vaginal stenosis using intravaginal estrogen or benzydamine douches are encouraging, but supported by only limited RCT data.	EL2

7. URETHRAL COMPLICATIONS OF VAGINAL FISTULA REPAIR

Apart from urethral involvement in genitourinary fistula, urethral injury can be of iatrogenic origin during the repair of genito-urinary fistula: urethral injury occurred in 2% of the patients during the repair of the genitourinary fistula. Urethral stenosis was reported in 5.63% of patients after repair of urethrovaginal fistula. [398]

The exact incidence of different urethral complications of VVF is very difficult to determine. In one report from Sierra Leone examination of 505 patients with genito-urinary fistula showed that only 56% of these patients were judged to have a normal urethra. [399] Similarly, Raassen and others found that urethral involvement occurred in 5% of patients with obstetric urogenital fistulae. [400]

Presentation is dependent on the site of the fistula along the urethra and the involvement of the bladder neck and the bladder. If theurethro-vaginal fistula is large or if there is involvement of the bladder neck and the bladder, continuous incontinence occurs as in cases of vesico-vaginal fistula.

On the other hand, if the fistula is proximal in position, patient may present with stress urinary incontinence. Distal fistula can be completely asymptomatic or may be associated with splayed urinary stream. Positional wetting, which is incontinence on rising after voiding due to filling of the vagina with urine during voiding may also occur in proximal fistulae.

Pushkar and colleagues suggested repairing a urethrovaginal fistula by circumferential incision involving the fistula. The urethra is then mobilized and closed transversely to avoid constriction of the urethra. They advised against extensive trimming of the fistula edges since there is usually minimal tissues left for repair. They tested the urethra for any residual opening using a metal sound inserted into the urethra. A second layer from the periurethral tissues was placed before closing the vagina. A urethral catheter was placed for 6-9 days. Using this technique obtained a success rate of 90.14%. Recurrent fistulae were re-repaired and were successful in all but one patient. [398]

The use of interposition tissue layer is always advisable. The Martius labial fat pad flap is the most easily accessible and the most widely used flap.[401, 402] Others have described the use of peritoneal flaps with similar success to that of Martius flap although most of the fistulae in that report were non-obstetric. They have shown as well that the use of full thickness labial flaps is feasible. Nevertheless, they used that particular technique in only three patients. [381]

Bruce and colleagues have described the use of rectus abdominis muscle flap as intervening layer between the urethral and the vaginal layers.[403] The use of autologous fibrin glue has been shown to function equally to the use Martius graft in complex genitourinary fistula. The clear advantage of this was shown in the form of decreasing the complexity of already complex procedure and decreasing operative time. Additionally in does not preclude the use of Martius graft simultaneously. [233, 358]

Stress urinary incontinence that develops after urethrovaginal fistula repair can be treated with suburethral sling whether autologous or synthetic. Most of the patients in one study (59.46%) were objectively cured, while (32.43%) expressed they were satisfied, and (8.11%) of the patients remained incontinent.[398]

Hilton and colleagues reported their preliminary experience of treating sphincter incontinence following repair of urethrovaginal fistula in six patients with autologous fat injection. Two patients were cured, two improved and two did not benefit from the procedure. [404] The committee felt that it is safer to use autologous pubo-vaginal sling to treat stress urinary incontinence in these patients whether simultaneously with the original repair or later on.

Conclusion

The level of evidence in the literature regarding urethral complications of VVF is quite low. It appears that most urethral complications of VVF are preventable. These complications are urethrovaginal

fistula, urinary incontinence, and urethral obstruction. Diagnosis of urethrovaginal fistula is mainly dependent on vaginal examination and can be facilitated by the use of methylene-blue and a urethral sound. Persistent urinary incontinence after successful repair of vesicovaginal fistula is mostly due to ISD but can be secondary to overactive bladder.

Treatment of urethrovaginal fistula is always surgical not true using anatomical closure with the use of tissue interpositioning. The use of fibrin glue can improve the results. Stress urinary incontinence is best treated with pubovaginal sling using autologous material such as rectus sheath or fascia lata.

Recommendation:

Involvement of the urethra in the original fistula may worsen the outcome of the repair and is associated with higher incidence of postoperative stress urinary incontinence.	EL3
Treatment of urethrovaginal fistula is always surgical fistula not causing symptoms don't need to be treated and needs special surgical techniques and tissue interpositioning.	EL3
Treatment of stress urinary incontinence following repair of urogenital fistula can be performed by autologous pubovaginal slings.	EL4
Urethrovaginal fistula are preferably treated by a vaginal approach	EL3
A variety of autologous tissue interposition techniques have been described, but their value remains uncertain	EL3
Urethrovaginal fistula repair may be complicated by stress incontinence, urethral stricture and urethral shortening necessitating long-term follow-up	EL3

8. URETERIC LIGATION / INJURY DUE TO VVF REPAIR

Injury to pelvic ureter is one of the most serious operative complications of gynaecological surgery. Vesico vaginal fistula (VVF) repairs lead to 10-15% of ureteric injuries.[215] Ureteric injuries can be either expected or unexpected, and they may be the result of carelessness or due to a technically challenging procedure.

We refer to the section in ureteric fistula for further reading.

9. NEUROLOGICAL COMPLICATIONS OF VVF

Prolonged obstructed labor results in pressure induced ischemia and necrosis of the vagina, bladder,(occasionally)ureters, urethra and rectum, often provoking profound genitourinary fistula formation. These injuries may be part of a syndrome called the obstetric labor injury complex, which can include damage to the urological, gynecological, gastrointestinal, neurological and musculoskeletal systems. [405]

Neurological complications of VVF can involve peripheral (peroneal) or perineal nerves. Peripheral nerve injury is estimated to occur in 5% of women exposed to obstructed labor and vesico-vaginal fistulae in Sierra Leone. Since most women in Sierra Leone do not deliver in hospitals, urgent medical attention such as cesarean section for prolonged obstructed labor is often substantially delayed or completely unavailable.[219] This incidence can be underestimated.

In a study in northern Nigeria, when the charts of vesicovaginal fistulae patients were reviewed, only 5.3% of 470 patients were noted to have peroneal nerve injury. In contrast, when patients were asked and examined specifically for symptoms and signs of peroneal nerve injury prospectively, 75.9% of them had either symptoms of signs of peroneal nerve injury. [215] This may reflect the importance for a focused neurological examination on receiving a patient with vesico-vaginal fistula. Etiology of this lesion is most probably related to compression of the lumbosacral trunk of the peroneal nerve in the pelvis or due to direct injury of the peroneal nerve due to prolonged squatting and pushing in the 2nd stage of labor. [406, 407]

Peroneal nerve injury is mostly unilateral and occurs more often on the right side. Neverthless, it can still occur on the left side and can be bilateral. In the study of Waaldijk and Elkins peroneal nerve injury occurred bilaterally in 47, on the right side in 211, and on the left in 146 out of 311 patients with peroneal nerve injury. Most of these injuries resolve spontaneously. Only 13.3% persisted beyond 2 years after the occurrence of VVF. [215]

Neuropathy associated with vesico-vaginal fistula can also involve the perineum. In a study, 68.18% of fistula patients presented with a clinical neuropathy in the perineum. When these patients underwent electromyography, all fistula patients with vesicovaginal fistula in this study showed a degree of denervation. In contrast, there was no detectable lesion either clinically or by electromyography.

The severity of this lesion ranged from moderate (36.37%) to severe (63.63%). The severity is related to age at presentation since it is more severe in younger women. Furthermore, it is more severe in primiparous woman. Interesting, it appears from that study that the success of repair is affected by the severity of the lesion since severely denervated cases are usually associated with repair failure or at least persistent vesicosphincter dysfunction. [405]

Complex neuropathic bladder disorder can occur as a result of obstetric vesicovaginal fistula. This has been discussed else where in this chapter.

10. INFERTILITY AS A COMPLICATION OF VVF

Vesico-uterine fistulae can present in different ways, depending on their location, size, and the degree of patency of the endocervical canal. The least troublesome vesicouterine fistulae do not result in incontinence, but are characterized by the absence of vaginal menstruation in the presence of cyclic haematuria ("menouria" or "Youssef's syndrome"), whereby the menstrual flow exits exclusively through the urinary tract .[103, 107]

Other vesico-uterine fistulae may be associated with various combinations of altered menstruation and either periodic or continuous incontinence. The finding most characteristic of an uterovesical fis-

tula is demonstrable loss of urine through the cervix (a finding that also occurs with vesicocervical fistulae).

Many patients sustain severe cervical damage as well as vaginal injury during the course of obstructed labour. It is rare to see a completely normal cervix when examining a fistula patient. In the worst cases, prolonged obstructed labour may result in complete cervical destruction, leaving the patient with no identifiable cervical tissue at all.

Unfortunately, detailed descriptions of the condition of the cervix have not been included in the case series of fistulae published to date. Since cervical competence is such an important factor in future reproductive performance, this is yet another clinical area that demands further study. Other studies have shown amenorrhea rates from 25% to 44% . [408]

Many of these patients undoubtedly have hypothalamic or pituitary dysfunction. [409] A follow up study by Browning et al. showed that while the amenorrhea rate was 58% pre-operatively, this rate improved to 29% at 6 months after surgery, suggesting a recovery of ovulation in a proportion of operated women. [410] While the high incidence of amenorrhea in vesicovaginal fistula patients is widely recognized, only one unpublished study has been done to date looking specifically at uterine pathology in the vesicovaginal fistula population.

Dosu Ojengbede of the University of Ibadan (personal communication) performed hysteroscopy on fistula patients in Nigeria and found that intrauterine scarring and Asherman's syndrome were common in these women. The combination of widespread amenorrhea, vaginal scarring, and cervical destruction leads to a tremendous problem of secondary infertility among these patients. To date, there have been no serious scientific efforts to explore treatment of cervical and uterine damage in vesicovaginal fistula patients.

Subsequent reproductive performance of women who have had an obstetric vesicovaginal fistula has been analyzed in a few articles. [408]Emembolu analyzed the subsequent reproductive performance of 155 fistula patients delivered at Ahmadu Bello University Teaching Hospital in Zaria, Nigeria, between January 1986 and December, 1990. [411] This series included pregnancies in 75 women who became pregnant after successful fistula closure and 80 women who became pregnant while still afflicted with an unrepaired fistula that had occurred in a previous pregnancy. In women with pre-existing, unrepaired fistulae who became pregnant but who did not register for antenatal care in the subsequent pregnancy, maternal mortality and morbidity in those pregnancies was high, reflecting continuation of the conditions that led to fistula formation in the first place.The commonest maternal morbidity, excluding recurrence of vesicovaginal fistulae, was haemorrhage requiring blood transfusion in 35 patients (27.3%). Others included ruptured uterus in 3 unbooked patients whose fistula had not been repaired, bladder injury at caesarean section in 1.6% and acute renal failure in 0.8%.

Maternal complications occurred more frequently in the patients whose fistula had not been repaired and who were also unbooked. The largest series is that of Aimakhu, who analyze a subsequent reproductive performance in 246 women who underwent successful fistula closure at University College Hospital in Ibadan, Nigeria, between 1957 and 1966. [408] Only 48 patients became pregnant following fistula repair with a total of 65 pregnancies. All but 6 of these were managed at University College Hospital. Five patients aborted prior to the 16th week of gestation, leaving only 60 viable pregnancies. The plan was to perform an elective caesarean section on all patients who became pregnant after fistula repair, but only 49 caesarean operations were carried out. The results of the vaginal deliveries were not encouraging.

Patients who underwent caesarean delivery fared better. There were 49 babies delivered and 47 survived. There was no recurrent fistula among women previously repaired who became pregnant and had a subsequent caesarean section. There was one maternal death from pulmonary embolism in a woman who underwent an emergency delivery at 32 weeks gestation due to a prolapsed fetal umbilical cord.

11. PSYCHOLOGICAL COMPLICATIONS

Women with urinary or fecal incontinence suffer from depression, anxiety, and abnormal levels of situational life stresses. It is likely that psychological changes are related to the symptom and related disability and distress than to specific urogynecological conditions. Feeling of insecurity, anger, apathy, dependence, guilt, indignity, feeling of abandonment, shame, embarrassment, depression and denial are also common. Women feel loss of self-confidence and self-esteem.

In addition to these physical problems, fistulae cause acute social problems. As a result of the continuous leakage of urine and/or feces into the vagina, affected women often have an offensive odor, leading them to be ostracized by their husbands, families, and community. For example, families do not want fistula survivors preparing food or participating in family events. Commuting in public transport and engaging in social activities such as weddings and naming ceremonies becomes difficult. Women tend to get socially disengaged and socially isolated. Psychological and functional decline prevails and the potential for institutionalization occurs. [412]

VII. MANAGEMENT OF RADIATION FISTULAE

In the oncological context, fistulae may occur as a result of primary or recurrent malignancy, or as a consequence of cancer treatment by surgery, radiotherapy, chemotherapy, or a combination of therapies.[413]

1. DIVERSION PROCEDURES

Because of the tissue changes surrounding radiotherapy-associated fistulae, several authors have suggested that urinary and/or fecal diversion should be seen as the treatment of choice in such cases. [275, 414, 415] Some authors use a routine policy of preliminary urinary and fecal diversion, with later undiversion in selected cases [416]. In a non-randomized cohort of rectourethral fistula repairs, Vanni and colleagues reported 100% closure at first operation in 35 non-irradiated patients, compared with 84% in 39 irradiated patients.[416] In addition, 97% of the non-irradiated patients subsequently underwent undiversion, whereas 31% of the irradiated patients required permanent fecal diversion because of a noncompliant rectum or severe sphincter dysfunction.[416]

Some authors have emphasized the place of repair in carefully selected cases of radiotherapy-associated fistulae.[417] Of 36 radia-

tion-associated or malignant fistulae in the series reported by Hilton, although 11 patients declined surgery or died before treatment and 6 underwent primary diversion, of the 19 (53%) who underwent repair, closure was achieved in 18 (95%) at first operation. Finally, some authors seem to take the view that diversion has little or no place in the management of radiation-induced VVF in particular [75]. Of 216 radiation-induced fistulae managed over a 47-year period by Pushkar and colleagues, 210 patients underwent a vaginal and 6 an abdominal repair procedure (it should be noted that this is a retrospective case series, and although not stated in the paper, it is possible that other patients not included in this review actually underwent diversion) (Pushkar et al, 2009). It should be noted, however, that with this almost exclusive use of the vaginal repair procedure, although a cumulative closure rate of 80% was eventually achieved after four or more operations, closure was achieved in only 48% after first repair, in 40% after a second operation, in 52% after a third operation, and in 35% after a fourth operation.

In view of the anastomotic problems associated with radiation-induced fistula, the transverse colon has often been favored over ileum as a conduit in this context, to avoid the risk of employing irradiated bowel and distal ureter [418]. Although these benefits seem clear, it should be noted that high perioperative morbidity (37%) and reoperation rates (20%) have been reported from this procedure [419].

As an alternative, where both urinary and fecal diversion are proposed, Hampson and colleagues described the technique of left colic urinary diversion with distal transverse end colostomy.[420] This technique allows a shorter operative time and avoids the necessity for an intestinal anastomosis. In patients wishing to remain sexually active after such procedures, the residual bladder or rectal wall may be used to augment the vagina [421]. Where VVF coexists with significant bladder contracture after surgery or radiation, an abdominal (transperitoneal) repair might be considered, along with simultaneous ileocystoplasty or coloplasty [422, 423, 424]. Fistula repair performed concurrently with vaginal reconstruction using sigmoidovaginoplasty has also been described by Verbaeys and colleagues [425]. Although one might anticipate very high operative and postoperative morbidity from such complex multiple procedures, the outcome in the very small numbers reported appears to have been good.

2. REPAIR TECHNIQUES

Several different techniques for the vaginal repair of fistulae have been reported, although the methods of flap-splitting or dissection and repair in layers [269, 426] and partial colpocleisis [267] have been the most widely advocated in radiation-associated fistulae. [75] When patients do not wish to maintain sexual function, complete colpocleisis may be used to good effect.[417] In a nonrandomized cohort study, Hilton reported anatomic closure by colpocleisis in 94.7% of patients with radiation-associated fistulae, compared with 96.1% for a range of repair procedures in fistulae of surgical cause.[216]

The technique of sigmoid exclusion or isolation has been described for the management of radiation-associated colovesical or enterovesical and colovaginal or enterovaginal fistulae[427]. Although the results have generally been good, with the avoidance of a permanent urinary or fecal stoma, Levenback and colleagues reported poorer results than after resection of the affected bowel, largely related to bleeding from the isolated segment and bacterial infection. [427]

The interpositional grafts mentioned earlier are particularly useful in radiation-induced fistulae.

3. OTHER MANAGEMENT APPROACHES

In patients with intractable urinary incontinence from radiation-associated fistulae, percutaneous nephrostomy or ureterostomy might be considered [81]. This may in some cases extend life perhaps inappropriately, and where life expectancy is deemed to be very short, ureteric occlusion might be more appropriate. Several methods have been described, including the insertion of coils [428] and other devices [429, 430, 431] These were reviewed by Avritscher and colleagues with success rates ranging from 50% to 100% for the different methods, and with an overall success rate of 77% in 150 cases from nine papers reviewed [432].

4. RECOMMENDATIONS

Although diversion is used more widely in radiation-associated fistulae of all types as compared with non-irradiated fistulae, there is low-level evidence that repair procedures can achieve successful fistula closure and continence in appropriately selected cases.	C
There is low-level evidence to support the use of interpositional grafts when repair of radiation-associated fistula is undertaken.	C
Where urinary and/or fecal diversions are required, attempts should be made to avoid using irradiated tissues whenever possible and to minimize the potential for anastomotic complications.	C
In patients with intractable urinary incontinence from radiation-associated fistula in whom life expectancy is very short, ureteric occlusion might be considered; there is insufficient evidence to recommend any particular technique.	C
Individuals with nonhealing urocutaneous fistulae caused by chronic infection should be evaluated for an occult source of the infection, and also undergo a nutritional evaluation because these individuals may be catabolic, immunosuppressed, and unable to mobilize adequate metabolic reserves to initiate wound closure. Other considerations in individuals with nonhealing urocutaneous fistulae include occult malignancy or an undiscovered foreign body.	C

C is level of evidence not recommendation

VIII. MANAGEMENT OF GI FISTULAE

1. LITERATURE REVIEW

The literature relating to the management of urinary fistula involving the gastro-intestinal tract is limited in quantity and quality. Recent systematic reviews on surgical and non-surgical management demonstrated lack of randomised and prospective trials. [433, 434, 435] Most fistulae involve the sigmoid to the bladder dome. [436]

2. NON-SURGICAL MANAGEMENT

In the context of colo-vesical fistulae associated with diverticular disease, a surgical approach is most commonly advocated. One non-randomised cohort of 30 patients included six who did not undergo surgery, four of whom remained well for periods of up to 14 years; of the 24 who underwent surgical treatment, five (21%) died in the postoperative period.[437]

Ileo-vesical fistula in Crohn's disease may be managed with antibiotics, nutritional support, often including total parenteral nutrition, and various combinations of immunomodulatory agents; in a non-systematic review of the management of internal fistulae in Crohn's disease, Levy & Tremaine describe the drugs that have been reported to close internal fistulae partially or completely including *azathioprine*, *6-mercaptopurine*, *mycophenolate mofetil*, *cyclosporine A*, *tacrolimus*, and *infliximab*.[438]

One case series of 500 patients with Crohn's disease included 17 with entero-vesical fistulae; all received *sulfasalazine*, and most were treated with corticosteroids and antibiotics intermittently, and eight in addition received *6-mercaptopurine*. Although it is not clear that their fistulae closed completely, six continued on medical treatment alone for several years.[170]

Present et al. reported a placebo controlled randomised trial of the tumour necrosis factor α (TNFα) neutralising agent *infliximab,* a murine/human chimeric monoclonal antibody that binds both the soluble subunit and the membrane-bound precursor of TNFα, in patients with externally draining fistulae associated with Crohn's disease.[439] Adverse events were very common, but complete resolution of all fistulae was achieved in 55%, and 50% reduction in fistulous drainage was achieved in 68% of patients on 5mg *infliximab.* This latter study did not include intestino-vesical fistulae, although a case of successful use of *infliximab* in an ileo-vesical fistula has been reported.[440]

A systematic review on the medical treatment for fistula from Crohn's disease demonstrated a 65.9% fistula closure for enterovesical fistula. [434]However, prospective studies are lacking.

3. SURGICAL MANAGEMENT

A systematic review on entero- and colo-vesical fistulae, with 961 patients, indicated that surgical management, for the majority of case was performed as a one-stage procedure, that is, primary resection of the affected area with anastomosis and closure of the urinary tract defect. [435] The review also demonstrated significant heterogeneity in the studies with a lack of consensus on patient selection criteria for surgery, timing of surgery and techniques for repair of the fistula.

There was no statistically significant difference in the risk of recurrence of the fistula when comparing one-stage to multistage surgery to treat the fistula. [436] This study also showed a higher risk of recurrence of the colovesical fistula in patients with a history of radiation treatment and more complex bladder repairs including bladder resection and omental or other interpositional flaps. Laparoscopic repairs are becoming more common. [435] [441]

A systematic review on open versus laparoscopic surgery for the treatment of diverticular colovesical fistulae demonstrated no significant differences in stoma rates, rates of anastomotic leaks, surgical site infection and mortality rates. [433] As the results were obtained from non-randomised studies, the authors concluded that further studies are required before recommending laparoscopy over the traditional open approach.

Case reports of novel endoscopic approaches have been reported, including simultaneous procedures via cystoscopy and colonoscopy. [442]

4. LEVELS OF EVIDENCE

There is limited evidence to support a non-surgical or conservative surgical approach in colo-vesical fistulae where there are minimal symptoms or evidence of limited bowel involvement	EL 3
There is only limited level evidence to support a non-surgical approach in colo-vesical fistula associated with diverticular disease; nevertheless, in the frail elderly, or in patients who have limited symptoms of urinary infection or urinary diarrhoea it is reasonable to consider a trial of conservative management	EL 3
There is evidence that infliximab is efficacious in the treatment of external fistulae, but only very limited low level evidence of efficacy in urinary fistulae in association with Crohn's disease	EL 4
A one-stage approach to surgery for intestino-vesical fistulae is appropriate in many cases.	EL 2
A laparoscopic approach to one-stage management has been shown to be feasible, although there is no high level evidence to allow comparison of outcomes with open surgery	EL 3

IX. MANAGEMENT OF URETERIC FISTULAE

1. GENERAL PRINCIPLES

The relevant clinical principles are related to prevention, diagnosis, management, and after care. [443] Patients at higher risk of ureteric injury such as those undergoing complicated childbirth, radical or repeated pelvic surgery, or surgery following pelvic radiotherapy require experienced surgeons who can identify and protect the ureter and its blood supply to prevent injury and also recognise injury promptly when it occurs. Immediate repair of any intraoperative injury should be performed observing the principles of debridement, adequate blood supply and tension free anastomosis with internal drainage using stents.[444] Delayed presentation of upper tract injury should be suspected in patients whose recovery after relevant abdominal or pelvic surgery is slower than expected, if there is any fluid leak, and if there is any unexpected dilatation of the pelvi-calyceal system. Fluid should be sent for creatinine determination to differentiate serous from urinary leak. Repair of such cases should be undertaken by an experienced team and may consist of conservative management with internal or external drainage, endoluminal management using nephrostomy and stenting where available, and early (< 3 months) or delayed (> 6 months) surgical repair when required.[445] Surgery should again adhere to the standard principles of tissue repair and safe anastomosis. Functional and anatomical imaging should be used to follow up patients after repair to guard against late deterioration in function of the affected renal unit. These general aspects of care of patients with trauma to the upper

tract and subsequent fistula formation are covered in standard textbooks of urology and guideline documents.[444, 445]

2. URINARY LEAK AFTER RENAL PRESERVATION SURGERY

A large case series identified urinary fistula, defined as urinary drainage from a drain site more than 14 days post-operatively, in 4% (45/1118) of patients undergoing partial nephrectomy.[446] This was associated with larger tumours, higher blood loss, and longer ischemia time, but not the mode of surgery (laparoscopic *versus* open). The majority resolved without intervention but 30% required ureteric stent insertion or percutaneous drainage. Another large series of 752 patients showed that 21 (2.8%) experienced urinary leakage.[447] four of the 21 patients with urinary leakage had spontaneous resolution, one patient underwent nephrectomy, and 16 patients were treated by retrograde ureteral stents insertion On univariate analysis, hilar renal masses ($p < 0.04$) and higher preoperative creatinine levels ($p < 0.01$) were found to be associated with higher rates of urinary leakage. None of these variables was significant on a multivariate analysis. Review of the urinary leakage rate over time revealed it has been constantly decreasing over time, from 4% in early cases to 1.3% among the most recent ones, suggesting that the decrease in incidence is related to the improved surgical skills, rather than to differences in tumours' or patients' characteristics. A poor quality quasi-randomised study involving 16 patients with persistent leakage after pelvi-calyceal surgery despite stenting found that use of intranasal desmopressin 40 µg daily resulted in a shorter time to resolution of leak compared to control.[448]

3. URINARY LEAK AFTER RENAL TRANSPLANTATION

A case series from Brazil observed a fistula rate of 2.9% (31/1046) presenting at a mean of 28 (1-131) days following transplantation predominantly due to distal ureteric necrosis and with most cases requiring open repair.[449] Fistula occurred more commonly in patients with diabetes and was associated with lower graft survival and two deaths from sepsis. A case series from China observed fistula development in 3.5% (43/1223) of patients presenting at a mean (range) of 6 (3-20) days following transplantation again primarily due to necrosis of the distal transplanted ureter.[450] Open intervention with re-implantation of the ureter into the bladder or native ureter was required in 34 patients, with one other patient requiring transplant nephrectomy. The occurrence of a fistula did not appear to prejudice graft or patient survival. Initial implantation of the transplant ureter into the native ureter appeared to result in a lower rate of fistula. A further case series form Serbia found a fistula rate following renal transplantation of 2.2% (5/224) and all required open repair.[451]

4. URO-ENTERAL FISTULAE FOLLOWING PERCUTANEOUS RENAL SURGERY

Case reports of ureterocolic fistulae occurring after renal cryotherapy, and gunshot trauma all resolved with insertion of ureteric stent. [452, 453] This is in line with previous accounts of this complication following percutaneous nephrolithotomy.[454]

5. URETERO-ARTERIAL FISTULAE

A systematic literature review found reports of 139 cases of uretero-arterial fistula published between 1999 and 2008.[455] All patients presented with haematuria with 25% also having other urinary symptoms or back pain. Virtually all cases had a relevant past surgical history particularly pelvic cancer surgery (54%) and arterial surgery with graft insertion (31%), and 61% had a ureteric stent in situ. The great majority affected the iliac segment and pre-operative imaging was not always diagnostic. A total of 18 (13%) patients died as a result of the fistula. Many vascular and urologic interventions were used either alone or in combination. Later cases suggested that endovascular repair of the arterial defect gave the best results with lower mortality. Another, more recent case series of 20 patients also showed a high mortality of 10 – 20% but did not find any difference in outcome between open or endovascular graft insertion techniques.[456] Kibrik et al. reported on endoureteral coil embolisation after failed endovascular coiling, resulted in successful closure of the uretero-arterial fistula. [457]

6. URETEROVAGINAL FISTULAE

Ureterovaginal fistulae occurring in the early post-operative phase predominantly after hysterectomy is the most frequent presentation to urologists of upper urinary tract fistula.

The use of ureteric stenting in patients with uretero-vaginal fistulae was reported in 11 studies, including 126 patients in total;[458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468] this resulted in closure in 63 cases altogether. Success rates were between 6% and 100%, although the overall closure rate across all series is calculated at 50% ± 18% (Fig. 10).

Li et al. reported on 46 patients with an ureterovaginal fistula who were treated with delayed ureteric stenting. Success was achieved in 45 cases, and urinary leakage was stopped 48 h after surgery. Of the 45 patients operated on, 16 had their double-J stents removed after 3-6 months, and 29 needed replacement every 6-12 months. In a postoperative follow-up of 6-36 months, 10 patients had recurrent stenosis needing ureteroscopic endoureterotomy or reexpansion with a balloon. No other complications occurred. [469]

Where retrograde stenting proves impossible, percutaneous nephrostomy and antegrade stenting might be considered if there is some degree of pelvicalyceal dilatation. Ureteroscopy may also be helpful,[463, 467] and a technique for combined antegrade and retrograde ureteroscopic cannulation has been reported.[460] In one report all cases of uretero-vaginal fistula were managed by temporary diversion using a percutaneous nephrostomy followed by delayed repair 4-6 weeks later,[470] and a similar approach was taken in the management of one uretero-uterine fistula.[471]

If endoluminal techniques fail or result in secondary stricture, the abdominal approach to repair is standard and may require end-to-end anastomosis, re-implantation into the bladder using psoas hitch or Boari flap, or replacement with bowel segments with or without reconfiguration. Recent case series suggest that this standard surgery can be performed safely and with reasonable operative times using laparoscopic or robotic techniques if the relevant skills and facilities are available.[472, 473, 474] A recent case report has sug-

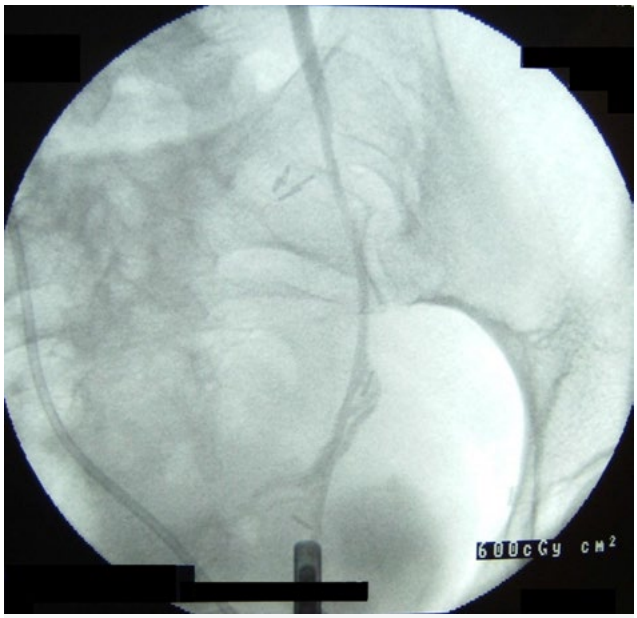


Fig 10. Conservative management of bilateral lower ureteric injury. Retrograde ureterogram showing successful cannulation of left ureter by guide wire and successful placement of right ureteric stent.

gested that open repair through the vagina is possible if abdominal access is problematic.[475]

7. URETERIC FISTULA ASSOCIATED THE TERMINAL PHASE OF PELVIC MALIGNANCY

Urinary leakage is very distressing for people dying of advanced pelvic malignancy but palliation by open diversion may be associated with a high rate of complications. Recent case series have described the technique of occlusion of the distal ureter with coils or other devices using an antegrade approach combined with chronic urinary diversion using nephrostomy tubes.[476, 477, 478] Natarajan et al reported successful management of five patients with two requiring repeat embolization but all achieving good palliation until death without adverse effects.[476] Shindel et al reported on 29 patients with bothersome urinary fistula despite chronic nephrostomy drainage, and poor performance status.[477] In all cases palliation of the urinary leakage was achieved. The majority of patients (23/29) died of their underlying cancer at a mean of eight months after the procedure. Three patients with benign disease subsequently underwent definitive surgical diversion with the remaining two lost to follow up. Coil migration was seen in one patient without serious consequence and there were no other complications specific to the embolisation. Kim et al used the technique to temporally palliate five women with ureterovaginal fistula prior to delayed definitive repair.[478] Jalaeian et al. performed 15 transrenal ureteral occlusions in 9 patients as palliation for refractory fistulae or leaks in the setting of malignancy not responding to percutaneous nephrostomy or uretericl stent. [479]

The algorithm for uretero-vaginal fistula can be found in figure 11.

8. LEVELS OF EVIDENCE

Prophylactic ureteric stent insertion does not reduce the risk of ureteric injury during gynaecological surgery	2
The use of desmopressin may hasten resolution of urinary leak after pelvi-calyceal surgery	3
Uretero-arterial fistula is associated with a high mortality rate	3
Antegrade endoluminal distal ureteric occlusion combined with nephrostomy tube diversion often palliates urinary leakage due to malignant fistula in the terminal phase	4

9. RECOMMENDATIONS

Surgeons undertaking complex pelvic surgery should be competent at identifying, preserving and repairing the ureter	D
Ureteric stents are not required as prophylaxis against injury during routine gynaecological surgery, while their role in more extensive surgery remains to be established.	B
Ureteric injury or fistula may be suspected in patients following pelvic surgery if a fluid leak or pelvi-calyceal dilatation occurs postoperatively	D
Uretero-arterial fistula may be suspected in patients presenting with haematuria with a history of relevant pelvic surgery and indwelling ureteric stent.	D
Elevated levels of creatinine in drainage fluid following pelvic surgery are suggestive of a urinary tract injury.	D
Most upper urinary tract fistula should be initially managed by conservative or endoluminal techniques where such expertise and facilities exist	B
Persistent ureterovaginal fistula should be repaired by an abdominal approach using open, laparoscopic or robotic techniques according to availability and competence	D
For patients with ureteric fistula associated with advanced pelvic cancer and poor performance status, palliation by nephrostomy tude diversion and endoluminal distal ureteric occlusion is an option.	C

X. GENERAL CONCLUSION

Fistulae can have a devastating impact on the quality of life of women. In developing countries the number of obstetric fistulae is still unacceptably high, due to poor peri-natal care in many countries. The experience and skill of several fistula surgeons should become available and transferable to many other surgeons, interested in this field. But more importantly major efforts are necessary to prevent fistula in those circumstances.

In the developed world, fistulae are less common and the outcome of fistula repairs seems to be reasonable. More prospective research is needed in this field.

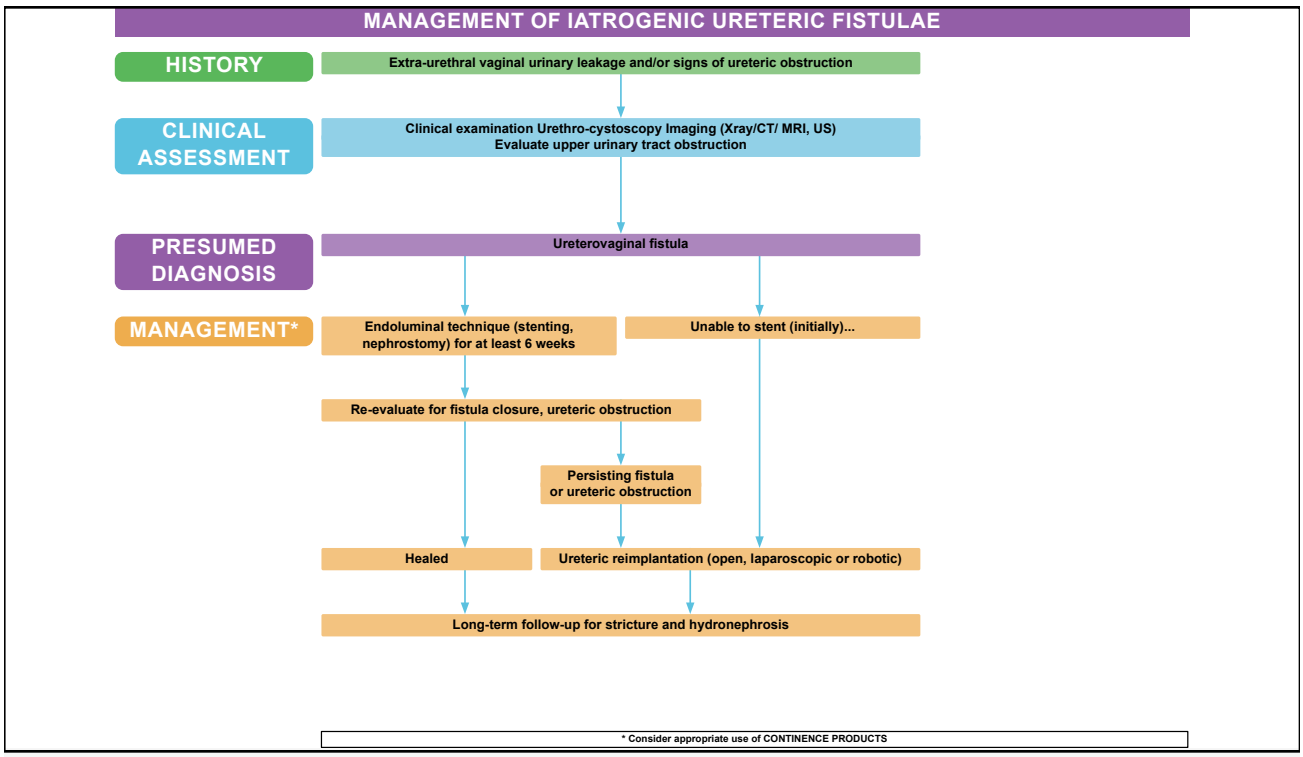


Fig. 11. Algorithm for uretero-vaginal fistula [1].Waaldijk K. Immediate catheter treatment for postpartum urine loss Waaldijk K, editor. Katsina, Nigeria Waaldijk, K. ; 2021 2021. 76 p.

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COMMITTEE 14

INCONTINENCE IN FRAIL OLDER ADULTS

Chair
Adrian Wagg (Canada)

Members
Wendy Bower (Australia)
William Gibson (Canada)
Ruth Kirschner-Hermanns (Germany)
Kathleen Hunter (Canada)
George Kuchel (USA)
Vikky Morris (UK)
Joan Ostaszkiewicz (Australia)
Anne Suskind (USA)
Motofumi Suzuki (Japan)
Jean Wyman (USA)

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I. INTRODUCTION

Older adults have the highest known prevalence of urinary incontinence (UI) of any group, other than those with specific neurological disease (e.g., spinal cord injury). As the proportion of older people in the populations of the developed world increases, so will the absolute numbers of those with either urinary (UI) or faecal incontinence (FI) or lower urinary tract symptoms [1]. The ageing of populations and the failure to increase the number of healthy years at the end of life means that the impact on future health care and long-term care costs will be profound [2].

No matter how those in later life, conventionally defined as those of 65 years and older, are described, this population is characterized by its variety, ranging from active, community-dwelling, working, healthy nonagenarians to bed-bound, chronically ill, functionally and cognitively impaired adults in their late 60's. Because the healthier group is closer in phenotype and physiology to middle aged adults than frail older adults, information relating to the management of urinary and faecal incontinence in this group is integrated into the other ICI chapters. This chapter focuses on frail older adults, emphasizing not only the different aetiologies and treatment of UI and FI, but the additional issues of disease burden, disability, altered responses to drug therapy and the role of caregivers.

The committee took the view that where there is a paucity of data reflecting the effectiveness or utility of approaches to the treatment of UI or FI in frail older adults, interventions aimed at community dwelling older adults should be employed with due regard to the likely benefits, harms, feasibility, expectations and outcomes of treatment, rather than not be attempted at all. In line with the recent ICS white paper on the ethical treatment of older adults, due recognition should also be given the burden that might be placed on an older adult when any treatment regimen is recommended [3]. The committee recognized that frail older people may be "victims" of therapeutic nihilism and may receive standards of care below those received by younger persons [4, 5].

The pathophysiology of UI in frail older adults requires a broader conception of "disease," centring on patient-level factors rather than just the bladder or bowel and its neurological control. UI and FI in frail older adults is normally a result of multiple interacting risk factors including age-related physiological changes, comorbidity, polypharmacy, functional and cognitive impairments and common pathways between them (Figure 1). Furthermore, the impact of UI or FI in frail older adults extends beyond the affected individual to their caregivers, leading to caregiver stress and an increased likelihood of institutionalisation [6]. Therefore, assessment requires a broader scope than that employed in the care of younger individuals. Failure to address the multifactorial nature of disease and treatment limits not only clinical care and research, but also important opportunities to improve function and quality of life [7]. Management of incontinence in frail older adults is necessarily multicomponent, and must address the many associated factors and shared underlying impairments with other geriatric syndromes (for example, by combining physical exercise with prompted voiding) [8]. Drug therapy must be placed in the context of altered pharmacology, pre-existing polypharmacy and an increased susceptibility to adverse events. The continuing challenge in this Consultation has been the relative dearth of Level 1 evidence for interventions. Research in frail older adults (and older people in general is hampered by substantial difficulty in recruiting to clinical trials due to either overt or covert exclusion and the additional challenge of intervening illness and death) [9]. Despite the oldest-old (those of 80 years of age and above) forming the fastest growing group of affected individuals, intervention studies continue to be rare. Moreover, trial outcomes need to be more broadly based, incorporating caregivers, a range of care settings, alternative models of care, and goals of care unique & meaningful to this population [10].

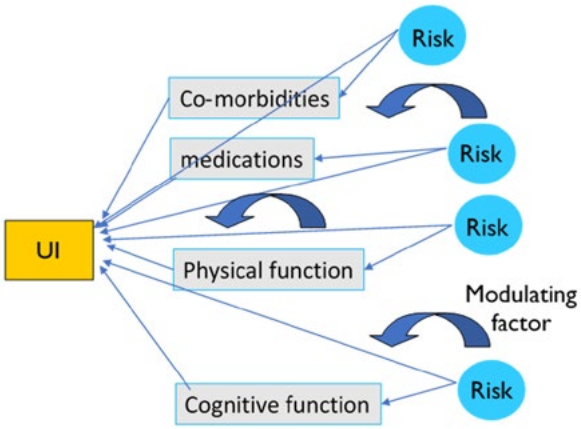

Figure 1. Incontinence as a geriatric syndrome

1. SEARCH STRATEGIES

Given the broad range of this report, we used multiple searches using the following MESH terms (in caps) and phrases, alone and in combination, using the PubMed and Ovid search engines: AGED, AGED OVER 80, ACTIVITIES OF DAILY LIVING, DEPRESSION, elderly, FALLS, frail, FRAIL ELDERLY, FRAILTY, function, geriatrics, LONG TERM CARE, MEDICATIONS, NURSING HOME, older, QUALITY OF LIFE, RANDOMIZED CONTROLLED TRIAL; and BLADDER, GYNAECOLOGICAL SURGICAL PROCEDURES, PELVIC FLOOR, PROSTATE, STRESS INCONTINENCE, SURGERY, URETHRA, URINARY INCONTINENCE, URINATION DISORDERS, UROGYNECOLOGY, UROLOGY, VAGINA, VOIDING DYSFUNCTION , nocturia OR nocturia OR "night-time voiding" OR "night- time voiding" OR "nocturnal voiding" OR "night- time voids" OR "night-time voids" OR "nocturnal voids" OR "night-time frequency" OR "night-time frequency" OR "nocturnal frequency" OR "night- time urination" OR "night-time urination" OR "nocturnal urination" OR "night-time micturition" OR "night-time micturition" OR "nocturnal micturition" OR "night-time polyuria" OR "night-time polyuria" OR "nocturnal polyuria" OR nocturia) OR ((noctur* OR night*) AND (void* OR urination OR micturition OR polyuria OR pollakiuria OR "LUTS" OR "lower urinary tract symptoms" OR "BPH" OR "benign prostatic hyperplasia")) AND ("aged, 80 or over" OR ageing OR elderly OR older OR "very old" OR senior OR "all aged" OR geriatric OR frail OR aged) AND ("double blind method" OR "double blind" OR placebos OR placebo OR "controlled clinical trial" OR "randomized controlled trial" OR "random allocation" OR "single blind method" OR "research design" OR "exp clinical trials" OR "clinical trial" OR "single blind" OR "double blind" or "triple blind" OR "single mask*" OR "double mask*" or "triple mask*") (longitudinal OR "natural history" OR cohort OR incidence OR remission OR progression OR prospective OR "community-based" OR "population-based" OR epidemiol* OR "follow-up"); TOLTERODINE; OXYBUTYNIN; SOLIFENACIN; PROPIVERINE; TROSPIUM, IMIDAFENACIN; DARIFENACIN; FESOTERODINE; MIRABEGRON; faecal incontinence OR, constipation, OR anal incontinence. Ovid Expert Search

Filter; Publication years 2015-20. We included, where possible, information from non-English language articles where an English language abstract with sufficient information was available. References in retrieved articles were reviewed for additional relevant articles. We also searched the Cochrane Database and National Guideline Clearinghouse for relevant systematic reviews, meta-analyses, and evidence-based recommendations. A research librarian aided this process.

2. FRAILTY

The proportion of older persons in the population is increasing in almost every country around the world. By 2050, approximately 2000 million people will be aged 60 years or over, and 400 million will be over the age of 80. Frailty is essentially a state of vulnerability to insult, which may be in the form of a relatively minor stressor, from which the individual does not fully recover. The Consultation has defined "frail older adults" as those over the age of 65 with a clinical presentation or phenotype combining impaired physical activity, mobility, balance, muscle strength, motor processing, cognition, nutrition, and endurance (including feelings of fatigue and exhaustion). This is consistent with the Fried phenotypic approach to frailty in which there is a clear distinction between frailty and disability, and with the accumulation of diseases (deficits) model of Mitnitski and Rockwood [11]. Among those meeting strict phenotypic criteria for frailty, only 22% also had both comorbidity and disability, 46% had comorbidity without disability, 6% disability without comorbidity, and 27% had neither comorbidity nor disability [12, 13]. Frail individuals do however usually have multiple chronic medical conditions, take multiple medications, require care from others and assistance to perform some or all of the activities of daily living (ADLs) (e.g., bathing, dressing, toileting, and mobility), are often homebound or institutionalised. They have a high risk of intercurrent disease, increased disability, hospitalisation, and death [1]. In the United Kingdom, an examination of 5,450 people aged 60 and over from the English Longitudinal Study of Ageing using Fried criteria found the overall weighted prevalence of frailty to be 14%. Prevalence rose with increasing age, from 6.5% in those aged 60–69 years to 65% in those aged 90 or over. Frailty was more common in women than in men (16% versus 12%). 93% of frail individuals had difficulties with mobility compared to 58% of non-frail individuals [14]. In the United States, using the Fried model of frailty applied to 7,439 participants in the 2011 baseline of the National Health and Ageing Trends Study of persons aged 65 and older, 15% (95% CI: 14%, 16%) of the older non-nursing home population was frail, and 45% were prefrail (95% CI: 44%, 47%). Frailty was more prevalent at older ages, amongst women, racial and ethnic minorities, those in supportive residential settings, and persons of lower income. Chronic disease and disability prevalence increased steeply with frailty [15]. In Latin America and the Caribbean, a meta-analysis of 29 studies including 43,083 people, of mean age of approximately 60 years, using a variety of frailty assessment scores, identified a prevalence of frailty of 19.6% (95% CI: 15.4-24.3%) with a range of 7.7% to 42.6% [16]. Likewise there have been an increasing number of epidemiological studies assessing the point prevalence of frailty, using a variety of definitions, across a number of countries such as Russia [17], China [18], South Korea [19] and Brazil [20] amongst others [21].

2.1. Frailty and incontinence

Several studies demonstrate a strong association between urinary incontinence and frailty. Incident UI in those over age 65 has been associated with a two-fold increased risk of impairment in ADLs, instrumental activities of daily living (IADLs – e.g., transportation, finances, shopping, laundry, housekeeping), and poor performance on three physical measures, suggesting that incident UI may be an early marker of the onset of frailty [6]. In a Taiwanese study of 440 men aged 80 years and older, the rate of frailty was determined to be 19.1% based on the clinical frailty scale. Frailty was more common among subjects with UI than those without (60.7% vs 32.3%). Men with UI also had increased rates of comorbidity, poorer physical function, were more likely to have depressive symptoms, impaired cognitive function, poorer nutritional status, polypharmacy and a higher likelihood of faecal incontinence compared to men who were not frail [22]. In a population-based study of older Mexican Americans, incident, but not prevalent, UI was independently associated with functional decline in ADLs, IADLs, and physical performance [23]. Another population-based study found an association between UI and IADL decline, but not ADL decline, nursing home admission, or death, after adjustment for age and comorbidity [2]. A Portuguese study found that older adults who presented with either "slowness" or "exhaustion" had a risk of UI almost five times greater than those without [24]. Among women ages >/=65 presenting to a urogynaecology practice in the United States, 16% were found to be frail and 31% reported functional difficulty in at least one ADL.[25]

2.2. Cognitive Frailty

Frailty is considered to be a *syndrome* that has both physical and cognitive components. Cognitive frailty is a heterogeneous clinical manifestation characterised by the simultaneous presence of both physical frailty and cognitive impairment. The key factors defining such a condition include the presence of physical frailty and mild cognitive impairment and excluding concurrent dementia, reflecting reduced cognitive reserve [26]. The exclusion of the dementias may not be useful in that the two features are often intimately intertwined. Conceptually, however, the definition may have clinical utility in terms of continence management, where the application of treatment options may vary depending upon the predominant factor influencing frailty. To be able to distinguish those with a vulnerability to cognitive decline amongst persons either with or without physical frailty may be of use, but again, the pathophysiological mechanisms leading to both entities are common and probably shared.

2.3. Dementia

The proportion of people living with dementia, a group of conditions also associated with an impairment in quality of life and physical function increases with age; prevalence estimates suggest that globally in 2010 35.6 million people lived with dementia with numbers expected to almost double every 20 years, to 65.7 million in 2030 [27][28]. In addition to the morbidity associated with urinary incontinence in older people, its presence with co-existent dementia increases the likelihood of institutionalisation [29]. Unfortunately, once there, there is evidence of institutional practices, such as *en masse* toileting, making incontinence more likely [30]. Likewise, caregivers identify looking after an older adult with dementia and incontinence as being burdensome [31, 32]. Management guidelines for urinary incontinence and lower urinary tract symptoms seldom consider the implications for management in those patients with co-existing medical conditions [33-35]; few discuss management in those with a dementia diagnosis [36]. The likelihood of incontinence increases in association with the severity of dementia but until recently longitudinal studies did not identify an association with incident cases [37, 38]. One longitudinal study of 6,349 community dwelling women found that a decrease in mental functioning as measured by a modified mini mental status exam (MMSE) was not associated with increased frequency of urinary incontinence over 6 years but did predict a greater impact [39]. Despite strong associations with baseline incontinence in the Canadian Study of Health

and Ageing, moderate or severe cognitive impairment, measured by the same modified MMSE, was not associated with incident UI over 10 years [40]. However, in a longitudinal study of 12,432 women aged between 70-75 years with a 3 year follow up there was a strong association with a dementia diagnosis (OR 2.34) [41]. Similarly, over 9 years follow up of 1,453 women aged 65, dementia was strongly associated with incident urinary incontinence (RR 3.0) [6]. Likewise, in a Scottish study, the prevalence of urinary incontinence increased with decreasing mini-mental state scores and was notably more common in those with impairments of attention and orientation, verbal fluency, agitation and disinhibition [42]. In a United Kingdom General Practitioner database, when compared with those without a dementia diagnosis, dementia was associated with approximately three times the rate of diagnosis of urinary incontinence. The incidence rates of first diagnosis per 1,000 person-years at risk (95% confidence interval) for urinary incontinence in the dementia cohort, among men and women respectively, were 42.3 (40.9-43.8) and 33.5 (32.6-34.5) [43]. When assessed urodynamically, most incontinence associated with dementia appears to be related to detrusor overactivity, resulting in urgency incontinence [44, 45].

Incontinence in dementia adds to caregiver burden [46], and influences decisions to relocate people to care homes [6]. Whether successful management of incontinence reduces either this associated burden or alters decisions to institutionalise these people is unknown, evidence is limited to case reports and anecdotal evidence. Family physicians identify dealing with incontinence in dementia as a significant challenge [47]. Likewise there is the concern regarding the influence of antimuscarinic medications on cognition, where there is increasing evidence of cognitive impairment and higher rates of incident dementia diagnosis associated with high antimuscarinic load and long exposure in older persons in epidemiological studies [48, 49], although data in those with pre-existing dementia are less consistent [50]. Data suggest that the majority of older adults with dementia living at home receive inadequate toileting assistance [51].

Once institutionalised, urinary incontinence becomes a major factor in those with dementia, In a study in Austrian nursing homes, urinary incontinence was present in 84.2% of residents with dementia versus 53.2 % of those without and was highly prevalent even in those with early dementia, affecting 64% of the 277 residents studied [52]. Once admitted to a nursing home, the presence of a dementia diagnosis is associated with a hastening of loss of continence, compared to those residents without. Incontinence is associated with a reduced quality of life and impaired nutrition and mobility in older people with dementia [53, 54], but is sadly neglected in terms of the amount of attention paid to it despite the acknowledged adverse effect on quality of life and the associated costs of management [55].

2.4. Managing incontinence in dementia

Most people with a dementia diagnosis living in the community can potentially be managed in a similar way to any other community dwelling adult, in line with current guidelines. As noted in the 6th International Consultation on Incontinence, the expectations of both patient and caregiver, the nature of the proposed treatments and likelihood of benefits, harms and burden should be taken into account [56].

Successful and safe management of incontinence in people with more advanced dementia presents additional challenges. For the most part, successful delivery of conservative or behavioural therapies in late life requires the ability for the individual to learn or change behaviour; the active engagement of a caregiver is also required [56]. A dementia diagnosis should not preclude an attempt to manage incontinence with behavioural methods, but for those with a compromised ability to retain behavioural change this is clearly inappropriate. A stepwise approach to initiating interventions and assessing the results seems like a reasonable first step in management, recognising that older people do appear to be more likely to need drug therapy for urgency incontinence than younger persons [57]. For prompted voiding to be successful, a three day trial should result in either a 20% reduction in wet episodes or an increase in spontaneous requests to use the toilet [58]. If this is not successful then the mainstay of management is a strategy of check and change of appropriately assessed containment products [36, 59]. The remaining option is to introduce a fixed voiding schedule, which requires no behavioural change, but this too may be impractical in circumstances where there is limited caregiver support or availability. Even in adequately staffed institutions, evidence suggests that for those who need toileting, the average number of toilet assists per resident is around two per day, sadly short of that which might be needed [60, 61]. The maintenance of mobility is paramount, and exercise interventions designed to maintain mobility led to a reduced burden of care for care partners and an improved quality of life for residents of congregate living. Unfortunately, once hospitalised, there is a statistically significantly increased change of a person living with dementia returning home incontinent [62]. A systematic review examining the evidence for conservative management approaches for those with dementia living at home concluded, unsurprisingly that there was insufficient evidence to make any recommendation; little, if any, specific guidance for practice in the community exists [63, 64]. Since the last ICI there has been little research into evidence informed interventions for those with dementia except a single study which examined the effect of an educational intervention followed by case conferences aimed at improving quality of life for frail older adults living with dementia. Sessions included dementia education (e.g., dementia symptoms, interaction with people with dementia and challenging behaviour) and incontinence education comprising presentations, group work and discussions. The trial resulted in no difference in incontinence, perhaps a success in the face of a deteriorating progressive condition but an improvement in QoL for most homes participating in the project [65].

Evidence on pharmacological treatment for UI in those with dementia is lacking; that which does exist is discussed in the pharmacological treatment section.

II. URINARY INCONTINENCE

1. AETIOLOGY & ASSESSMENT

1.1. Background

The aetiology of UI in frail older adults is grounded in the concept of a classical geriatric syndrome, involving multiple interacting risk factors, including age-related changes, comorbidity, and potentially common pathways between them. This section addresses these components.

1.2. Quality of the data

The data on aetiology of UI in frail older adults remain limited, and observational studies of varying quality constitute much of this literature. Additionally, longitudinal studies of large numbers of frail individuals are difficult to carry out because of paucity in

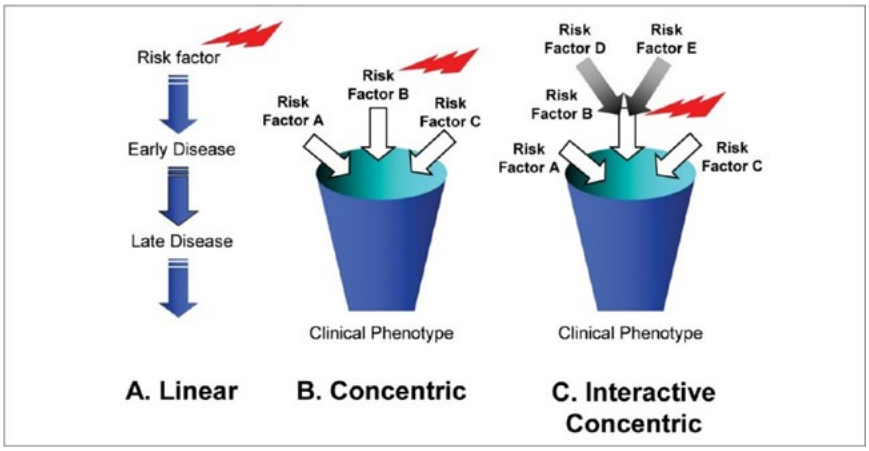

Figure 2. The mechanistic geriatric syndrome

recruitment and the high rate of natural attrition. Despite the lack of such studies, many relatively large, careful descriptive studies and case series, as well as expert consensus processes, have made important contributions to our understanding of the aetiology of UI in this population.

1.3. UI as a geriatric syndrome

In older adults, especially those who are frail, UI forms a classical geriatric syndrome, many of its risk factors are not directly related to the genitourinary tract [66, 67]. Geriatric syndromes have been defined as ‘‘multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges” [66]. Thus, large numbers of different baseline as well as precipitating risk factors may interact with each other in influencing the ability of an older individual to remain continent in the face of common daily challenges. This multifactorial complexity, combined with the fact that most individual risk factors typically account for only a small proportion of the overall risk, have greatly complicated the development of a pathophysiological framework for the study of common geriatric syndromes [66]. **Figure 2**

Nevertheless, because common risk factors (e.g. arm and leg weakness, sensory and affective impairment) may be shared by different geriatric syndromes (such as UI, falls, and functional dependence) [68], they may represent particularly attractive sites for the development of interventions [66]. For example, the presence of brain white matter hyperintensities within critical periventricular and subcortical regions could represent key risk factors for the development of different geriatric syndromes such as falls, impairment in executive cognitive function, depressive symptoms, and UI [69]. F unctional magnetic resonance imaging (fMRI) studies have identified central nervous system areas that are particularly relevant to urinary storage symptoms and urgency [70, 71]. Therefore, failure of activation within orbitofrontal regions may contribute to an older individuals’ decreased ability to suppress urgency [72]. Connectivity pathways within the right insula and anterior cingulate gyrus may also play a role in maintaining continence supporting the concept that decline in connectivity [72] and coordination between different brain regions represent early critical events in ageing. These findings suggest the possibility that interventions to prevent the development of white matter hyperintensities, such as control of vascular risk factors, could also prevent UI.

2. AGE RELATED CHANGES RELEVANT TO UI IN FRAIL OLDER ADULTS

2.1. Introduction

Age-related changes in the lower urinary tract (LUT) can function as risk factors for the development, continuation, and worsening of UI in frail older adults (**Table 1**). At the same time, they rarely are alone sufficient to cause UI, and in some persons have no effect on lower urinary tract symptoms (LUTS) or UI. Furthermore, the literature on “normal” LUT ageing has many potentially confounding methodological limitations. Normal ageing changes are difficult to study, because longitudinal data including large numbers of individuals spanning many years are necessary to definitively separate “normal LUT ageing” from confounding factors and comorbidity. Cross sectional studies are subject to confounding by comorbidity and time-dependent cohort effects, such as change in labour and delivery practices. Thus, to date many studies actually describe “age-related” associations, as opposed to normal ageing. Other limitations include derivation of much of the cellular and neurochemical data from animal studies; morphologic studies based on cadavers with unknown parity, comorbidity, and LUT symptoms; “age-effects” derived from studies of symptomatic persons; and use of surgical patients at tertiary centres as “normal” controls. Even the definition of “normal” can be difficult: is it continence?, absence of LUTS?, lack of comorbid disease, or normal physiological testing [73]? The following sections focus on findings from more robust and, where possible, confirmatory studies. Moreover, the influence of sex on changes in the biology and physiology of the lower urinary tract with ageing extends beyond obvious anatomical differences [74].

2.2. Bladder

Understanding age-related changes in the bladder is complicated by a paucity of longitudinal data, variable definitions of “normal,” and use of potentially biased (and symptomatic) referral populations. It is difficult to isolate such factors as the role of decreased blood flow, poor voiding habits, comorbidity, central and peripheral nervous system innervation, and reflex patterns as determinants of bladder function in older persons. The research focus has been urodynamic function, neurohumoural responsiveness of detrusor smooth muscle, and ultrastructure. While the key role of the urothelium and afferent systems on micturition are increasingly appreciat-

Table 1. Age related changes in the lower urinary tract

Age-Related Change	Potential Effects on Continence
Bladder ultrastructure on electron microscopy Dysjunction pattern Muscle and axon degeneration	Bladder overactivity and urgency UI Impaired bladder contractility, increased residual urine, and decreased functional bladder capacity
Bladder function Decreased capacity Decrease sensation of filling Increased detrusor overactivity Decreased bladder contractile function Increased residual urine	 Increased likelihood of urinary symptoms and UI
Urethra Decreased closure pressure in women	 Increased likelihood of stress and urgency UI
Prostate Increased incidence of benign prostatic obstruction Increased incidence of prostate cancer	 Increased likelihood of urinary symptoms and UI
Decreased oestrogen (women)	Increased incidence of urogenital atrophy related symptoms Increased incidence of recurrent urinary tract infections
Increased night-time urine production	Increased likelihood of nocturia and night-time UI
Altered central and peripheral neurotransmitter concentrations and actions	Increased likelihood of lower urinary tract dysfunction
Altered immune function	Increased likelihood of recurrent urinary tract infections
Increased prevalence of white matter hyperintensities in brain	Increased prevalence of severe urge / urgency, link to cognitive impairment and impaired mobility

ed (See Committee 2, Cell Biology; Committee and Committee 3, Pathophysiology), there are only limited human data on urothelial changes with age. Urodynamic changes associated with age have typically included smaller voided volume, increased residual volume, smaller bladder capacity, and increased involuntary detrusor contractions (detrusor overactivity (DO)). Correlations with age are often small, suggesting that other factors are at least as important [75]. Urodynamic findings may not relate to symptoms: in a urodynamic study of community-based healthy adults over age 55, DO was found in 42% of continent women, one-third of whom were totally free of LUTS [73]. In another study, charts of 53 consecutive females over age 80 undergoing multichannel urodynamics according to ICS standards were retrospectively analysed. These older patients presented with LUTS, yet in 11% urodynamic studies were reported as being normal, with considerable other discordance between symptoms and urodynamic findings [76]. Nevertheless, in a cross-sectional study involving ambulatory, cognitively intact, community-dwelling older female volunteers, maximum urethral closure pressure, detrusor contraction strength, and urine flow rate all declined significantly with age, regardless of whether DO was present or not [77].

The ability of the bladder to empty efficiently also declines in healthy older men and women who have no evidence of bladder outlet obstruction (BOO) or significant confounding disease [73, 78]. A variety of different risk factors associated both with ageing and common comorbid conditions may contribute to age-related declines in detrusor contractile function, which may ultimately lead to detrusor underactivity [79, 80]. Decreased contractile function during voiding in older persons is associated with lower urine flow rates and a small increase in post voiding residual volume (PVR) (generally to < 50 ml) [79]. Even in men with BOO, an elevated PVR may reflect decreased bladder contractile function rather than obstructed voiding [80]. A large cross-sectional study revealed that maximum detrusor contraction power was lower in older as compared to younger individuals and that these differences with ageing were greater in women than men [81]**.** While some studies suggest a myogenic origin of impaired contractility, others suggest that impaired blood supply, with concomitant ischaemic-reperfusion injury causing patchy denervation, leads to decreased contractility (see Committee 3, Pathophysiology). More recently, Smith highlighted the potential contribution of age and disease-related declines in bladder afferent sensory activity in contributing to impaired voiding performance seen with detrusor underactivity [82]. Incomplete bladder emptying from all such causes can reduce functional bladder capacity, and thereby contribute to the urinary frequency and nocturia common in frail older persons [79]. The development of a model allowing continuous uroflow in mice has led to studies evaluating the impact of normal ageing on overall LUT performance [83, 84]. While ageing did not influence measures of detrusor expulsive strength, pre-contraction pressures, intervoid intervals, per-void volumes and voiding flow rates all increased with ageing [83]. Moreover, aged animals demonstrated a decreased homeostatic capacity to respond to the challenge of continuous bladder filling, with indirect measures suggesting a role for decreased bladder volume sensitivity [83, 85].

In human studies, the observation that bladder volume at the initial desire to void declines with age may be confounded by comorbid conditions and concurrent medications [86]. Furthermore, unlike the positive association between detrusor contraction strength and DO found in younger subjects, older adults demonstrate a decline in DO-associated detrusor contractile function [77] and detrusor contractility [87] . Moreover, many frail older adults with UI present with a combination of DO on filling and poor emptying during voiding, an association termed detrusor hyperactivity with impaired contractile function (DHIC) [44, 79, 88]. In such cases, the bladder contraction does not empty the bladder fully, leaving a large PVR otherwise not explained by BOO. Because DHIC symptoms can include urgency UI, stress and mixed UI, dribbling, frequency, and nocturia, they may be mistaken for other conditions. At the same time, DHIC may be mistaken for DO with normal contractility function because significant detrusor underactivity may be present in the absence of any relevant symptoms. Thus, while it is not possible to speak of precise cutoffs when differentiating between “normal” and “abnormal” PVR values, PVR assessments do provide crucial information into age- and disease-related alterations in overall LUT performance [89].

A study of older women with an elevated PVR (> 100 ml) revealed on average a higher detrusor pressure at Qmax and greater bladder capacity than women with a normal PVR (PMID: 25400112). Also, with higher PVRs (> 200 mL) history of back surgery or injury (odds ratio (OR) = 4.30, 95% confidence interval (CI) = 1.16-15.91) and pelvic surgery (OR = 4.42, 95% CI = 1.51-12.95) were significantly associated with incomplete bladder emptying in multivariate analysis [90]. All of these considerations highlight the importance of an approach to older patients with elevated PVR that is systems-based and grounded in physiological principles [89]. One of

the major clinical challenges arises from the fact that while impaired bladder emptying is a well-recognized cause of lower urinary tract symptoms, many different terms are used to describe these issues plus the symptoms produced do not always relate to voiding, and may include frequency, urgency and incontinence. Ultrastructural studies demonstrate cellular changes associated with age-related changes in detrusor function. One series of such studies involved symptomatic and asymptomatic persons aged 65 - 96, using urodynamic testing and electron microscopy of bladder biopsy specimens, which were read in a blinded fashion using explicit protocols [91-94]. A consistent, one-to-one correlation between specific urodynamic findings and bladder ultrastructure was observed, although there has been considerable debate about the veracity of these findings and they have not been reproduced and have been disputed by the findings of a later study which found the ultrastructural changes described evenly distributed between normal women (n = 15) and women with detrusor overactivity (n = 22) [95]. In the small number of asymptomatic patients with no DO, normal contractility, and no obstruction, detrusor muscle fascicles were largely intact, with two distinctive ultrastructural findings that may be related to ageing alone: muscle cell membranes characterized by numerous “dense bands” and markedly depleted caveolae, and slightly widened spaces between muscle cells with limited content of collagen and elastin. Depletion of caveolae may be related to de-differentiation of muscle cells, which could eventually result in the reversion of actively contractile cells to inactive, synthetically immature cells. A similar phenomenon has been reported in atherosclerotic blood vessels and postmenopausal myometrium and may be related to reports of increased collagen in bladders from older women [91, 96]. Moreover, lack of oestrogen contributes to, and oestrogen replacement reverses, both caveolar depletion and detrusor fibrosis [97, 98]. Thus, both ageing and post-menopausal decline in oestrogen levels may contribute to bladder muscle cell differentiation and contractile function [79].

The natural history of these ultrastructural changes remains largely unknown. From the ultrastructural studies described above, a subset of 23 patients was followed longitudinally [99]. The previously observed one-to-one correlation between ultrastructure and function was maintained, but it was unclear whether urodynamic or ultrastructural changes occurred first in subjects who developed or had a change in LUTS. The pattern of dense-bands and non-disruptive muscle cell degeneration varied over time: the DO with dysjunction pattern developed in some subjects, and impaired detrusor contractility and the corresponding degeneration pattern was observed to progress in severity or develop. Other investigators have found similar results but without the one-to-one correlation (e.g., see Brierly *et al* [100, 101]). Clearly, further work is needed understand the associations between changes in ultrastructure, urodynamic features and clinical syndromes.

In addition to such alterations in ultrastructure, a variety of changes involving relevant nerve fibres, receptors and signalling pathways have also been described in bladder tissues from aged animals, and to lesser extent human biopsies. For example, with ageing overall, sympathetic nerve fibre density may decrease [102, 103]. Bladder biopsies from older subjects with normal urodynamic profiles typically show little or no evidence of axonal degeneration and the density of some CGRP-positive sensory nerves is maintained in old age, yet the impact of ageing on other categories of sensory fibres or on motor fibres remains unknown [91, 102]. Examples of other changes include decreased contractility and calcium fluxes in response to cholinergic agonists or depolarization [104]; increased responsiveness to adrenergic agonists with increased expression of the alpha 1D-adrenergic receptor [103]; declines in phosphodiesterase 5 (PDE5) levels and possibly signalling [105]; as well as decreased P_{2X1} purinergic receptor expression [106]. Unfortunately, the interpretation and generalisability of these findings is often limited by a failure to include intermediate age-points which would allow investigators to distinguish changes attributable to ageing as opposed to maturational processes [107, 108].

More recent studies have suggested a role for decreased A_2B receptor expression in lower ability of adenosine to relax the detrusor [109]. Also, use of permeabilised bladder muscle strips suggested that IP_3-induced calcium release is primarily responsible for the contractions in older rats, thus ageing-related decline in carbachol contractions may result from decreased calcium-induced calcium release rather than carbachol-induced calcium sensitisation [110]. The use oxidative stressors has shown that mechanisms possible related to the TRPM8 (cold sensing TRP melastatin 8) ion channel may compromise urothelial function in aged bladders [111]. Studies conducted with human bladder muscle strips suggested an age-related increase in carbachol-mediated contraction via Rho Kinase pathways [112], associated with lower MLCK expression [113]. Finally, studies conducted in aged mice from a systems-based perspective demonstrated that an increase in neurogenic power during filling accompanies augmented centrally mediated compliance enhancement with ageing, thus suggesting the existence of a bladder control model in which brain processes related to micturition may compensate for age-associated changes [114].

2.3. Urethra

Due to their common embryological origin, the urethra undergoes age-related mucosal and stromal changes like the vagina, and urethral changes in older women can be partially inferred from examination of vaginal tissue. Because of the difficulty of obtaining non-cadaveric urethral tissue, data on urethral smooth and striated muscle changes with age are complicated by confounding factors and definitions of controls. Urethral closure pressure decreases with age [115, 116]. Based on a sample of 82 women aged 20-70, urethral closure pressure was found to decrease by 15 cmH_2O per decade [117]. A number of anatomical and physiological changes may account for this decline. Mucosal thinning and lack of proteoglycans reduce urethral wall apposition; this also may contribute to retrograde movement of perineal bacteria into the bladder causing urinary tract infections [118]. These mucosal changes may extend up to the bladder trigone, causing irritation of sensory afferent nerves, and possibly triggering DO [119]. The submucosal venous plexus in the proximal urethra loses its corkscrew shape, the number and volume of arterial vessels decrease, and vascular pulsations lessen [120]. Several studies, using different measurement techniques, have shown that urethral vascular density and blood flow decrease with age, but not vascular flow velocity [121-123]. However, age explained only 9% of the variability in vascular density in one study [121], and none of the studies controlled for vascular risk factors such as hypertension and diabetes. The relative importance of decreased vascular volume versus hypoxia on urethral functional integrity is unclear. Other alterations in the urethral stroma are increased volume of connective tissue, decreased ratio of proteoglycans to collagen, and decrease in nerve density [124, 125]. Both oestrogen receptor alpha ($ER\alpha$) and oestrogen receptor beta ($ER\beta$) are present in paraurethral tissues [126]. Although there were no apparent differences in the expression of these genes between women with stress urinary incontinence (SUI) versus controls, levels of $ER\alpha$ and $ER\beta$ mRNA were lower with the menopause and ageing, respectively [126].

Cadaver studies suggest that the number and density of urethral striated muscle fibres decrease with age, especially in the ventral

wall of the proximal urethra [127, 128]. These authors estimated that striated fibres decrease by 1% per year. Large inter-individual variations were observed, with age and parity accounting for only a small part of the variability, suggesting that other yet to be defined factors are important. These studies also found that cross-sectional striated muscle fibre area decreased while fibre diameter was preserved. Another cadaver study by the same group found that circular smooth muscle width was 25%-50% higher in younger women (aged 20-39 years) than older (aged 70-89), and that younger women had higher fibre counts [129]. Smooth muscle loss in the older women correlated with loss of striated muscle in the anterior urethra. Moreover, a recent study raised the possibility that TNF-alpha may contribute to age-related rhabdosphincter satellite cell death and muscle loss with ageing [130]. Urethral sensation, measured as current perception thresholds, was significantly higher in older women in two studies (by the same authors), one comparing 48 asymptomatic women and 13 with urgency UI [131], and another in asymptomatic women [119]. The authors concluded that age-related LUT sensory neuropathy could contribute to the higher prevalence of overactive bladder (OAB) symptoms with age; however, urethral sensation thresholds were higher in women with urgency UI when controlled for age and parity [131], and the "asymptomatic" older women may have had urodynamic DO [119].

With age, the urethral meatus generally moves toward the vaginal introitus, and may be difficult to see if there is considerable introital stenosis. Caruncles, benign violaceous soft swellings, often appear at the meatus and are not problematic unless they cause discomfort or obstruction. Urethral diverticula can be a diagnostic challenge, especially in older women, because the symptoms (dysuria, pain, UI, frequency, urgency, dyspareunia) may be attributed to postmenopausal changes, age, OAB, or urgency UI [132]. Diverticula should be considered in women who have repeatedly failed "conventional" UI treatment. Diagnosis requires imaging by voiding cystourethrography, ultrasound, or magnetic resonance scans. Urethral obstruction is relatively uncommon in older women and is nearly always secondary to other LUT dysfunction (e.g., pelvic organ prolapse) or is iatrogenic (from LUT/pelvic surgery or radiation. In men, age-related decrease in striated sphincter muscle cell density also occurs, [133, 134] and has been associated with increased muscle cell apoptosis [133]. While some investigations describe an increase in resting prostatic urethral pressure with age, [135] others note the increase occurs only to the sixth decade then subsequently decreases, along with a shortening of sphincteric urethral length [136]. These discrepancies may reflect differences in prostate volume and morphology.

2.4. Pelvic floor

Pelvic floor changes in normal older men have not been well studied. In women, the effect of age on pelvic floor structure and function is difficult to differentiate from the effects of hormonal status and parity [137]. A number of studies are cross sectional rather than longitudinal and focus on symptomatic women. For example, a questionnaire study of over 4,000 community women aged 25-84 found no association between age and stress UI (SUI), OAB, or anal UI, after adjustment for obesity, birth history, menopause, and hormone use [138]. Similarly, in a random sample of 343 Austrian women aged 18-79 years, impaired pelvic muscle contraction (graded by the Modified Oxford Scale) was weakly associated with parity and body mass index but not age [139]. In contrast, a study combining an interview, physical exam and transperineal ultrasound identified age as a weak (r = -0.25) but statistically significant predictor of pelvic muscle weakness and levator ani morphometry even after controlling for obvious confounders [140]. A recent MRI study was able to distinguish distinct patterns of change in pelvic support in women with stress as opposed to mixed urinary incontinence[141]. Evidence of denervation and changes in pelvic striated muscle fibre number, type, and diameter have been found in asymptomatic and nulliparous women (see Committee 2,Neural Control & Cell Biology). For example, in a sample of 82 nulliparous women, neither levator function (measured by resting vaginal closure force and augmentation of vaginal closure force) nor pelvic organ support (on pelvic exam) showed an association with age [142]. A histomorphometric study, using levator ani muscle from 94 female cadavers (aged 15-58), 10 male cadavers (aged 23-35), and 24 women undergoing pelvic surgery, found that myogenic cell damage was associated with both parity and age (</> age 35), but there was no difference between nulliparous women, men, and women with pelvic organ prolapse and/or UI [143]. Total collagen content in pelvic muscle and fascia declines with age, with increased cross-linking and decreased elasticity, [144] but this association does not imply a direct causative effect of "ageing." Constipation may independently contribute to pelvic floor dysfunction in older women [145, 146]. Finally, while vaginal atrophy was as expected more intense in women aged >60 years, no difference was found in pelvic floor muscle strength with ageing in continent women [147]

2.5. Vagina

The prevalence of age-related changes in the vagina varies with hormonal status, coexistent vascular disease, and the continuation or lack of sexual activity [148]. The postmenopausal decrease in oestrogen plays a part in many age-associated vaginal changes. Oestrogen is trophic for much of the LUT in women, with oestrogen receptors found in the vagina, vestibule, distal urethra, bladder trigone, pelvic muscles, and ligamentum rotundum [149]. Yet, as the Women's Health Initiative trial has shown, one cannot assume that the association between low oestrogen levels and physiological changes implies that hormone replacement will reverse these changes, restore function, or reduce symptoms [150, 151]. Moreover, the data are equivocal whether and how LUT oestrogen receptors change in number, density, or function with age [120].

Following menopause, the vaginal epithelium loses the majority of its superficial and intermediate layers. Mucosal thinning may be associated with inflammation, evident as erythema, telangiectasia, petechiae, friability, and erosions. This may be responsible for urgency and frequency in some frail older women. In addition, there is loss of epithelial glycogen and lubrication, and mucosal pH increases from 4.5-5.5 to 7.0-7.4 [152]. These changes can lead to loss of normal adherent flora (lactobacilli), colonisation with pathogenic organisms such as E. coli and enterococci, and the observed increase in bacteriuria and recurrent symptomatic urinary tract infections (UTIs) in older women [153].

Vaginal blood flow, which is important for mucosal integrity and submucosal fullness, decreases with age. Whether this is oestrogen related, and/or due to concomitant vascular disease is not known. Collagen and lipofuscin deposition in the stroma increases and may be accompanied by invasion by lymphocytes and plasma cells [153]. The combined epithelial and stromal changes are associated with vaginal wall thinning and flattening of rugae [149]. The vaginal vault may shorten and narrow, and the introital opening decrease (and in severe cases become stenotic), which may make vaginal examination, intercourse, and use of pessaries difficult. However, it is not clear that vaginal shortening is clinically relevant: in one case series of over 3,000 women attending a general clinic, total vaginal length decreased by only 0.08 cm every 10 years [154]. Vaginal shape also may be altered by POP. Because of the multiple potential confounding factors discussed above, a causal relationship between urogenital atrophy and urogenital symptoms/LUTS

should not be automatically assumed. Very few randomised trials of oestrogen (oral or topical) for urogenital symptoms include women over age 75, use patient-defined outcomes in addition to physiological measures, or evaluate quality of life outcomes [155]. There are insufficient data to provide an evidence-based approach to symptomatic urogenital atrophy in older women. Oral oestrogen should not be used, but expert opinion supports topical oestrogen treatment (cream, intravaginal tablets, or oestrogen-impregnated pessary-like ring). The validation of vaginal self-swab collection specimen collection offers new opportunities for extending relevant questions to epidemiological studies of older women living in the community [156]. Nevertheless, despite all reported biological changes, ageing did not interfere with the ability of fibroblasts obtained from older women with prolapse to be successfully reprogrammed [157].

2.6. Prostate

Histological benign prostatic hyperplasia (BPH) is strongly age-related [158], and may lead to prostate enlargement (BPE) and outlet obstruction (BOO). While many LUT changes in women are associated with lower oestrogen levels, BPH results from the development of an oestrogen-predominant hormonal milieu in the prostate. The trophic prostatic androgen, dihydrotestosterone, is formed by the 5-α reduction of testosterone. Dihydrotesterone levels decrease with age, while oestradiol concentrations increase in the prostate stroma and remain constant in epithelial tissues, leading to an increase in the oestradiol/dihydrotesterone ratio and promoting stromal proliferation [159, 160]. Epithelial hyperplasia in turn is mediated by an array of stromal factors [161].

Histological BPH occurs in nearly 80% of men by age eighty [158]. Mean prostate volume increases with age but is very variable; its strongest predictor is prostate specific antigen level of >1.4-2 ng/mL [162]. LUTS in men increase linearly over time, with the fastest increase during the seventh decade, such that by age 80 approximately one-third of men have received treatment for moderate to severe LUTS [163]. Natural history studies and randomized intervention trials, however, consistently demonstrate that symptomatic progression of benign prostate disease is not inevitable. LUTS remit in about one-third of symptomatic men without treatment [164]. Approximately one-third to one-half of affected men develops DO. Thus, even in the presence of demonstrable BPE and/or BOO, the aetiology of LUTS is multifactorial, making prostate related LUTS in older men a diagnosis of exclusion. Nevertheless, age-stratified normative values for prostate volume, PSA level, as well as indicators of clinical symptoms, quality of life measures and urodynamic parameters may help in such decisions [165].

Although most patients are asymptomatic at the time of prostate cancer diagnosis, this is another possible cause of LUTS, including urgency UI, in older men. However, evaluation for prostate cancer in frail older men is rarely if ever indicated, given the high likelihood of limited remaining life expectancy.

The evidence as to whether prostatic inflammation, either acute or chronic, contributes to urinary retention and LUTS in frail older men is contradictory. In a single institution case series of 374 men undergoing TURP for acute urinary retention (AUR) or LUTS, pathological evidence of acute inflammation was significantly more common men presenting with AUR than LUTS (70% vs. 45%) [166]. However, in a much smaller case series of 70 men presenting with AUR, there was no association between inflammation from prostate infarction and AUR [167]. Nevertheless, a recent study demonstrated phenotypic changes and an increased differential expression of a variety of genes involved in inflammation and oxidative stress within glandular adjacent stroma microdissected from young and aged mouse prostates [168]. Such changes may play a role in promoting the development of BPH, BPE and cancer in aged prostates [169]. However, recent studies conducted using both human tissues and animal models support the hypothesis that senescence-associated inflammatory pathways contribute to the pathogenesis of BPH [170].

2.7. Other changes

The role of various neurotransmitters in the central and peripheral nervous system in UI is under active investigation (see Committee 2, Cell Biology & neural control). Nevertheless, age-related changes in the actions of these neurotransmitters, their receptors, or the cellular events they stimulate may contribute to the development of UI in frail older adults.

The prevalence of both asymptomatic bacteriuria and UTIs increase with age [171], and the two are often found together in frail older adults. Age-related changes in immune function, vaginal epithelium, faecal incontinence, and insufficient hygiene related to disability, cognitive impairment, and/or lack of caretakers may predispose the frail older adult to bacteriuria and recurrent UTIs. However, the role of otherwise asymptomatic bacteriuria (often found in association with pyuria) [172], in the aetiology of UI in frail older adults remains unclear [173]. Treating otherwise asymptomatic bacteriuria in frail older patients with chronic, stable UI does not, in general, reduce UI severity [174]. UTI symptoms may be subtle and non-specific in this population, and include worsening of UI, delirium in patients with dementia, or a minor but important decline in functional ability [174]. At the same time, current consensus criteria for UTI are poorly sensitive and only moderately specific for UTI in older adults. In a prospective cohort of 340 nursing home residents, in which UTI was defined as pyuria (>10 white cells) with >100,000 colony forming units on culture, the McGeer, Loeb, and revised Loeb UTI criteria had sensitivities of only 19-30% and specificities of 79-89% [175, 176]. [177]

2.8. Role of biological ageing

In recent years, there has been a tremendous growth in our knowledge in the basic biological mechanisms that drive ageing processes at the level of organisms, systems, organs and individual cells [178-180]. This has led to the emergence of two major concepts within the recently established field of Geroscience [178-180]. First, it has been proposed that interventions designed to target multiple mechanisms which are known to contribute to biological ageing, would have the capacity to prevent or slow the impact of ageing on clinically relevant physiological mechanisms. To that end, the recent observation that dietary restriction in rats reduces ageing-related declines in LUT function together with increases in inflammatory mechanisms, suggests that such interventions could represent a promising direction for future research. Conversely, a number of ageing changes involving the LUT appear to be augmented in a mouse model of accelerated senescence [181].

Second, the concept of Geroscience suggests that since ageing represents the predominant risk factor for many chronic diseases such as atherosclerosis, cancer, dementia and others, such chronic diseases are also likely to share common mechanisms with both ageing and each other; and therefore strategies designed to target such pathways would have the potential to delay the onset of such chronic diseases, thus enhancing function, independence and health span in older adults [178-180]. Although there is growing evidence that atherosclerosis and other forms of ageing-related cardiovascular dysfunction [182, 183], contribute to declines in LUT function and symptoms in old age, from the perspective of mechanisms this hypothesis remains to be explored in the context of

genitourinary ageing. Although much still remains to be defined and understood, evidence that lower urinary tract symptoms are associated with physical performance [184] [184], frailty [185] and adiposity [186] raise the possibility that inflammation, cellular senescence and other biological hallmarks of ageing represent potentially modifiable targets for geroscience-guided therapies [187].

III. FACTORS OUTSIDE THE LOWER URINARY TRACT CAUSING OR CONTRIBUTING TO URINARY INCONTINENCE

A hallmark of UI in the frail older adult population is the wide variety of factors and conditions outside the lower urinary tract that can cause or contribute to urinary leakage **(Table 2).**

Table 2. Comorbid conditions that can cause or contribute to UI in frail elderly persons

Conditions	Comments	Implications for Management
Comorbid medical illnesses		
Diabetes mellitus	Poor control can cause polyuria and precipitate or exacerbate incontinence; also associated with increased likelihood of urgency incontinence and diabetic neuropathic bladder	Better control of diabetes can reduce osmotic diuresis and associated polyuria, and improve incontinence
Degenerative joint disease	Can impair mobility and precipitate urgency UI	Optimal pharmacological and non-pharmacological pain management can improve mobility and toileting ability
Chronic pulmonary disease	Associated cough can worsen stress UI	Cough suppression can reduce stress incontinence and cough-induced urgency UI
Congestive heart failure Lower extremity venous insufficiency	Increased night-time urine production at night can contribute to nocturia and UI	Optimizing pharmacological management of congestive heart failure, sodium restriction, support stockings, leg elevation, and a late afternoon dose of a rapid acting diuretic may reduce nocturnal polyuria and associated nocturia and night-time UI
Sleep apnoea	May increase night-time urine production by increasing production of atrial natriuretic peptide	Diagnosis and treatment of sleep apnoea, usually with continuous positive airway pressure devices, may improve the condition and reduce nocturnal polyuria and associated nocturia and UI
Severe constipation and faecal impaction	Associated with double incontinence (urine and faecal)	Appropriate use of stool softeners Adequate fluid intake and exercise Disimpaction if necessary
Neurological and psychiatric conditions		
Stroke	Can precipitate urgency UI and less often urinary retention; also impairs mobility	UI after an acute stroke often resolves with rehabilitation; persistent UI should be further evaluated Regular toileting assistance essential for those with persistent mobility impairment Optimizing management may improve mobility and improve UI
Parkinson's disease	Associated with urgency UI; also causes impaired mobility and cognition in late stages	Regular toileting assistance is essential for those with mobility and cognitive impairments in late stages
Normal pressure hydrocephalus	Presents with UI, along with gait and cognitive impairments	Patients presenting with all three symptoms should be considered for brain imaging to rule out this condition, as it may improve a ventricular-peritoneal shunt
Dementia (Alzheimer's, multi- infarct, others)	Associated with urgency UI; impaired cognition and apraxia interferes with toileting and hygiene	Regular toileting assistance essential for those with mobility and cognitive impairment in late stages
Depression	May impair motivation to be continent; may also be a consequence of incontinence	Optimizing and phamacological management of depression may improve UI
Medications	See Table 3	Discontinuation or modification of drug regimen
Functional impairments Impaired mobility Impaired cognition	Impaired mobility and/or cognition due to a variety of conditions listed above and others can interfere with the ability to toilet independently and precipitate UI	Regular toileting assistance essential for those with severe mobility and/or cognitive impairment
Environmental factors Inaccessible toilets Unsafe toilet facilities Unavailable caregivers for toileting assistance	Frail, functionally impaired persons require accessible, safe toilet facilities, and in many cases human assistance in order to be continent	Environmental alterations may be helpful; supportive measures such as pads may be necessary if caregiver assistance is not regularly available

2.1. Medications

The risk of difficulty controlling urination in community dwelling older women taking medications with LUTS effects was about 30% higher compared to those who did not take such medications (OR 1.31 CI 1.05-1.62). This did not occur in men (OR, 1.08; 95% CI, 0.97-1.21) [188]. Overall, 20.5% of these women reported incident incontinence at Year 4 (3 years from baseline) [194]. Several studies have implicated alpha blockers as causing UI in women with an adjusted OR of 4.98 (95% CI, 1.96-12.64) [189, 190] and increasing to OR 8.81 (95% CI, 1.78-43.53) in conjunction with loop diuretics [191]. Oestrogens have been shown to increase risk of incontinence in women OR 1.6 to 2.0. [190, 192] A wide range of medications have been implicated in causing UI with varying degrees of evidence [193]. There has even been a case report of hydroxychloroquine causing UI [194]. A retrospective analysis of drug dispensing data in a Japanese cohort found that polypharmacy was associated with the use of medications known to contribute to urgency [195]. Similarly, a Canadian cross-sectional study identified a strong association (OR, 4.9; 95% CI, 3.1-7.9) between polypharmacy, defined as 5 or more medications, and the prescription of a medication known to cause LUTS [196]. In an acute care hospital setting in Korea, polypharmacy was one of the predictors of UI in both sexes (OR, 3.35; 95% CI, 1.89-5.92) [197]. However, there is little evidence that polypharmacy in the absence of drugs that cause incontinence has an impact on the lower urinary tract, and it is likely that the association between polypharmacy and urgency relates to the fact that the more drugs an individual is prescribed, the higher the odds that one of them will be a drug known to induce urgency. Older patients commenced on new treatments should be monitored for changes in urinary symptoms. Many classes of medications commonly prescribed for frail older adults can cause or contribute to the development of UI **(Table 3).**

2.2. Prevalence, incidence & impact

Not only UI but also faecal incontinence (FI) is more prevalent in frail older adults, and both are associated with cognitive impairment, decreased mobility and decreased levels of physical activity and reduced quality of life. The prevalence of UI varies by the study settings. In a single large University hospital setting (n = 1,556), 29.8% of geriatric patients had UI and poorer health literacy and cognitive impairment were independently associated with an increased likelihood of nursing-reported UI [198]. Among the elderly receiving home hospice care (n = 15,432), the prevalence of UI was 32% and female sex (Hazard ratio (HR) 1.30, P<0.001), age (HR 1.02, P<0.001), dementia (HR 1.68, P<0.001), and stroke (HR 1.72, P<0.001) were associated with a greater risk of UI.[199]. Among the community care recipients in New Zealand (n = 93,462), prevalence of UI, FI, and double incontinence (DI) was 36.6%, 9.9%, and 13.2%, respectively. Epidemiological surveys of continence status among older individuals living in nursing homes had been conducted in the US (n = 2,416,700), Norway (n = 898) and Japan (n = 2,517) [200-202]. The prevalence of UI, FI, and DI were 49.6%, 43.4%, and 35.5% in the US; 72.0%, 42.8%, and 40.2% in Norway; 66.9%, 42.8%, and 41.1% in Japan, respectively. Physical and cognitive impairments were significant predictors of both UI, FI, and DI [202].

In a group of subjects with Medigap insurance advancing age has been associated with an increase in the prevalence of UI (37.5% in 5,530 subjects). Comorbidities associated with UI including arthritis of the hip or knee (Relative Risk Ratio (RRR) = 1.21, P<0.001), arthritis of the hand or wrist (RRR = 1.15, P = 0.001), stroke (RRR = 1.18, P = 0.078), other heart conditions (RRR = 1.19, P<0.001), and having any cancer (RRR = 1.13, P = 0.0020). Obesity and being overweight increased the likelihood of having UI (RRR = 1.32, P≤0.001 and RRR = 1.14, P = 0.0013, respectively),

Table 3. Medications that can cause or contribute to UI in frail elderly persons

Medications	Effects on Continence
Alpha adrenergic agonists	Increase smooth muscle tone in urethra and prostatic capsule and may precipitate obstruction, urinary retention, and related symptoms
Alpha adrenergic antagonists (Alpha blockers)	Decrease smooth muscle tone in the urethra and may precipitate stress UI in women
Angiotensin converting enzyme inhibitors	Cause cough that can exacerbate UI
Anticholinergics	May cause impaired emptying, urinary retention, and constipation that can contribute to UI. May cause cognitive impairment and reduce effective toileting ability.
Calcium channel blockers	May cause impaired emptying, urinary retention, and constipation that can contribute to UI. May cause dependent oedema which can contribute to nocturnal polyuria
Cholinesterase inhibitors	Increase bladder contractility and may precipitate urgency UI
Diuretics	Cause diuresis and precipitate UI
Lithium	Polyuria due to diabetes insipidus
Opioid analgesics	May cause urinary retention, constipation, confusion, and immobility, all of which can contribute to UI
Psychotropic drugs Sedatives Hypnotics Antipsychotics Histamine (H1) receptor antagonists	May cause confusion and impaired mobility and precipitate UI Anticholinergic effects Confusion
Selective serotonin re-uptake inhibitors	Increase cholinergic transmission and may lead to urinary UI
Sodium-glucose cotransporter 2 (SGLT2) inhibitor	Glycosuria and polyuria, increased propensity to urinary tract infection
Others Gabapentin Glitazones Non-steroidal anti-inflammatory agents	Can cause oedema, which can lead to nocturnal polyuria and cause nocturia and night-time UI

compared with being at normal weight. Incontinence remained a significant predictor of lower quality of life [203].

Frailty is associated with UI, and predicts incident UI and/or death, even up to 12 months following hospitalization. A prospective cohort study conducted in a large teaching hospital in Singapore to address whether ability of frailty could predict incident UI. Frailty predicted incident UI over time (at discharge, OR 2.98, P = 0.050; at 6 months, OR 2.86, P = 0.027; at 12 months, OR 2.67, P = 0.025), after adjusting for age, sex, and severity of illness. Greater emphasis should be given to identifying and managing UI during hospitalization and after discharge, especially among frail older adults [204-210].

Moreover, the prevalence of UI is increased in the presence of frailty. The older individuals are prone to frailty and commonly have co-morbid medical illnesses. In a large population-based observation study UI (defined as use of pads) was independently associated with one or more other geriatric conditions (cognitive impairment, injurious falls, dizziness, vision impairment, hearing impairment) in 60%, two or more conditions in 29% and three or more in 13% [211]. Older subjects with UI had a 2.9-fold greater chance of becoming more frail over a 12-month period than those without (p=0.007) [212]. In a cross-sectional survey conducted in Taiwan (n = 1,014), presence of UI was a predictor for frailty among older adults living in rural communities (OR 1.951, P = 0.037) [213].

In a sample of 572 older Latinos participating in a programme to increase walking, medical comorbidity was independently associated with higher rates of UI (OR, 1.66; 95% CI, 1.30-2.12). More physical activity was independently associated with lower UI (OR, 0.77; 95% CI, 0.60-0.98). Hypertension, congestive heart failure, arthritis, depression and anxiety were associated with a higher prevalence of UI. A linear correlation was found between prevalence of UI and the number of comorbid conditions (correlation coefficient = 0.81) [214]. In an observational study of 6,361 community dwelling women, aged 65 and older, participating in the study of Osteoporotic Fractures, after adjusting for confounders, women with recent physical function decline (a worsening of 1 standard deviation from baseline) were more likely to report weekly incontinence (OR, 1.31; 95% CI, 1.09-1.56) for decline in walking speed over 6 metres and (OR, 1.40; 1.19-1.64) for decline to stand from sitting [215]. The Nurses' Health Study found that moderate-intensity low impact physical activity, including walking, resulted in a 20-25% reduction in the risk of developing UI in older women particularly stress rather than urgency UI [216]. Factors associated with persistent UI were similar to those associated with increasing incidence including lower physical activity levels. The strongest factors for persistent UI were older age, white race and obesity [217]. Likewise, impaired cognition is associated with an increased likelihood of UI. For example in a UK cross-sectional survey of over 15,051 subjects, persons with cognitive impairment (Mini Mental State Exam score <= 23, prevalence 18%) were significantly more likely to have UI (adjusted OR 1.3), impaired hearing (OR 1.7), poor vision (OR 1.7) have had at least two falls in the previous six months (OR 1.4), and report poorer health (OR 1.9) [218].

The Jerusalem Cohort Longitudinal study assessed the same community dwelling subjects at age 70, 78 and age 85. UI increased from 14.1% to 31.3% and to 42.5% at age 85. This was associated with an increase in comorbidity and Charlson's comorbidity index of 7.3, 11.7 and 21.7 respectively and an increase in geriatric syndromes [219].

A study of 6903 participants (mean age 82.2) in Europe and Ontario receiving home care services identified an increase in Geriatric syndromes (GS) in the presence of associated diseases. Participants presented with an average of 2.6 diseases and 2 GS. UI was present in 47% [220]. A study of 270 subjects aged 65 to 89 reported 26.3% moderate or severe UI in the preceding 12 months in 3 groups: frailty (7.4%), pre-frail (45.9%) and non-frail (46.7%). In a second sample of 300 frail subjects aged 90 to 107, 37.4% reported moderate or severe incontinence. Incontinent subjects were 6.5 times more likely to be in the frail group and 2.3 times in the pre-frail with respect to continent subjects. The authors concluded that UI was a marker of frailty [221]. In a cross-sectional study of 521 community Brazilian adults > 60 years were assessed for the association between frailty and geriatric syndromes. Subjects were classified as frail (≥ 3 criteria), pre-frail (1 or 2 criteria) or robust elderly. Urinary/faecal incontinence occurred in 23.7%,12.8% and 9.2% respectively. The commonest Geriatric syndrome was cognitive impairment (54.7%). In this study, there was no association between incontinence and frailty (OR, 0.76; 95% CI, 0.16-3.57) [222]. A study of 447 community dwelling nursing home eligible elderly with diabetes found a prevalence of UI of 44%. Older age, dependence on others for ambulation or transferring and cognitive impairment were associated with UI [223].

Comorbid conditions can affect incontinence through multiple mechanisms e.g., diabetes mellitus, present in approximately 15-20% of older adults may cause UI by diabetes associated lower urinary tract dysfunction (DO, OAB, cystopathy and incomplete bladder emptying) or by poor diabetic control (hyperglycaemia causing osmotic diuresis and polyuria). The Nurses Health Studies, NHS and NHS II [224] showed an increase in weekly urgency incontinence (OR 1.4) in women with type 2 diabetes compared to those without. Findings from the NHANES 2001- 2002 Survey showed that prevalence of UI was significantly higher in women with impaired fasting glucose and diabetes mellitus compared to those with normal fasting glucose. Two microvascular complications caused by diabetes, peripheral neuropathic pain and macroalbuminuria were positively, but not statistically, significantly associated with weekly UI [225]. In diabetic women, peripheral neuropathy has been significantly associated with LUTS and metabolic syndrome has been associated with OAB [226]. In a younger population of mean age 59 years, the Diabetes and Ageing Study found the prevalence of occasional UI to be over 65%. HbA1c level was not associated with the presence or absence of UI. Women with HbA1c .≥9% had more limitations in daily activity due to incontinence, defined as self-reported "quite a bit" or "extremely" in the preceding 12 months compared to women with HbA1c <6% [227]. Higher glycated haemoglobin levels have been associated with increased symptoms of OAB [228]. From the findings of the SABE study (Health, Well-being, and Ageing) including the older people living in seven countries in Latin America and the Caribbean, the risk of UI was greater among the older women aged ≥60 years with past history of cancer (other than skin) (incidence relative risk, 2.66; 95% CI, 1.33-5.31; P = 0.006) and those with diabetes (incidence relative risk, 1.70; 95% CI, 1.03-2.80; P = 0.037) [229].

Incontinence impairs quality of life (QOL) in older adults [230]. In a cross-sectional study of 1,124 subjects over 70 (mean age 79.5 years), prevalence of UI was 18% and the severity of UI increased with age. UI was more common in women and was associated with worse self-reported health. Incontinent subjects were more likely to require assistance with ADLs, had more depressive symptoms and worse physical performance. Increasing severity of incontinence was negatively associated with QOL as measured by the Short Form-36 [231].

UI affects mortality, a population-based cohort study with 1,580 participants aged ≥65 years living in Fukushima, Japan, urgency UI was substantially associated with the occurrence of death (HR, 2.29; 95% CI, 1.22-4.31). The risk of death was further exacerbated in older adults with severe urgency UI (HR, 4.18; 95% CI, 1.78-9.79) [232]. A population-based cohort study with 2,282 community dwelling individuals aged ≥50 years in Canada, frailty individuals with UI were at higher risk for death (HR, 1.39; 95% CI, 1.13-1.72); however, after adjustments for the frailty index, the association between UI and mortality was no longer significant (HR, 1.10; 95% CI, 0.89-1.36) [233]. In a nursing home setting with 267 residents aged ≥65 years in Korea, a multivariate logistic regression analysis revealed that UI was associated with risk of death (OR, 2.04; 95% CI, 1.16-3.61) [234].

2.3. Neurological & psychiatric disorders

A more detailed summary of neurological disorders and their impact on UI is covered in the Chapter on Specific Neurological Diseases. Neurological and psychiatric disorders are highly prevalent in frail older people. Neurological conditions in the elderly commonly associated with UI include stroke, Alzheimer's dementia (AD), multi-infarct dementia or mixed AD and vascular dementia, Diffuse Lewy body (DLB) disease and Parkinson's disease. Less common conditions include normal pressure hydrocephalus (NPH), progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). Each of these conditions are associated with the development of brain lesions that can interfere with the micturition pathway and interfere with the normal ability to inhibit voiding as well as affecting cognition. These conditions are associated with impaired mobility and can interfere with the ability to toilet independently.

In Alzheimer's disease, UI is often associated with severe cognitive decline whereas in DLB it usually precedes severe cognitive impairment. Occurrence of UI was significantly earlier 3.2y in DLB compared with 5.9y in AD [235]. NPH should be a diagnostic consideration in any frail older patient who presents with new onset of UI in association with gait disturbance and cognitive impairment. A subset of these patients benefits from surgical implantation of a cerebrospinal fluid shunt [236, 237].

LUTS, UI and urodynamic DO are common in older adults with Parkinson's disease. A logistic regression analysis of 3,414 Parkinson's disease patients found a significant correlation of orthostatic hypotension and UI with age and duration of the disease. The presence of UI in persons with Parkinson's disease may in turn increase their risk for disability: in one series of patients with Parkinson's disease, UI increased the risk of falling by nearly six-fold. Urinary symptoms are often non-responsive to L-dopa therapy [238]. The efficacy of behavioural therapy, including pelvic floor muscle training, bladder training, fluid and constipation management was limited in improving OAB symptoms; however, it could significantly improve quality of life and ICIQ-OAB bother [239]. MSA presents with a combination of impaired autonomic function, parkinsonism (MSA-P) or cerebellar ataxia (MSA-C) or both [240]. It frequently begins with bladder dysfunction and erectile dysfunction in males and is associated with bladder symptoms of DO, often progressing to incomplete emptying and urinary retention [241]**.** High post-void residual (PVR) may help in pointing to a diagnosis of MSA-P rather than Parkinson's disease [242]. Recently, several studies revealed neuromodulation therapies including deep brain stimulation (DBS) and tibial nerve stimulation (TNS) were effective in improving of UI Witte *et al.* performed a *post-hoc* analysis of a randomized clinical trial with 128 advanced Parkinson's disease patients (NSTAPS study). UI and urinary frequency significantly improved after subthalamic nucleus DBS treatment in male and female patients. Nocturia and night-time incontinence due to parkinsonism did not improve after DBS, irrespective of sex [243]. Scelzo *et al.* reported the efficacy of DBS therapy for Parkinson's disease. Of note, the rates of mild cognitive impairment, UI, nocturia and falls were lower in the surgical cohort than the group of medically treated patients [244]. A prospective cohort study including 416 patients with Parkinson's disease, DBS surgery is effective in improving urinary function in patients, primarily reflected by the alleviation of urinary frequency, urgency, and incontinence. Female patients with Parkinson's disease displayed better urinary function outcomes from DBS treatment than did males [245]. A retrospective study with a cohort of 17 patients with Parkinson's disease who have used TNS, efficiency was seen in 10 patients (59%), on nocturia and/or UI for 9 patients. Three patients found TNS was not effective, and four patients did not use it long enough to evaluate [246].

With the introduction of magnetic resonance brain imaging into routine clinical practice, radiology reports in older patients have increasingly emphasised the presence of structural abnormalities involving the white matter [247]. Terminology has also undergone a great change, moving away from subcortical atherosclerotic encephalopathy (Binswanger's disease, a specific and relatively rare form of dementia), towards leukoaraiosis [248] and, most recently, to the concept of white matter signal abnormalities (WMSA) [247, 249]. Brain MRI identified subjects with leukoaraiosis as more likely to have urinary dysfunction which may precede cognitive impairment particularly in grade 1 disease [250]. White matter hyperintensities (WMH) have been linked to severity of incontinence rather than to its presence [251]. The disorder of bladder control resulting from white matter disease (WMD) has been termed vascular incontinence [252]. WMH load appears to progress in association with ageing and the amount of frontal WMH are predictive of UI in amnestic mild cognitive impairment and AD [253].

White matter lesions were found to be a more significant contributor to OAB and incontinence than AD in older adults [254].

2.4. Depression

As in younger persons, frail older adults with UI have a higher risk of depression, a finding that has been replicated across cultures. Depression in older persons with UI may be under-diagnosed and under treated: in one study of homebound adults with UI and severe depression, only 35% carried a previous diagnosis of depression and only 34% had been prescribed an antidepressant [255]. UI may add to the burden of depression by decreasing life satisfaction [256] and self-rated health, [257] and by its association in frail older adults with comorbidity [258].

Studies of the association of depression and UI in older adults are consistent across several depression measures. The validated Center for Epidemiologic Studies-Depression was used in two U.S. studies: a cross-sectional analysis of nearly 10,000 community-based persons found an adjusted risk ratio for depression with UI 1.39 [95% CI 1.24, 1.55]), [259]. A large community-based study of older Mexican Americans reported UI was predictive of high levels of depressive symptoms (adjusted OR for depression, 1.94; 95% CI, 1.46-2.59) [260]. The emotional disturbances and social isolation subscales of the Nottingham Health Profile Questionnaire was associated with urgency but not stress incontinence [261] and have included studies in Asia [262]. Although no association between UI and depression was found in a Korean study of 135 community living older adults greater than 85 years, it used a higher cut-off (>7) on the Geriatric Depression Scale and, unlike many other studies, found no association between UI and mobility [263]. Self-report of depression or sadness has [264] and has not been associated with

UI [265]. In another Korean study of 444 inpatients aged 65 and older, patients with depression were more likely to have poor UI-related QOL (OR, 8.54; 95% CI, 1.43–51.15) [0001]. In the Korean Study of Women's Health Related Issues with 3,000 female subjects between 65 and 75 years, the prevalence of stress UI, urgency UI, and mixed UI were 45.7%, 39.6%, and 33.1%, respectively. Depression and stress levels were significantly higher in women with UI than those without UI ($p<0.001$).

2.5. Psychological distress and quality of life

Psychological distress, assessed by the General Health Questionnaire, was associated with UI in African Americans (adjusted OR, 5.60;95% CI, 1.88–16.67), but not in whites, in a cross-sectional study of community based older persons with mean age 67y. However, a longitudinal analysis of the same population over 13 years found that persons with UI and psychological distress were more likely to report UI-specific functional impairment (e.g., avoidance of social activities, shopping, and physical activities) (adjusted OR, 6.55;95% CI, 1.94-22.12). Additionally, persons with UI and condition-specific functional loss were more likely to develop psychological distress (OR, 3.66;95% CI, 1.61–8.33) [266, 267].

The EpiLUTS study, a large cross-sectional internet study showed significant impairments in mental health and HRQOL when different urinary symptoms were combined [268, 269]. The US sample of the EpiLUTS study involving 2,485 men and 2,877 women aged 65 and older found OAB was associated with significant impairment in HRQOL. Rates of Anxiety of ≥8 on the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) were 16.4% for men and 23.6% for women with OAB compared to 3.3% and 8.6% with minimal or no symptoms. Similarly rates for depression on the HADS-Depression (HADS-D) were 17.3% and 15.7% for OAB compared to 4% and 6.4% in those with no or minimal symptoms. A case-controlled study of 100 older men attending a Urology outpatients matched with 100 age matched controls from the community and Geriatric outpatient clinics found those with moderate to severe LUTS had worse HRQOL. This was evident in a number of symptoms including depression, decline in feelings of general well-being, decreased sexual performance, decreased muscle strength [270].

The direction of the causal relationship between UI and depression in frail older adults is unclear, as nearly all studies were cross-sectional. The results of the one longitudinal study suggested that it is not UI itself but UI-specific functional loss (e.g., avoidance of social activities, attending church, etc.) that is most closely associated with psychological distress, even after controlling for important covariates [255].

2.6. Falls

Urinary urgency and UI, urinary frequency, and nocturia have been identified repeatedly as risk factors for falls among community-dwelling older adults [271-277]. Mixed incontinence (a combination of urgency and stress incontinence) has also been associated with falls risk in women 70 years and older [278]. Brown and colleagues [277] performed a secondary analysis of data from an osteoporosis cohort study, examining a group of 6049 community-dwelling older women using regular self-completed questionnaires sent to all participants every four months. In this cohort, followed for an average of three years, those with at least one weekly UUI episode were more likely to fall (OR 1.26, 95%CI 1.14-1.40) than those without. Weekly UUI was also associated with higher odds of sustaining a non-spinal fracture (hazard ratio 1.34 95%CI 1.06-1.69). In this study, stress incontinence was not associated with higher odds of falling (adjusted OR, 1.06; 95% CI, 0.95-1.19) or sustaining a fracture (relative hazard, 0.98; 95% CI, 0.75-1.28). In a national population study conducted in New Zealand involving 57,781 females and 35,681 males aged 65 and older, high falls risk was common, found among 8.8% of women and 12.4% of men; and 43.7% of women and 33.7% of men reported some incontinence. For women, the adjusted odds ratio of increasing falls risk was 1.24 (95% CI, 1.18-1.30) for those with occasional UI, 1.36 (95% CI, 1.29-1.43) for those with frequent UI, and 1.19 (95% CI, 1.13-1.26) for those with any FI compared with their continent counterparts. Among men, the adjusted odds were 1.49 (95% CI, 1.41-1.58) for any UI and 1.18 (95% CI, 1.10-1.27) for any FI.

Analysis of the Concord Health and Ageing in Men Project, a longitudinal study of community-dwelling men in Australia followed 1090 men over a period of 2 years. Here, the presence of urgency incontinence, defined as weekly episodes of UUI, was associated with a higher incidence of falls (OR 2.57 95%CI 1.51 – 4.3) and men with a higher International Prostate Symptom Score storage sub-score, defined as a score of 19 and above, had a higher incident rate of falls (incident rate ratio 1.72 (95%CI 1.24-2.38) [279]. A Japanese study of patients with Parkinson's disease found that increased micturition frequency either by day or night was not associated with falls, but that the presence of urinary urgency was strongly associated with a large increase in the odds of falling (OR 5.14 95%CI 1.51-17.48). Only 14% of the falls reported in this study occurred on the way to or from the toilet [280].

A systematic review of the association between falls and LUTS in community-dwelling men aged 60 years and over identified six cross-sectional studies and three prospective cohort studies. The identified data were only suitable for qualitative synthesis, but UI and storage LUTS were consistently shown to have a weak to moderate association with an increased likelihood of falls. None of the identified studies examined potential causes for these associations; the categorisation of continence or not and degree of accounting for confounding variables was inconsistent across the included studies [281]. A small cross-sectional analysis of community dwelling women aged 65 and over in the US examined the association between nocturia, nocturnal enuresis and falls. Neither severity of UI nor severity of nocturia was associated with an increased risk of falls, but there was a statistically significant association between nocturnal enuresis, impairment of physical function and the presence of frailty. However, in the multivariable regression model, which included age, physical function, and the frequency of nocturnal enuresis episodes, only physical function remained as significant risk factor for falls [282]. One study, a prospective cohort study of older men in the USA, identified a statistically significant association between straining to void and falls, with a 60% increase in falls risk for those reporting the need to push or strain to initiate urination at least half the time [283]. In hospital, UI is associated with an increased propensity to fall in older inpatients [284, 285]. UI is also associated with falls in institutionalised older adults [286, 287]. The underlying reason for the association is not yet clear, although several and multiple mechanisms are most likely. A UK case control study in older community dwelling women presenting to an urban Emergency Department found that only 6% of those with a fall attributed this to their LUTS [288].

2.7. Stroke

Conservative interventions (e.g., bladder training, pelvic floor muscle training and prompted voiding) have been shown to have some effect in Cochrane systematic reviews but have not had their effectiveness demonstrated with stroke patients. UI may have worse prognostic implications after stroke, being associated with greater mortality, a poorer functional recovery and an increased likelihood of institutionalisation than those following strokes who regain continence [289]. Of 1,187 patients aged 60–96 with stroke, those with

low bladder maintenance scores (more dysfunction) fared worse with rehabilitation than those with higher scores [290]. There has been little advance in care since the 6th International Consultation. A survey of stroke unit practice in Australia showed that less than half had a formal plan for continence care and in the UK, as part of the national sentinel audits of stroke, there was little advance in continence care [291, 292]. A comparative study of stroke nursing found a dearth of evidence and treatment focused on containment and social continence, highlighting the need for systematic assessment and management [293]. The burden on caregivers of those with incontinence following stroke has been acknowledged [294]. Thomas *et al.* reviewed randomised or quasi-randomised controlled 20 trials with 1,338 participants after stroke. Five trials assessed complementary therapy using traditional acupuncture, electroacupuncture and ginger-salt-partitioned moxibustion plus routine acupuncture. Low-quality evidence from these trials suggested that complementary therapy may increase the number of participants continent after treatment; participants in the treatment group were approximately three times more likely to be continent (RR, 2.82; 95% CI, 1.57-5.07). Adverse events were reported narratively in one study of electroacupuncture, reporting on bruising and post-acupuncture abdominal pain in the interventional group. The authors concluded that there was insufficient evidence to guide continence care of adults in the rehabilitative phase after stroke. As few trials tested the same intervention, conclusions are drawn from few, usually small, trials. Confidential intervals were wide, making it difficult to ascertain if there were clinically important differences. Only four trials had adequate allocation concealment, and many were limited by poor reporting, making it impossible to judge the extent to which they were prone to bias. More appropriately powered, multicentre trials of interventions are required to provide robust evidence for interventions to improve UI after stroke [295].

Recommendations for research

Further research is required to:

- Examine the effect of treatment for UI in older adults with Parkinson's disease
- Examine the temporal association and mechanism underlying falls and LUTS/UI in frail older adults
- Determine the effect of structured treatment for UI in older adults following stroke.
- Examine the impact of interventions comorbid disease on the experience and outcomes of UI in frail older adults

Recommendations for practice

Clinicians need to assess and manage coexisting comorbid conditions which are known to have an impact on continence status or the ability to successfully toilet.

1. ENVIRONMENTAL FACTORS

This section addresses factors unrelated to underlying pathophysiology that can affect the UI status of frail older adults in organisational settings such as nursing homes and hospitals. These key factors are conceptualised here as either related to: (i) the physical environment or (ii) organisational processes of care. We define organisational processes of care as organisational practices and procedures that can increase a frail older adult's risk of UI. They include:

- A lack of assessment
- A lack of knowledge about UI among healthcare practitioners and/or formal caregivers
- Practices that reduce/restrict the frail older adult's mobility and functional abilities
- Limited or inconsistent access to toileting assistance
- A lack of privacy and attention to the frail older person's dignity
- Reduced staffing
- The overuse and misuse of continence products

The following information describes the potential influence of the physical environment on frail older adults' UI status, followed by organisational processes of care.

In this section, we define processes of care as the instrumental procedures involved in the assessment and management of incontinence relating to frail older persons.

Although the physical environment is considered a risk factor for incontinence in frail older adults, there continues to be limited research on this topic.

1.1. The nursing home physical environment

Previously described research about the potential influence of the nursing home physical environment on residents' risk of developing UI was conducted over 40 years ago [277, 278] prior to the establishment of internationally agreed standards for reporting trial data. Three were published from a series of projects conducted in the USA to examine the impact of the physical environment on specific problems of people with Alzheimer's disease and related disorders [279-281]. One qualitative study was identified that employed an ethnographic design [282].

Attempts to evaluate the effects of enhancing the physical environment on rates of incontinence in nursing homes were reported by Chanfreau-Rona [296, 297]. In both studies, the intervention involved enhancing visual access to the toilet by painting toilet doors in bright colours and strategically locating pictorial signs and other visual cues. In addition, staff were asked to accompany residents to the toilet at predetermined 'peak times' and to employ operant conditioning techniques to reinforce residents' appropriate toileting behaviour. In the first of these trials, 24 older female residents, most of whom had cognitive impairment, were purposively assigned to either the intervention, or to usual care for seven weeks [297]. The same procedures were repeated in a subsequent trial [296]. Although reductions in incontinence were noted for residents in the experimental groups compared to the control groups, the extent to which these reductions were related to the intervention is difficult to determine as both studies lacked power and did not control for confounding factors. Nonetheless, these studies represent an early, multifaceted intervention that involved evaluating the effect of changes to the physical environment to reduce incontinence among frail older adults in long-term care.

According to the first of a series of projects conducted by Namazi and colleagues, the overall physical environment has a considerable impact on the well-being and quality of life of individuals with Alzheimer's' Disease (AD), affecting their ability to function in the face of incontinence, distraction and disorientation [298]. One of the projects focused on the clinical utility of using environmental cues (i.e. signage, colour differentiation and images) in a dementia-specific unit to assist compensate for resident' visuo-perceptual deficits

[299]. The most effective environmental cue in terms of orienting individuals with AD to the toilet was a combination of using a sign with the word “toilet”, together with “wayfinding” arrows on the floor. No single strategy was suitable for all individuals with AD due to the variability in the ability of individuals with AD to perform all of the tasks associated with successful toileting. The researchers therefore recommended “to maximize the remaining strengths of those who are afflicted with AD, each component of the morphology which creates difficulties for AD patients must be identified and treated individually”. In essence, individuals with AD may need individually targeted cues that address identified specific deficits.

In a second project, Namazi and colleagues [300] systematically examined toilet use in a dementia- specific unit under two conditions: with the toilet highly visible to residents, and with the toilet concealed. The frequency of toilet use increased when toilets were visually accessible during the 45 hours of observation. Visibility and accessibility of toilets may be an important factor in supporting frail older adults to maintain continence.

Toilet accessibility also featured highly in a qualitative study conducted by Sacco-Peterson and Borell [301]. Using ethnographic methods, the researchers collected over 200 hours of field observational data and conducted in-depth interviews with nine nursing home residents. They reported that different aspects of the physical and socio-cultural environment of the home influenced residents’ abilities to maintain autonomy in self-care. For example, there was an inadequate number of toilets, inadequate privacy for toileting, inappropriate toilet heights, excessive distances to the toilet, and a lack of call light, toilet paper, soap, paper towels, lighting and commodes. Despite the challenges of negotiating this ‘defeating ward geography’, many residents attempted to participate autonomously in toileting, whilst others were deterred because of a fear of falling.

1.2. The hospital physical environment

A recent study addressed the physical environment of hospitals to ensure they are elder friendly. Aranda *et al.*, (2019) and Arenas *et al.*, (2019) described a cross-sectional observational study that focused on changes to the physical environment of a hospital to better meet the needs of hospitalised older adults with dementia. The implemented measures were: (1) Informative Posters for delirium prevention and stimulation of early mobilisation. (2) Triptychs with information for families: dementia and terminally ill patient. (3) Bedside magnetic codes for: Mobility, Risk of delirium, Dysphagia, Continence and Sensory Deprivation. (4) Door signs for private interviews and terminally ill patients. At 3 months, compliance with the use of bedside codes up to 90% of patients, with an average use of >60% [302].

2. ORGANISATIONAL PROCESSES OF CARE IN THE NURSING HOME

2.1. Introduction

Continence in nursing home residents declines over time [303] and those with a diagnosis of dementia lose continence at a more rapid rate than those without dementia [304]. Incontinence in this setting is likely to be multifactorial in aetiology. For example, in a systematic review of the prevalence and risk factors for urinary incontinence in long-term aged care homes, Offerman and colleagues [305] identified 46 risk factors for urinary incontinence. The researchers grouped these factors into 1) locomotion, 2) cognitive function and 3) drugs. However, in addition to these risk factors, the reviewers stated, “differences in the care process and quality of care can also influence urinary incontinence prevalence; reasons for a less-than-optimal approach in long-term care homes may include, for example, inadequate knowledge of and skills for urinary incontinence in general, inability to use guidelines for urinary incontinence care, insufficient staff and poor communication among healthcare professionals” (p.291). They recommended that risk factors related to care processes be further investigated. Two studies offer qualitative data on how processes of care in nursing homes may represent a risk factor for incontinence. For example, descriptive information derived from semi-structured interviews with six elderly women from two nursing homes in Canada, suggests that some residents experience an environment characterised by rituals and routines, limited assistance with pad changing, restrictions on the number and type of continence products available, set times for toileting and pad changes, ageism, and a lack of recognition of residents’ attempts to maintain continence [306]. Sacco-Peterson and Borell [301] also found that ‘toileting assistance was provided at set times, and ‘if residents required more assistance other than at set times, pads were used‘. Pad use also correlated with residents’ mobility level, rather than their cognitive or continence status. Additionally, night-time use of pads often started following a fall at night. Residents did not divulge their difficulties to staff and were reluctant to ask for help and thus staff members were unaware of residents ‘difficulties and efforts. Residents valued the capacity to exercise some power and autonomy with regard to self-care, and didn’t want to be ‘a bother to the nurse ‘. Thus, their attempts to maintain continence may be undermined by care processes that unintentionally diminish an individual’s independent toileting [301].

Ostaszkiewicz [307-309], conducted a grounded theory study to describe and explain the context that affects continence care in nursing homes. The findings suggest a basic social problem that is characterised by multiple constraints to residents’ overall care. Factors that contribute to this problem include: (i) a highly regulated work environment; (ii) ethically challenging care; (iii) highly dependent residents; and (iv) a devalued role. Staff responses to this problem include accommodating strategies such as acquiescing, concealing, protecting, adapting, prioritising, normalising, compromising, and ritualising, as well as self-protective distancing strategies such as blanking out, using distancing language, and reframing care. The researcher called for a comprehensive multifaceted research-based strategy that addresses the social, regulatory, organisational, and personal constraints to evidence-based, ethical, resident-centred care, including continence care. There is a need to counter the pervasive belief that quality continence care for frail older adults is a function of cleaning and containing incontinence. In countries that rely on education about incontinence from the continence product manufacturing industry, the strategy should also counter the dominance of industry-based education. Although independent quality performance standards have been developed for disposable absorbent products there is an absence of standards to promote ethical relationships between healthcare consumers and the continence product manufacturing industry [310].

2.2. A lack of assessment in nursing homes

A comprehensive assessment to determine type and causes of UI is an essential precursor to appropriate management. However, evidence suggests many frail older people with UI in nursing homes do not have access to this assessment and are therefore at risk of remaining incontinent (Table 4).

Since the last Consultation, two further studies were identified that support previous research indicating a lack of assessment of UI in nursing homes. They include a descriptive, correlational study using primary data from 1,560 randomly selected residents from

815 different nursing homes in the USA and a large observational cross-sectional study of 42,693 older adults in the USA who were continent on admission to a nursing home [311, 312]. Harrison *et al.*, (2019) investigated care and staff skill factors that predicted quality continence care. They found an overall UI rate of 48.4% (n = 755) and the risk of developing UI over a ten-year-period in a nursing home was 6%. Forty-six percent of residents with UI had no care plan for their incontinence. Moreover, the majority of UI care plans (65%) were not based on that resident's voiding pattern and needs. Bliss *et al.,* (2017) conducted a large observational cross-sectional study of 42,693 older adults in the USA who were continent on admission to a nursing home to determine the prevalence of older continent adults who received primary prevention of incontinence at admission, assess whether there were racial or ethnic disparities in incontinence prevention, and describe factors associated with any disparities. Only 12% resident admissions received incontinence prevention and there was a significant disparity (2%) in incontinence prevention for Blacks (P < 0.05) compared to Whites (10.6%).

2.3. A lack of knowledge about UI among healthcare practitioners and/or formal caregivers in nursing homes

A number of studies reveal gaps in nurses' and nursing aides' knowledge about, and attitudes toward older people with incontinence in nursing homes [313-332]. This lack of knowledge about UI and its management could operate as an antecedent to care processes that inadvertently promote incontinence. Specifically, a lack of knowledge that incontinence is a symptom of a potentially treatable condition, may have the unintended effect of hindering access to diagnosis and treatment.

2.4. Practices that reduce/restrict the frail older adult's mobility and functional abilities in nursing homes

The role that mobility and functional status play in a frail older adult's ability to maintain continence cannot be underestimated. Impaired mobility and ability to perform activities of daily living (ADLs), such a toileting ability, can cause or contribute to UI in frail older adults in any setting.

UI is associated with severe impairment in ADLs in nursing homes, [333,334,335] and subsequent research confirms this association [336,337,338]. A structural equation modelling examined the relationships between UI in institutional older adults with dementia and a range of factors, including agitated behaviours, depression, cognitive function and activities of daily living. Li *et al.* (2019) recruited 226 older adults with dementia from 15 long-term care facilities in southern Taiwan. Activities of daily living performance was found to be significantly associated with UI; however, age, cognitive function, depression and agitated behaviours were not significantly related. Age did not have effects on any of the variables tested in this model. However, activities of daily living performance was significantly associated with cognitive function and depression. Results further showed that cognitive function and depression were mediators between activities of daily living and agitated behaviours. In nursing home settings, a decline in functional status is correlated with a decline in continence status. According to an a analysis of longitudinal data conducted with 196 older adults from one of 10 nursing homes in the city of Natal-RN (Brazil), the cumulative probability of maintaining continence is 82.6% at six months (confidence interval [CI], 95%: 76.5%-87.3%); 74.7% at 12 months (CI, 95%: 67.8%-80.4%); 66.9% at 18 months (CI, 95%: 59.4%-73.2%); and 49.3% at 24 months (CI, 95%: 40.1%-57.9%). Among the cohort, 105 (53%) older people maintained their continence status during the period, 21 (10.7% improved at one or more assessment and 76 (38.8%) declined. Factors that predicted a decline in continence status were disability (hazard ration [HR] = 4.03;P<0.001), functional decline (HR=3.02; P=0.001), and potentially inappropriate medication (HR-1.84; P=0.008). In the same cohort, the cumulative probability of maintaining functional capacity was 78.2% (CI 95%: 72.8±82.7%), 65.1% (CI 95%: 58.9±70.5%), 53.5% (CI 95%: 47.2±59.5%) and 44.0% (CI 95%: 37.7± 50.2%) at 6, 12, 18 and 24 months, respectively [339]. Continence decline was one of sev-

Table 4. Evaluative studies on assessment of UI in frail older adults in nursing homes

Study	Objective	Sample	Method	Findings
Bliss *et al.*, 2017	To determine the prevalence of older continent adults who received primary prevention of incontinence at NH admission, assess whether there were racial or ethnic disparities in incontinence prevention, and describe factors associated with any disparities.	42,693 older adults free of incontinence at NH admission	An observational cross-sectional study of a nation-wide cohort	There was a significant disparity (2%) in incontinence prevention for Blacks (P < 0.05): Fewer Black admissions (8.6%) were observed to receive incontinence prevention than was expected had they been part of the White group (10.6%). The percentage of White admissions receiving incontinence prevention was 10.6%.
Harrison *et al.*, 2019	To explore the associations between interpersonal and skill measures that may predict quality measures in nursing facilities.	1,560 residents from 815 nursing facilities in the USA	A descriptive correlational study using primary data	Overall, of the 1,560 residents, 48.4% (n = 755) experienced UI. The risk of developing UI over a ten-year-period in a nursing facility was 6%. Only 54% of residents with UI had a care plan for their incontinence. For those with a UI plan in their chart, 143 (35%) had a person entered UI plan developed based on that resident's voiding pattern and needs. The more satisfied the resident was with the response to their calls for help with voiding the more satisfied with the nursing facility

Study	Objective	Sample	Method	Findings
Georgiou *et al.*, 2001	To evaluate the recommended outcome measures in clinical practice	1125 residents in 17 residential homes, 14 nursing homes and 5 long-stay wards in UK.	Analysis of data on the UI section of the Royal College of Physicians Continuous Assessment Review and Evaluation Scheme audit tool	Rates of full clinical assessment were 48% for people in residential homes 24% for people in nursing homes 36% for people in long- stay wards
Rodriguez *et al.*, 2007	To explore continence prevalence, knowledge and care	66 care homes in Birmingham, UK	Survey completed by managers or other senior staff	Only two respondents gave information indicative of a full assessment. Most respondents had difficulty identifying the process of assessment.
Pringle-Specht *et al.*, 2002	To determine patterns and treatment of urinary incontinence	145 residents with dementia (mean age 83.3yrs) from 13 special care units in long-term care facilities in USA	Retrospective audit of residents' medical histories using 'Incontinence Patterns Tool' (IPT)	55% of residents with UI and dementia had a documented care plan for treatment of UI 2.1% (n=3) had a current medical diagnosis of bladder incontinence
Wagg *et al.*, 2008	To assess the quality of continence care for older people	Patients from 138 primary care trusts, 195 secondary care trusts, and 27 care homes in UK	Audit of patients' clinical records	Poorly documented aspects of a clinical assessment across all settings: rectal examinations and post-void residual urine volumes. In secondary care trusts, 919/3509 (25%) of histories had documentation of an assessment to determine UI type or cause
Watson *et al.*, 2003	To assess the use of the Agency for Healthcare Policy and Research Guideline for managing UI in nursing homes	200 residents with new UI or newly admitted with UI from 52 nursing homes in upstate New York, USA	Retrospective chart review and Nursing Assistants screening interviews	4 new cases of UI per 100 beds over 12 weeks UI Guideline standards met 20% of cases (0-45%). Aspects of assessment rarely performed rectal examination (15%) digital examination of prostate (15%) pelvic examination (2%)

eral predictors of functional decline in this setting (HR = 1.85; p = 0.002). The others being severe cognitive impairment (HR = 1.96; p = 0.001) and incidence of hospitalizations (HR = 1.62; p = 0.020), adjusted by the incidence of depression, age, education level, presence of chronic diseases and low weight.

According to the findings of a multicentre descriptive cross-sectional prevalence study of 2,044 people from 30 nursing homes throughout Germany, UI is not only strongly associated with impaired mobility, but can also negatively affect residents' health-related quality of life. Using the International Consultation of Incontinence Questionnaire Short Form (ICIQ-SF), the researchers found chronic, severe UI exerted the greatest impact on health-related quality of life [340]. Given these findings, greater emphasis should be given to interventions that reduce the risk of functional decline that may subsequently prevent or delay the onset of incontinence and, thus, increase their health-related quality of life.

Moreover, practices that restrict or minimise a person's mobility and ability to function hinder their ability to reach and use the toilet autonomously are likely to cause disability incontinence. The use of physical restraints is one such practice. Although restraint-free care has been recommended as standard, restraints remain widely used in long-term aged care homes, ranging from 12-47% internationally [341]. In a multivariate analysis of data from 2,014 residents from 270 USA Medicaid-certified nursing homes, Brandeis and colleagues [334] identified that UI was independently associated with a number of factors, including the use of restraints of the trunk (OR = 1.7; CI = 1.5,2.0), restrained to a chair (OR = 1.4; CI = 1.2,1.6), and bedrails (OR = 1.3; CI = 1.1,1.5).

Another important consideration is the potential unintended negative effects of interventions designed to reduce the risk of falls in frail older people. Several studies identify UI as a risk factor for falls among older adults [342].[343] [281] [344]. Schluter reported 'older people with urinary urgency or UUI are significantly more likely to fall and sustain injury compared to age-matched controls, with estimates of the odds ratio for falls ranging from 1.5 to 2.3. A Cochrane review of interventions for preventing falls in older people in care facilities and hospitals [286] categorised interventions as: exercise, medication (drug target) interventions which include interventions targeting vitamin D and medication reviews, environment or assistive technologies including bed/chair alarms or the use of low/low beds, social environment interventions which target staff members and changes in the organisational system, knowledge interventions and multifactorial interventions. Although UI was not identified as an adverse event, it is likely that interventions such as low/low beds that restrict a person's movement or hip protectors that are difficult to remove, could cause disability associated incontinence. Further research on strategies to promote continence among frail older adults who are at risk of falling are required.

2.5. Limited or inconsistent access to toileting assistance in nursing homes

Interview data with family members of nursing home residents suggests timely assistance to use the toilet is an important indicator of the quality of care. Ostaszkiewicz and colleagues (2016) conducted qualitative interviews with relatives of five residents in Australian residential aged care homes in order to explore their understandings and expectations about the concept of 'quality continence care'. The family members placed a high value on staff being able

to interpret the behaviours of cognitively impaired residents regarding their need for help to use the toilet and provide them with timely assistance to use the toilet and equated this practice with protecting a resident's autonomy and dignity [345]. A more recent quantitative study reinforces the importance of timely assistance to use the toilet. In their investigation of factors that predicted quality continence care, Harrison *et al.*, (2019) found residents' satisfaction with the nursing home correlated with their satisfaction with staff response to their calls for help with voiding [311]. This is an important finding that should inform efforts to improve the quality of continence care in nursing homes.

Despite the importance resident and family members' place on being access to access timely toileting assistance little is known about the actual care needs of nursing home residents who require assistance to use the toilet; a condition hereafter referred to as 'toileting disability'. Consistent with the disablement process model (WHO 2001), and as proposed by Yeung *et al.*, (2019), we define 'toileting disability' as practices, procedures, or disease conditions that result in an individual requiring physical assistance using the washroom [toilet] to urinate and/or defaecate in a timely manner. According to the findings of a scoping review led by Yeung *et al.*, (2019) about toileting disability in older people residing in long-term care or assisted living facilities, 15% of older adults without dementia living in this setting (a subgroup that comprised 34% of all residents), have a toileting disability [346]. This finding was based on a cross-sectional analysis data from 2,395 adults aged 65 years or older, without dementia and residing in a residential aged care facility [333]. In addition to identifying toileting disability rates, a logistic regression model identified an association with fair or poor health, living in a facility with four or less residents, living in a for-profit facility; having bowel incontinence, UI, an increased number of physical impairments, visual and hearing impairments; and needing assistance with bathing, dressing, and transferring.

Based on a cross-sectional nationwide point prevalence study nursing home residents from 969 (41.4%) facilities in Japan, 44.2% (2,144) of residents were offered toileting assistance – most commonly, timed voiding (59.3%) followed by prompted voiding (26.6%) [202]. Reasons for not providing toileting assistance to the 2,707 (55.8%) residents were:

- (24.4%) were able to ambulate to the toilet independently,
- (45.1%) usually voided in diapers or pads,
- (2.2%) refused toileting assistance
- (28.3%) unknown.

The 41.4% of residents offered toileting assistance in Japan compares with 8% reported by Jerez-Roig *et al.*, (2016) who conducted a cross sectional study of 321 elderly, mostly female aged care residents from 10 nursing homes in Brazil. The prevalence of UI was 58.88% (CI 95%: 53.42–64.13) and the final model revealed a statistically significant association between UI and white race, physical inactivity, stroke, mobility impairment, and cognitive decline. The most frequent UI type was functional UI [347].

Several trials describe an intervention designed to improve rates of toileting assistance in nursing homes. Most are now over 20 years old. However, one recent trial reported improvements in rates of UI following a toileting assistance programme [202] and the other reported increases in the number of UI assessments conducted, increased toileting assistance rates and improvements in residents' quality of life [348] (see section on interventions).

In an effort to support staff to make informed decisions about toileting assistance programmes *vis-à-vis* a containment programme at an individual level, van Houten *et al.*, (2020) designed a Toileting and Containment Decision Support Tool. The tool was developed by a multidisciplinary group of experts following a review of literature and was validated by continence specialists in 8 countries. The tool is designed to guide the non-specialist health care professional in carrying out a rapid and focused incontinence assessment resulting in a person-centred management strategy tailored to individual characteristics and circumstances [349]. Further validation of the tool is required to determine its effects on practice and patient outcomes.

2.6. A lack of privacy and attention to the dignity of frail older adults in nursing homes

Privacy to void or defaecate are important social factors unrelated to underlying pathophysiology which may affect the continence status of frail older adults. It is possible a lack of toileting privacy may cause a person to defer or ignore the urge to void or defaecate. According to the findings of a cross sectional survey of 120 adults with faecal incontinence aged 65 and over and living in either their own homes, a nursing home, or an acute or rehabilitation, privacy to defaecate is usually attainable in one's home, but not in a nursing home. Privacy to defaecate was reported by 23% of respondents in a nursing home, 53% of those in rehabilitation wards, and 50% of those in acute wards [350]. Further research is required to explore the relationship between a lack of toileting privacy and incontinence in frail older adults.

Since the last ICI, there has been an increased interest in the privacy and dignity of individuals with continence care needs, part due to widespread concerns about a lack of attention to the dignity of older people who need assistance with toileting, incontinence or bladder or bowel care in health or social care settings that provide long-term care. A lack of dignity in the personal care needs of care dependent older people is a recurrent theme within a number of reviews and enquiries, including The Francis Report of the mid- Staffordshire NHS Foundation in the UK and the Royal Commission into Aged Care Quality and Safety in Australia (2021) [351] [352].

In 2009, Billings *et al.*, undertook a mixed methods study involving non-participant observations and interviews to: (i) identify and validate person-centred attributes of dignity in relation to continence; (ii) develop reflective guidelines for dignified care; and (iii) produce recommendations for best practice. The researchers concluded that the definition of dignity was a complex, shifting concept, dependent upon individual context and interpretation and whilst aspects of dignity were directly related to continence, such as privacy and hygiene, in general it interrelates to all aspects of care and cannot be separated, and thus, was not measurable [353].

In 2020, Ostaszkiewicz *et al.,* conducted a concept analysis of dignity-protective continence care for this population group. The researchers identified 50 individual attributes which were categorised in 6 domains (respect, empathy, trust, privacy, autonomy and communication). A further 15 attributes were identified that related to the environment (6 physical and 9 social). Key consequences of undignified continence care were also identified and categorised into 3 levels of impact (resident/family member, staff or organisation). This conceptual understanding of dignity protective continence care can be used as a value or guiding principle in an ethic of care for older people who require continence care. It could also inform the development of education programmes for nursing home staff, and methods to evaluate whether continence care is delivered in a way that protects a person's dignity [354].

2.7. Reduced staffing levels in long term care

Estimating and achieving the optimal level and skill mix of any workforce is a challenge. In long-term aged care homes where residents' have chronic health problems and complex health needs, maintaining sufficient staffing levels is exacerbated by a high staff turnover. Nurses consistently cite inadequate staffing levels as a major barrier to providing optimal continence care [355-359]. The extent to which patients and residents' continence care needs are considered in formulae designed to establish the right staffing level and skill mix is unclear. The time, resources, knowledge and skill required to conduct an assessment, and offer active, effective management to prevent and/or manage incontinent episodes require consideration in service planning.

Over 150 studies have been documented that confirm a 'strong positive impact of nurse staffing on both care process and outcome measures' [360]. These studies have mainly been conducted in the U.S, Canada, United Kingdom, Germany, Norway, and Sweden. They highlight the contribution of organisational factors to care quality, such as having a high professional staff mix (ratios of RN to total staffing levels), low staff turnover rates and use of agency staff, and consistency in staffing. The strongest positive relationships are found between RNs (with two to four years of training) and quality, which is stronger than the relationship between licensed vocational/practical nurses (LVNs/LPNs; who have less training than RNs) and quality. Total nurse staffing levels (which includes RNs, LVNs/LPNs, and certified nursing assistants [CNAs; with about two weeks of training]) are also related to quality.

Evidence presented in the last ICI highlighted the importance of considering the number of staff, their skill mix and how they work and the association with the quality of UI care in nursing homes. Temkin-Greener *et al.*, [361] analysed data from 46,044 residents in 162 nursing homes in New York State, for June 2006–July 2007, and survey responses from 7,418 workers in the same homes. They reported an association between incontinence and nursing home work environment attributes such as teams, consistent assignment and staff cohesion. After adjusting for other factors, they found residents in homes with stronger staff cohesion had a significantly lower odds of incontinence (OR = 0.924; p < .001). A one standard deviation (0.23) increases in the staff cohesion score resulted in 7.6 percent lower odds of incontinence. Likewise, in a longitudinal correlational study, Yoon *et al.* [362] examined the impact of organizational factors on the quality of UI care (i.e. defined as improvement in UI status or maintenance of continence) post admission to Korean long-term care hospitals. After controlling for other factors, they found higher Registered Nurse to patient ratios was significantly associated with better resident UI outcomes.

Two further studies further reinforce the need to consider the influence of staffing on the quality of continence care in nursing homes. Harrison *et al.*, (2019) investigated care and staff skill factors that predicted quality continence care. After controlling for gender, and age, there was an association between the creation of a UI plan of care by a Registered Nurse for a resident with UI and the resident's self-rated health [311.] Boscart *et al.*, (2018) explored the relationship between staffing characteristics and residents' quality of care indicators. Staff and resident characteristics were examined and data on 13 practice sensitive RAI-MDS 2.0 quality indicators, including indwelling catheter use and urinary tract infections were collected. Most direct care (76%) was provided by the NAs. The number of hours of care a resident receives from Nursing Assistants (NAs) is significantly associated with higher quality of resident care (p = < 0.01).

2.8. The overuse and misuse of continence products in nursing homes

For many people, continence products represent a means by which they can achieve effective and discrete containment of incontinence, minimise physical discomfort and optimise psychological and social function [363]. At the same time, their overuse and misuse may represent a risk factor for incontinence and, for pads, urinary tract infection. Although continence products have an important place in the containment of incontinence, their use in the general community, in hospital settings, and in nursing homes is widespread (see Table 5). For example, in the largest and widest audit of continence care conducted in the UK and involving over 6,000 patients across primary and secondary care trusts, and care homes, containment strategies (i.e., the use of continence products) far exceeded all other forms of documented continence management [364].

We located eight studies that provide data about the use of continence products in nursing homes. These were conducted in the UK [365, 366], the USA [334, 367], and in Norway [368]. Wagg and colleagues reported that of 488 residents from 27 care homes included in the national audit of continence care in the UK, 307 (63%) used a containment strategy to manage their incontinence [364]. Rodriguez and colleagues reported similar rates based on interview data from managers of 66 care homes in Birmingham [366]. An international comparison of the dependence levels of 90,000 nursing home residents from four countries (including UK, Spain, New Zealand and Australia) reported 87-94% of residents used incontinence pads (1998-2009) [369]. A cross-sectional survey of 810 older people in long-term care facilities in Taiwan reported 639 (78.9%) of the total residents wore diapers, and of these, the most common form of diaper was an adhesive-tape diaper (74.3%). Of those residents using diapers, 99 (12.2%) were able to ambulate independently and 247(51.5%) were able to stand for 30 seconds [370].

In the USA, Brandeis and colleagues reported a high rate of pad use (84%) in their sample of 2,014 residents from 270 Medicaid-certified nursing homes [334]. Eighty-four percent were managed with pads/briefs, and more than one third of incontinent patients were managed with two modalities. An evaluation of the use of urinary collection devices by 57,302 residents from skilled nursing facilities found that pad use remained relatively stable over a 12 month period [371]. Pad use among a sample of 11,549 newly admitted 75–84-year-old residents was 58.7% at admission and 61.1% twelve months later. This rate was higher for residents aged 85 years of age and older (i.e., 60.3% at admission and 62.6% one year later). In a survey of patterns and treatments of urinary incontinence in 13 special care units in the USA, Specht and colleagues (2002) reported that 72% (n=105) of residents used a continence product: the most common type of product being a continence brief or pad (n=93) [367].

According to Omli and colleagues, who estimated the daily pad usage of 153 elderly residents from six nursing homes in Norway, 77% of residents use pads [368]. They also found that residents' pads were changed infrequently (i.e., an average of 2.3 times a day (range 0.5-8.0) for female residents and 3.1 times a day for male residents (range 1.0-9.0). Moreover, urinary tract infections were associated with pad use (41 vs. 11%; P= 0.001): but not with fluid intake or number of pad changes. Residents pad usage did not correlate well with the volume of their incontinence:

As inappropriate use of continence products may contribute to the onset, or continuation of, UI, it is important that clinicians who ad-

vocate or authorise their use, are familiar with evidence-based guidelines that advocate an active approach to diagnosis, prevention and treatment.

Table 5: Evaluative studies on the use of continence products (pads and briefs) in nursing homes

Long-term care / nursing homes / skilled nursing facilities / residential aged care / care homes				
Study	**Objective**	**Sample**	**Method**	**Results**
Brandeis *et al.*, 1997	To describe the frequency and correlatessnip of potentially treatable causes of urinary incontinence	2014 residents (mean age 84.3 ± 8.7) from 270 Medicaid-certified nursing homes in USA	Review of MDS data / Interview with the nursing home staff, and interaction and observation of residents	990/2014 (49%) of residents were incontinent. Of these, 84.0% were managed by pads/briefs. More than one-third (n = 350) of the incontinent residents were managed with two modalities
Boyd *et al.*, 2012	To describe an international comparison of dependency of long-term care residents	90,000 nursing home residents from Spain, New Zealand, Australia and the UK.	A descriptive correlational study	Prevalence of dependent mobility ranged from 27 to 47%; chronic confusion, 46 to 75%; and double incontinence, 29 to 49%. Continence trends over time were mixed, chronic confusion increased, and challenging behaviour decreased.
Omli *et al.*, 2010	To determine daily pad usage & association with UTI, and fluid intake	153 residents (mean age 83 ± 8.2 yrs) from 6 nursing homes in Norway	Number and weight of pads per/resident calculated over 2 days	118/153 (77%) used pads 36/48(75%) men 82/105(78%) women Average number of pad changes p/day-2.7 UTI correlated with pad use but not fluid intake or number of pad changes
Specht *et al.*, 2002	To describe the prevalence, patterns and complications of UI in older adults residing on dementia special care units	145 residents with dementia from one Special Care Unit	Descriptive correlational survey	48% had UI compared to 6% on admission. 72% of resident used incontinence aids, the most common being incontinence briefs and padding
Roderiguez *et al.*, 2007	To explore incontinence prevalence, knowledge and care	66 care homes in Birmingham, UK	Questionnaire to care home managers	Several methods to manage incontinence were cited however briefs and pads accounted for over 50% of responses
Rogers *et al.*, 2008.	To assess use of urinary collection devices (external, intermittent, and indwelling catheters; pads or briefs) and examine predictors of indwelling catheters in skilled nursing facilities	57,302 patients admitted to skilled nursing facilities in five states in the USA in 2003 who remained there for 1 year	Retrospective cohort study	The prevalence of indwelling catheterization was 12.6% at admission and 4.5% at the annual assessment (P<.001). Intermittent and external catheterization were infrequently used (<1% at admission and annual assessment). Paraplegia, quadriplegia, multiple sclerosis, and comatose state were strongly associated with indwelling catheterization. Male residents were more likely to use an indwelling catheter at every assessment, as were obese patients; individuals with diabetes mellitus, renal failure, skin conditions, deep vein thrombosis, aphasia, or end-stage disease; and those who were taking more medications.

Long-term care / nursing homes / skilled nursing facilities / residential aged care / care homes				
Study	**Objective**	**Sample**	**Method**	**Results**
Tsai *et al.*, 2018	To investigate the prevalence and continence care strategies among elderly population living in the long-term care institution.	810 residents from long-term care institutions in Eastern Taiwan	A cross-sectional survey	Prevalence of UI was 40%, and 7.8% for fecal incontinence and 29% with double incontinence. Inability to stand or hip lifting had significantly higher risks of wearing diapers, (OR 29.86, p <.0001). In addition, unable to stand but able to lift hip for 30 seconds still obtain a higher risk on diaper use (OR 6.77, p <.001). In related to diaper use, 639 (78.9%) of the total participants wore diaper, and use of adhesive-tape diaper is 475 (74.3%). For the people using diapers, 99 (12.2%) of them could ambulate independently without assistance but still wearing diapers. And 247(51.5%) of the subjects who wear adhesive-tape diaper were able to stand for 30 seconds.
Wagg *et al.*, 2008	To assess the quality of continence care for older people	2717 patients from 138 primary care trusts in UK	Audit of patients' clinical records	Containment strategies were used by 1294/2717 (48%) of patients

Table 6: Evaluative studies on assessment of UI in frail older adults in hospitals

Long-term care / nursing homes / skilled nursing facilities / residential aged care / care homes				
Study	**Objective**	**Sample**	**Method**	**Results**
Artero-Lopez *et al.* (2018)	To assess the existence of therapeutic inertia in the nursing care of patients with UI during the patient's time in hospital, together with the sociodemographic and professional variables involved	600 medical records reviewed	A prospective observational study with nonparticipative observation of medical practice units and review of patients' medical records.	In 50% (n = 301), the use of a rating scale was not reflected. In over 90% (n = 560) of cases, the type of incontinence was not recorded. In no continuity of care report were recommendations regarding incontinence included, nor was the type of continence products recommended indicated
Mulrooney *et al.* (2017)	To examine whether incontinence was assessed by admitting doctors and nurses in an acute medical assessment unit	40 patients from an acute medical unit. Average age 72.25 (SD=16.3264) years, of whom 17 were females.	A cross sectional analysis of medical admission notes and nursing patient assessment sheets	In 50% of cases, incontinence was not documented on the admission note by doctors. Duration, frequency, management and cause of incontinence were documented in 8.3% of patients. In contrast the nursing pro-forma patient assessment sheet had 95% documentation rate of bladder and bowel continence in both the continent and incontinent patients.
Randles *et al.* (2019)	To determine whether appropriate assessments of continence in older adults presenting to the hospital setting were completed and documented.	31 medical records	A one day audit of patient's medical records in a general medical ward and a specialist geriatric medicine ward	42% UI of whom 40% had completed documentation Six of the patients with documented incontinence had their symptoms/ type of incontinence documented
Redley & Barker (2019)	To test the mnemonic Have you SCAND MMe Please? as a framework to audit nursing care to prevent harms common to older inpatients	A random selection of 400 medical records of inpatients over 65 years of age with an unplanned admission of longer than 72 hr in acute medical wards from four hospitals in Victoria, Australia	Retrospective audit of medical records	The most often documented assessments were skin integrity (94%-97%), mobility (95%-98%) and pain (93%-97%), however only 4%-31% were assessed gaps in assessment of continence (4%-31%), nutrition (9%-49%), cognition (delirium, depression and dementia) (10%-24%) were most common. No patient record had evidence of all eight factors being assessed. Almost 80% of records had interventions documented for one or more factors that contribute to preventable harms. In almost 20% of patient records, a new preventable harm was documented during hospitalisation.
Redley & Raggatt (2017)	To scope the preventable harms addressed by standard forms used to screen and assess older people and how standard forms are operationalised in hospitals across Victoria, Australia	152 standard assessment forms to assess older people at 11 health services in Victoria, Australia in 2015	Mixed methods study: (1) cross-sectional audit of standard risk screening and assessment forms (2) 9 focus groups with a purposive sample of 69 participants at 9 health services.	Assessments of skin integrity and mobility loss (including falls) were consistently included in forms; however, nutrition, cognitive state, pain and medication risks were inconsistent; and continence, venous thromboembolism risk and hospital acquired infection from invasive devices were infrequent. Qualitative analyses revealed five themes explaining issues associated with current use of assessment forms: (1) comprehensive assessment of preventable harms; (2) burden on staff and the older person, (3) interprofessional collaboration, (4) flexibility to individualise care and (5) information management.

Table 7: Evaluative studies on the use of continence products (pads and briefs) in acute/hospital/secondary care

Acute care / hospital / secondary care				
Study	**Objective**	**Sample**	**Method**	**Results**
Condon *et al.*, 2018	To explore the appropriateness of using continence containment products (CCP) in hospitals	435 inpatients (>=18) in a large university hospital in Galway, Ireland	A point prevalence study with assessment of pre-admission and current use of CCP, function based on the Barthel Index (BI) and frailty according to the Clinical Frailty Scale (CFS). Baseline characteristics and the Charlson Co-morbidity Index	CCP usage was 39.8% of inpatients aged >=18 and increased to 57% >=70. All-in-one pads (69% of all CCP) were the most common type used. In all, 62/435 (14%) inpatients used a urinary catheter. There was a 21% increase in all-in- one pad usage compared to premorbid levels (27% versus 6%, p < 0.001). Inappropriate use of all-in-one pads was 64% and was significantly more common in patients with established frailty (p = 0.02) and those with functional impairment as judged by the BI, currently on review (p < 0.001) or at baseline (p = 0.001). Age was independently associated with use of
Fernandez *et al.*, 2017a, 2017b;	To establish views on wait times and hypothesized that they may vary depending upon perspective, circumstance, and incontinence type.	Eligible patients were inpatients, 65 years and older, in a single tertiary acute care hospital.	Cross-sectional, descriptive survey	There was patient-provider mismatch for daytime urinary incontinence: 90% of patients but only 44% of DCPs reported urinary soiling more than 1 hour in the daytime as unacceptable (38.0 vs 85.0 minutes; P <.0001). A significant majority (80%-90%) of both groups reported short acceptable wait times for fecal incontinence (<15 minutes). The odds of being tolerant to any soiling were significantly higher in patients who were prior residents of care facilities (odds ratio [OR] = 6.2; 95% confidence interval [CI], 1.3-28.1; P =.019), previously used incontinence products (OR = 2.0; 95% CI, 1.0-3.8; P =.036), or used walking aids (OR = 4.0; 95% CI, 1.1-14.7; P =.039). Actual wait times were significantly longer than deemed acceptable by either patients or DCPs.
Goes *et al.*, 2020	To identify reasons for the indiscriminate use of diapers and bladder catheters in hospitalized elderly	10 professionals from the nursing team of a hospital in northeastern Brazil	Qualitative methods using the focus group as the collection technique	Factors such as shame (modesty), fear of getting wet and the greater need for help from the team for support at this time, influenced this practice. The majority of the team didn't assess patients' previous states of continence when it is was not related to the reason for the admission
Kadir, 2004	To determine the incidence and appropriateness of incontinence aid use	333 elderly patients in an acute hospital (Singapore)	Survey – patient self-report	200/333 (60%) - using some form of aid 101 (50.1%) could have been managed with alternatives

Acute care / hospital / secondary care				
Study	**Objective**	**Sample**	**Method**	**Results**
Murphy *et al.*, 2015	To explore why clinicians, decide to place indwelling urethral catheters in acute medical care.	in the emergency department and acute medical wards of a 1200+ bed hospital, undertaking 30 retrospective think aloud and 20 semi-structured interviews with nurses and physicians who made the decision to place an IUC. A purposive sample and thematic analysis were used.	Qualitative interviews	Opinions on when an IUC was warranted varied considerably. Inconsistency in decision-making was caused by differing beliefs on when an IUC was appropriate for each clinical indication. Numerous patient and non-patient factors, including clinical setting, resources, patient age and gender and staff workload, also impacted on each decision. Assessing when the benefit of an IUC outweighed the risk could be problematic due to conflicting goals
Ostaszkiewicz, *et al.*, 2008	To determine the prevalence of UI & FI + pad use + documentation of incontinence	447 inpatients (mean age 70 ± 18.7yrs) admitted to 3 acute and 1 subacute care hospitals in Australia	Point prevalence survey + an audit of medical records	266/446 (60%)- using a continence product/ device 50/121 (41%) of patients using pads had no UI or FI in the preceding 24 hrs. 18/113 (16%) patient with UI or FI in preceding 24hrs had no continence product/device
Palese *et al.*, 2007	To evaluate the incidence of pad use and explore appropriateness and reasons for use	396 patients (mean age 76.8 ± 11.8yrs) admitted to medical units in 2 acute care units in Italy	Survey – interview + clinical assessment 3 x day each day during hospitalization	Inpatient use of pads – 218/396 (55.1%). Of this cohort, 120/396 (30.3%) had incontinence prior to admission. Rationale for pad use: urinary incontinence associated with acute confusion or dementia
Percival *et al.*, 2021	To identify factors that help or hinder good continence care for patients aged 65 years and over in hospital medical ward settings	27 nursing, medical and allied health practitioners in three hospitals.	Qualitative interviews	Good continence care was said to be advanced through person-centred care, robust assessment and monitoring, and a proactive approach to encouraging patient independence. Barriers to quality care centred on lack of oversight, automatic use of incontinence products and staffing pressures. Suggested improvements centred on participatory care, open communication and care planning with a higher bladder and bowel health profile.
Wagg *et al.*, 2008	To assess the quality of continence care for older people	3683 patients from 195 secondary care trusts (hospitals) in UK	Audit of patients' clinical records	2070/3683 (56%) patients used containment strategies
Zisberg 2011	To determine incidence of incontinence brief [pad] use	465 older patients (mean age 78.6 ± 5.8 yrs) who were not using incontinence briefs prior to admission to medical acute care units in a 900-bed teaching hospital in Israel	Admission interview and then every day after first 48 hrs	65/465(14%) used incontinence briefs during most of their hospitalisation. Brief use was associated with low mobility

3. ORGANISATIONAL PROCESSES OF CARE IN HOSPITALS

There has been an increased interest in research on incontinence in hospitals since the last ICI, identifying hospitals as an organisational setting that potentially increases the risk of a frail older person developing UI. According to a retrospective review of 182 medical records, there is a significant relationship between hospitalisation and new onset UI (p = .007), and an increased length of stay increases the likelihood of developing a form of incontinence [62]. Similarly, in a prospective cohort study of 282 hospitalised adults aged 70 and older who were admitted for a non-disabling problem, Zisberg *et al.* [372] found in-hospital continence care was directly and indirectly (through its relationship with mobility) related to functional decline at discharge. This important finding may indicate that low mobility and use of continence products form a "double jeopardy" and should be addressed simultaneously in-hospital.

3.1. A lack of assessment in hospitals

A study on nursing practices for patient with UI in hospital noted what the authors called inertia in continence care. The researchers analysed 600 records from 132 nurses and found little documentation of assessment or diagnosis of UI in hospital inpatients [373]. Similar findings were reported by Mulrooney *et al.* (2017) who examined whether admitting doctors and nurses in an acute medical assessment unit assessed and documented patients' incontinence. The researchers found in 50% of cases, incontinence was not documented on the admission notes by doctors and only 8.3% of patients' records contained information about the duration, frequency, management and cause of incontinence. Randles *et al* (2019) also reported low rates of documentation of patients' continence status in a sample of 31 patients over 65 years of age in a general medical ward and a specialist geriatric medicine ward in Ireland. Only 6 of the patients with documented incontinence had their symptoms/type of incontinence documented [374].

In Australia, Redley and Raggatt (2017) reviewed 152 standard assessment forms from 11 Victorian acute care health services and found the forms rarely included a prompt for healthcare practitioners to screen patients' continence status. Whilst assessments of skin integrity and mobility loss (including falls) were consistently included in forms; nutrition, cognitive state, pain and medication risks were inconsistent; and continence, venous thromboembolism risk and hospital acquired infection from invasive devices were infrequent [375]. Roggeman *et al.* (2020) reported similar gaps in the quality of screening and assessment processes to identify falls associated with lower urinary tract symptoms (LUTS). Their review of literature found a total of 23 fall risk scales, from which 11 were applicable for in-hospital patients and 12 were applicable for community-dwelling older people. In nine of the 11 scales for in-hospital patients, a LUTS or LUTS-related parameter was included. There were no LUTS included in the risk assessment tools for community-dwelling older people [376].

Having identified gaps in the quality of screening/assessment tools for hospital-acquired conditions/harms, Redley and Barker (2019) also developed and tested the mnemonic *Have you SCAND MMe Please?* as a framework to audit nursing care to prevent harms common to older inpatients. The mnemonic brings together eight factors known to contribute to preventable harms common in older hospitalised patients, including incontinence. The researchers reviewed a random selection of 400 medical records of inpatients over 65 years of age with an unplanned admission of longer than 72 hr in acute medical wards from four hospitals in Victoria, Australia for the frequency of documented evidence of assessments, interventions or new problems related to the eight factors. The most often documented assessments were skin integrity (94%-97%), mobility (95%-98%) and pain (93%-97%), however only 4%-31% were assessed for incontinence [377].

3.2. A lack of knowledge about UI among healthcare practitioners and/or formal caregivers in hospitals

Several studies reveal gaps in hospital based nurses' knowledge about incontinence and its management [329, 378-383]. A new integrative review of nine studies reported nurses lack knowledge or motivation to thoroughly assess UI in hospitalised older adults, often focusing on containment strategies, rather than conducting an assessment and promoting continence [384].

3.3. Practices that reduce/restrict the frail older adult's mobility and functional abilities in hospitals

Urinary incontinence is associated with severe impairment in ADLs for frail older people in acute and sub-acute care settings. Hence, care processes or practices that reduce or restrict a frail older person's mobility and functional status requires attention. Chong *et al.*, (2018) found frailty in hospitalised older adults predicted incident UI and/or death over time (at discharge: OR 2.98, 95% CI 1.00-8.91, P = .050; 6 months: OR 2.86, 95% CI 1.13-7.24, P = .027; 12 months: OR 2.67, 95% CI 1.13-6.27, P = .025), adjusting for age, sex, and severity of illness [210]. Similarly, Mallinson *et al.*, (2017) conducted a retrospective, cohort study of 425,547 Medicare patients discharged from inpatient rehabilitation facilities in 2005 and found 26.6% of men and 22.2% of women were incontinent on admission and their continence status was significantly associated with discharge to institutional care, particularly among orthopaedic patients [385]. According to the findings of a co-design study that aimed to improve service delivery for hospitalised frail older people, continence care is one of five areas of care that needs to improve; the other areas being improved mobility; improved access to food and hydration, improved patient information and improved collaboration along the integrated care continuum [386].

3.4. Limited or inconsistent access to toileting assistance in hospitals

The last ICI reported on a large mixed methods study led by Thomas *et al.*, [387] that explored the organisational context for embedding a systematic voiding programme for patients with UI after stroke in secondary care settings. The researchers concluded there was a focus on containment of UI that was not conducive to therapeutic continence management [388]. They also found toileting dependence to be the most problematic aspect for patients after a stroke. The researchers conducted a cross-sectional correlation study of 107 adult inpatients, hospitalized for a stroke. Boltzmann sigmoid modelling revealed that the total scores required to obtain a response at 50% of the maximal value for the required components of toileting ranged between 2.691 and 34.962 points, for the components of "wearing pants" and "cutting the toilet paper," respectively. A generalized linear model showed that the Berg Balance Scale score was a significant predictor for independent performance on most component activities of toileting. The component of toileting that was easiest to carry out was cutting the toilet paper, and the most difficult was wearing pants. Balance impairment was an independent predictor of independent toileting after stroke. Further research is required to assess the motor and process skills required for independent toileting among different groups of hospitalised older people.

3.5. A lack of privacy and attention to the dignity of frail older adults in hospitals

The lack of attention to the privacy and dignity of frail older people in nursing homes also extends to frail older people in hospital settings. Using an ethnographic design Boddington and Featherstone (2018). examined the complex systems of dominance, hierarchy, and the social and institutional routines in five hospitals in England and Wales. The aim was to examine the ways in which the recognition of personhood is negotiated, achieved, and threatened among hospitalised older adults with incontinence and dementia.

The researcher reported routines and prioritisation dilemmas pose barriers to patients' control over their elimination needs and disrupt the presence of the patient in the social life of the ward. They described the way in which that which was private becomes open to control by others, i.e., people no longer have control over how others see them, and it is no longer unusual for people to be viewed during intimate moments, or for their continence care needs to be delayed or interrupted by the competing priorities of others. Importantly, the researchers stated 'the coexistence of a diagnosis of dementia and needing continence care creates a double jeopardy not only for the dignity and moral status of the patient, but also for those involved in their most intimate care, who must complete the pressing routines and timetables of medication rounds, personal care and continence care etc. throughout a shift. This sets the conditions within which the loss of personhood and dehumanization of people living with dementia can flourish' [389]. According to the findings of a qualitative descriptive exploratory study about patients' end of life preferences for continence care, dignity is often threatened as a result of having to receive continence care, with most patients acquiescing to staff recommendations for management approaches as being easiest [390]. Moreover, as patients approached end of life, they were willing to give up dignity if it was required to address symptoms causing them more distress, like pain.

3.6. Reduced staffing in hospitals

The relationship between nurse staffing and quality of care is much debated. We found no studies that specifically describe the association between staffing and the quality of continence care in hospitals or UI rates among frail older persons in hospitals. At the same time, there are several large studies that reveal an association between the number of nurses, their education, length of stay, cost and hospital mortality. The most recent of these is a study of 231,902 patients from 27 hospitals in Queensland, Australia. 142,986 patients in intervention hospitals and 88 916 in comparison hospitals were assessed at baseline (2016) and 257,253 patients (160,167 in intervention hospitals and 97,086 in comparison hospitals) were assessed in the post-implementation. After implementation, mortality rates were significantly lower than at baseline in intervention hospitals (0·89, 0·84–0·95, p=0·0003) [391-393].

3.7. The overuse and misuse of continence products in hospitals

Rates of continence product use in elderly patients in acute care across several countries are similar and range from 55.1% in Italy [394], 56% in the UK [365] to 60% in Singapore [395] and Australia [396]. Not only are they widely used but they are often used indiscriminately. One of the earliest studies to draw attention to an overreliance on continence products was conducted by Starer and Libow [397] who found more residents using pads than those with incontinence. More recently, Ostaszkiewicz and colleagues found that in the inpatient care setting, pads were inappropriately used for some patients, and were underused for others [396]. Of 121 patients who were using pads at the times of the survey, 50(41%) reported no UI or FI in the preceding 24-hours. However, 18% of patients who had no pad did report such an episode. This mismatch between incontinence and pad use has been noted in other research [394, 398].

The last consultation reported that in-hospital use of continence products was associated with new onset UI at discharge, according to a prospective cohort study of 684 hospitalised older adults admitted for a non-disabling problem [398] based on a mixed-methods study that explored the organisational context for embedding a systematic voiding programme for patients with UI after stroke in a secondary care setting, in the UK. It also reported that the focus of UI care is on containment of UI rather than therapeutic continence management [387]. Since then, five new research studies have been identified that examined the use of continence products in hospital settings (see Table 7).

Timely changing of incontinence products is important since patients are at risk of developing incontinence-associated dermatitis. A cross-sectional survey of hospitalised older adults who required continence products and their direct care providers investigated the length of time they thought was acceptable for patients to spend in a soiled pad during the day and the night [399]. Data on patients' previous continence status, pad use, use of mobility aids and place of residence (community, institution) were also collected. The researchers reported a mismatch between patients and provider in their tolerance for waiting related to daytime pad change related to UI. Specifically, 90% of patients but only 44% of direct care providers reported urinary soiling more than one hour in the daytime as unacceptable (38.0 vs 85.0 minutes; P <.0001). A significant majority (80%-90%) of both groups reported short acceptable wait times for faecal incontinence (<15 minutes). The odds of tolerating any soiling were significantly higher in patients who were prior residents of nursing homes (odds ratio [OR] = 6.2; 95% confidence interval [CI], 1.3-28.1; P =.019), previously used incontinence products (OR = 2.0; 95% CI, 1.0-3.8; P =.036), or used walking aids (OR = 4.0; 95% CI, 1.1-14.7; P =.039). Actual wait times were significantly longer than deemed acceptable by either patients or direct care providers. The actual wait times patients and direct care providers reported were also markedly different, with patients reporting generally shorter wait times than direct care providers during the day (74.6 vs. 148.8 min; p<0.0001). The majority of direct care providers (86%) reporting wait times of 91-120 minutes at night vs. a range of times by patients (155.4 vs. 128.4 min for patients and direct care providers, respectively; p=0.024).

Concerted efforts are required to tackle the inappropriate use of continence products in hospital settings according to the findings of a point prevalence survey of 435 inpatients, median age 72 +/- 23 years. Based on hospital policy and NICE guidelines (2015), the researchers deemed the use of all-in-one pads appropriate for patients who scored zero on the bowel section of the Barthel Index, indicating faecal incontinence and/or zero on the transfer section indicating major assistance or a hoist to transfer from bed to chair [400]. Inappropriate use of all-in-one pads was 64% and was significantly more common in patients with established frailty (p = 0.02) and those with functional impairment as judged by the Barthel Index, currently on review (p < 0.001) or at baseline (p = 0.001). Age was independently associated with use of any product, including pads and urinary catheters (p < 0.001).

Qualitative interviews with health care professionals from a hospital in north-eastern Brazil suggest patients' impaired mobility was the main reason for promoting the use of continence products in a hospital setting [401]. Other factors included the anticipation of shame and fear for the resident, and the lack of team support to promote

the patient's continence. Qualitative interviews with 27 nursing, medical and allied health practitioners in three hospitals study from the UK also found a high reliance on the use of incontinence products that staff reported was due to staffing pressures [402].

According to the findings of a qualitative study in the emergency department and acute medical wards of a 1200+ bed hospital, decision-making regarding the use of indwelling urinary catheters is also arbitrary and influenced by multiple factors [403]. These included patient and non-patient factors, including clinical setting, resources, patient age, sex and staff workload, also effected each decision. The researchers advocate for greater understanding of the complexity and lack of clarity clinicians face when making the decision to insert a catheter.

4. ORGANISATIONAL INTERVENTIONS

4.1. Assessment and communication interventions

Since the last consultation, four peer reviewed publications were identified that describe an organisational intervention designed to improve the assessment and communication of UI in organisational settings. Grainger *et al.*, (2019) describe an intervention focusing on communication between the acute hospital and community teams responsible for care home residents after discharge from acute care. The team designed a discharge summary template that addressed 8 core domains, including continence. The introduction of the template resulted in 90% of discharge summaries being completed [404]. Similarly, Tazeen *et al.*, (2017) described the development and evaluation of a new continence assessment form for completion by ward nurses. Supported by regular ward visits and education sessions from the continence team, ward staff were encouraged to refer appropriate patients to the continence out-patient service. A follow up audit of 36 patients found 100% compliance with completing the screening and assessment form and 7 new cases were identified and referred to the continence team for further assessment [405]. Improving the assessment and documentation of UI in nursing homes was also the focus of a randomised controlled trial led by Gencbas *et al.*, (2018) in Turkey. Thirty-two female residents were randomised to the 12-week intervention and 30 to a control usual care group. The intervention consisted of education to staff about three Standard Nursing Languages (Nursing Diagnosis: Definitions and Classification; NIC: Nursing Interventions Classification; NOC: Nursing Outcomes Classification) and their application to residents' continence care plans. The researchers reported statistically significant improvement in all NOC scales in the intervention group compared to the control group (i.e., assessment and documentation about urinary elimination, urinary continence, tissue integrity, self-care toileting and medication response). They also reported significant and positive differences in the ISI (P = 0.001), UDI-6 (P = 0.001), and I-QOL (P = 0.001) scale scores for the IG group post-intervention [406]. A similar approach was taken by Hödl *et al.*, (2019) who evaluated the effects of introducing 29 evidence-based nursing recommendations about the conservative management of UI in 12 Austrian nursing homes. The intervention group (n=216) received conservative UI management strategies for 12 weeks and the control group (n=165) received usual care. The intervention group had a lower risk of daily UI (P = 0.02), were less likely to receive absorbent products (P = 0.01) and were five times more likely to receive recommended interventions (P = 0.001) than residents in the usual care group [407]. Finally, Trad *et al.*, (2019) reported using the Joanna Briggs Institute Practical Application of Clinical Evidence System and the Getting Research into Practice tools to review the nursing assessment and management of adult patients with urinary and faecal incontinence, and to develop local resources to assist nursing staff to assess and manage incontinence in a large hospital in Australia. Nursing staff received education about 10-best practice criteria for incontinence assessment and management. A pre–post audit revealed notable improvements in the nursing documentation, and in assessment and management.

4.2. Exercise programmes

The last ICI reported on two trials in a nursing home setting [408, 409] that revealed reductions in the frequency and severity of incontinence from exercise programmes that aim to improve frail older person's functional status. No further trials have been identified.

4.3. Technological interventions

A new technological intervention designed to augment and enhance the assessment of UI in frail older adults offers promise. Electronic monitoring systems designed to detect moisture in incontinence pads can augment existing assessment processes for aged care residents with complex conditions in long-term care homes or geriatric hospitals. A health technology report that examined the effectiveness of budget impact of, and patient values and preferences about the technology reported the system would cost $6.4 million in the first year of implementation and $1.6 million in subsequent years. As only one observational was identified, the authors concluded that the effectiveness of using the electronic monitoring system to assess UI was uncertain because of the very low quality of the evidence and introducing it would result in incremental costs, and there would be savings only if the systems substantially reduced incontinence [410]. Further trials on this technology are required.

4.4. Night-time continence care practices

According to a recent study, 80% of hospitalised older patients experience nocturnal LUTS during sub-acute hospitalisation [411] which may affect the quality and duration of their sleep and increase their risk of falling at night. It is unclear if the symptoms relate to physiological function or to disruptions caused by care practices. According to an evaluation of a night time intervention for 21 nursing home residents with dementia in Japan, continence care routines are common practice. Mizaguchi *et al.*, (2017) examined the effects on sleep and activity following an intervention designed to manage UI during the night for 21 nursing home residents with dementia in Japan. The intervention involved changing diapers immediately after urination and taking residents to the bathroom according to their individual needs, rather than leaving them in a wet diaper. The researchers reported the number of times per night that residents received continence care during the control period was 1.35 (+/- 1.40) compared with 4.47 (+/- 1.39) during the intervention. The volume of UI during the control period was reportedly 271.78 (+/- 393.50) ml while during the intervention period it was 242.22 (+/- 211.46) ml showing residents were less likely to develop UI during the intervention period. The researchers reported improvements in residents' total sleep time at night and improvements in daytime activeness, particularly among residents with milder cognitive impairment [412].

4.5. Toileting assistance programmes

There were three new trials that describe an evaluation of a toileting assistance programme in a nursing home setting. Lai and Wan (2017) examined the effectiveness of the use of prompted voiding by nursing home staff to manage UI among residents over a 6-month period in a randomised controlled trial conducted with 52 nursing home residents from five nursing homes in Hong Kong.

The intervention was delivered by usual care staff who were trained in the protocol. At six months both groups had improved, but there were significant differences between the two groups in the number of UI episodes per day, UI rate per day, and total continent toileting per day. A decrease of 9.1% was observed in the incontinence rate of the intervention group [413]. According to the findings of a randomised trial conducted in 13 nursing homes in Japan, prompted voiding that is augmented with ultrasound technology to identify residents' individual urine volumes, is more effective than prompted voiding alone [414]. The ultrasound-assisted prompted voiding intervention was characterised by caregivers regularly evaluating each resident's bladder urine volume using an ultrasound device and prompting them to void when the volume reached close to the individually optimized bladder capacity. The researchers reported statistically significant reduction in the volume of daytime UI in the intervention group (median, −80.0 g) compared to the usual care group (median, −9.0 g; P =.018) and a reduction in the proportion of elderly individuals with daytime urine loss compared to residents who received prompted voiding alone. Resident's quality-of-life scores and caregivers care burden scale scores did not differ between groups. However, the care burden scale score of caregivers was significantly worse in the usual care group (P =.010) after the intervention.

The other study, conducted in residential care facilities in Sweden, focused on a person-centred approach to incontinence care for older adults with cognitive decline [348]. The study involved 79 residents from 3 facilities and 20 health care workers (including nurses and nurse aides). The ten-month intervention consisted of five education sessions for the health care workers about a person-centred approach to continence care and to take the lead in coaching and supporting their colleagues in implementing the intervention. The training comprised how to approach and interview residents using a person-centred approach, how to transform significant elements of residents' narratives into a tailored care plan and evaluate the effect of individualised actions. They additionally received training in incontinence assessment, planning, caring actions, and outcome follow up. A usual care control group facility was matched by resident case-mix and geographic region. Introduction of a person-centred approach showed an increase in residents' quality of life in the intervention group compared to baseline and the control group. A positive effect was found on the number of UI assessments conducted ($p < 0.05$). In addition, the number of person-centred caring actions (e.g., toilet assistance) was significantly higher during and 6 months after implementation.

4.6. Education

Improvements in knowledge about UI among healthcare professionals among are possible. Szonyi and Millard [415] reported a significant improvement in GPs knowledge about incontinence following receipt of an education package. Likewise, Mathis *et al* [416] and Ehlman *et al.* [417] demonstrated improvements in knowledge among nursing home staff following an educational intervention as did Kholer *et al*., [65] and Wijk *et al.*, [348] in more recent research. A subsequent systematic review of 19 studies that included the studies by Mathis *et al.* [416] Ehlman *et al.*, [417] and Kholer *et al.*, [65] found educational interventions about UI improved nurses' and nursing assistants' knowledge, but the effects on practice and patient outcomes were mixed. Uncontrolled trials reported improvements in nursing home residents' and community-dwelling patients' continence status, but this effect was not observed in a large, controlled trial. Similarly, two studies set in inpatient rehabilitation found no significant differences in patient continence outcomes following an educational intervention targeted to nurses [418]. Martin-Losada *et al.* (2019) reported on an organisational intervention that included education for hospital staff about the management of UI in hospitalised older patients in Spain. The Joanna Briggs Institute's Practical Application of Clinical Evidence System and Getting Research into Practice audit tools were used to promote staff compliance with best practice recommendations related to assessment of UI, type of UI, documented plans, appropriate management, changing of continence products, staff education, and discharge assessment. Local champions delivered 10 short educational sessions about the definitions and types of UI prevalence, associated problems, evaluation and treatment, and areas for improvement. In a 6-month follow-up, the researchers reported rates of adherence of 82-100% [419]. There is a need to better understand strategies that successfully facilitate knowledge implementation about evidence-based approaches to UI in organisational settings such as hospital. A multidisciplinary team of nurses and physiotherapists or occupational therapists were appointed to facilitate the implementation of an evidence-based protocol for UI in patients aged 65 or older undergoing hip surgery in two hospitals in Sweden. The teams were supported by external facilitators who shared knowledge about UI and implementation science. The intervention raised the internal facilitators' awareness of UI risks associated with hip surgery, which in turn increased staff awareness. More time and managerial support were required to implement evidence-based UI care [383, 420]. Blachman *et al.* (2017) reported that a programme that addressed UI management for older adults enhanced learners' communication, collaboration, and comprehensive primary care to vulnerable older adults [421]. A similar interdisciplinary programme was described by Jonsson *et al.*, (2018) who reported participants' satisfaction [422]. Wilkinson *et al.* (2017) described a novel podcast as a means of educating multi-disciplinary teams about ageing. With over 7,000 downloads for the first 10 episodes, the researchers claimed the rapid accumulation of a large audience (including non-geriatric specialists) demonstrates that podcasts are an effective way to deliver geriatric education across disciplinary and locational boundaries [423]. DuFour & Northwood (2017) used a Delphi technique to gain consensus among an expert group of 12 panellist on the connection between falls and UI into action and to develop a preliminary set of consensus-based practice principles related to falls prevention and UI for relevant stakeholders in community-based primary health care. There is a need for better reporting of educational interventions about UI. [424] . This would allow comparisons between programmes and to address the key question of what works best in terms of the educational duration, delivery mode, content, expected learning outcomes, assessment methods, and extent to which the teaching methods accommodate different cultural, literacy, and contextual learning needs. The review revealed existing content emphasis is on a biomedical construction of UI that has cure as the underlying aim, rather than care or on strategies to help people adjust to changes in bodily function that affect their identity, autonomy, control, and independence. As such, researchers should evaluate measures of care as well as cure.

4.7. Facilitation

Since the last ICI, a large randomised controlled trial was published which evaluated the effects of different methods of facilitation to promote the uptake of evidence-based recommendations for UI management in nursing homes. The trial was conducted in four European countries across 24 long-term nursing care sites for people aged 60 years or more with documented UI. The primary outcome was the documented percentage compliance with the continence recommendations, from reviews of 2,313 records assessed at baseline, then at 6, 12, 18, and 24 months after the intervention. The quantitative analysis revealed no statistically significant differences in compliance with continence recommendations between the groups and hence, it was not possible to identify whether different

types and "doses" of facilitation were influential within very diverse contextual conditions.no significant differences in the primary outcome (documented compliance with continence recommendations) between study arms and all study arms improved over time [425].

The research team also conducted a realist process evaluation to answer the question of what worked (and did not work), for whom, how, why and in what circumstances during the process of implementing the facilitation interventions in practice. The researchers reported 'the success of intervention implementation was largely dependent on whether sites prioritised their involvement in both the study and the facilitation programme'. The personal characteristics and abilities of Internal facilitator, including personal and formal authority combined the managerial support facilitated the potential for learning over time [426].

4.8. Advanced Practice Nursing Care

One study was identified that examined the effects of employing advanced practice nurses to drive organisational changes in the management of UI in nursing homes [427]. Residents received tailored, conservative continence treatment from a Nurse Continence Specialist for 12 weeks. Interventions included pelvic floor muscle exercises and bladder retraining with a focus on deferment strategies, on fluid intake, on optimising bowel function and increased physical activity, and life-style changes. Prompted voiding, techniques to improve bladder emptying, prescription of anticholinergics and oestrogen cream were also recommended to some residents. Mean urine loss fell significantly by 60 ml per day (P = 0.024) and there was a significant reduction in pad changes per week by a mean of 4.3 (P = <0.0005). Scores on the ICIQ-SF improved statistically by 2.84 (P = <0.0005) but there was no significant improvement in any other quality of life or activities scales. The number of pads used per week reduced by a mean of 4.3 with a significant reduction of pad costs per week (mean NZ$2.43/16%). There was no significant different in carers' cost or additional laundry costs. The total cost of providing the intervention for 12 weeks (NZ$247.75 minus cost-savings NZ$12.48), was NZ$235.27 per participant.

5. INSTRUMENTS TO EVALUATE THE QUALITY OF CONTINENCE CARE FOR FRAIL OLDER ADULTS IN ORGANISATIONAL SETTINGS

Although there are several instruments that measure the incidence and prevalence of UI and quality of life, to the best of our knowledge, few instruments specifically address the quality of continence care in organisational settings. We identified two new instruments:

- Instrument for Structural Assessment of Wards for the Preservation of Urinary Continence in Older Adults which consists of 27 items, distributed in three dimensions: "physical structure", "human resources", and "material resources". It requires clinical validation [428]
- The ICIQ-Cog - a 12-item scale measuring disease-specific bother (ICIQ-Cog-P) and a four-item scale assessing efforts associated with care of people with incontinence and cognitive [429].

Three other instruments are in development. They include:

- The ICF-Incontinence Assessment Form [430, 431]
- The Dignity in Continence Care Scales (self-report version)
- The Dignity in Continence Care Scales (staff version) [432]

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IV. ASSESSMENT OF THE FRAIL OLDER ADULT WITH URINARY INCONTINENCE

Recommendations for the basic assessment of frail older adults with UI are summarised in the algorithm (see Summary Document). Because UI in the frail older adult is almost always multifactorial, a comprehensive assessment should be conducted wherever possible. Collaboration between primary care physicians, geriatricians, surgical specialists, nurses, other health professionals and caregivers, both formal and informal, may be necessary for optimal assessment and management.

The number of guidelines in the area of urinary incontinence has proliferated since the 6th Consultation, the majority of these are consistent in their approach. For example, the European Association of Urology has developed its published guidelines on UI which bear relevance for frail older men and women. These remain largely based on the findings of the 5th ICI but now include consideration of anticholinergic load when prescribing for older people. Other than this guideline, the impact of associated comorbidity is seldom considered; there remains a need for consideration of this area in both robust and frail multimorbid older adults

1. IDENTIFICATION OF FRAIL OLDER ADULTS.

Health care providers can case find in older patients with UI for frailty using the Vulnerable Elders Survey, which can be administered in person or by phone [434]. Persons with a score of 3 or greater have four-fold increase in the risk of death and functional decline compared with persons with lower scores. A patient self-reported scale in which those people classified as either frail or pre-frail had higher frequency of hospitalisation, a higher probability of co-morbidity and higher mortality than those classified as non-frail has also been reported [435]. There has also been increasing interest in the detection of frailty in patients undergoing surgery (see later), as its presence predicts poorer outcomes from hospitalisation and surgery. The use of the Clinical Frailty Scale has increased since the last ICI. It has proven utility in the prediction of outcomes following surgical treatment in terms of complications and needs for addition-

al care. It has a close relationship to the Frailty Index, initially derived from the 78 items of the Comprehensive Geriatric Assessment [436]. However, caution still needs to be exercised when classifying an older individual as frail as there is considerable heterogeneity within this group [437]. There may also be a clear distinction between cognitive and physical frailty.

2. PRIMARY CARE ASSESSMENT

Physician education using a modified version of the ACOVE model to reach a large group of primary care physicians resulted in between 80% and 92% of them planning to make a change in their practice behaviour [438], although no formal assessment of carry through was undertaken. Geriatricians' and primary care physicians' (PCPs) UI assessments were compared in a randomised multicentre study involving 364 subjects, 42% of whom self-reported UI to the investigators. Geriatricians were significantly more likely to detect UI (59% of cases vs. 16%), regardless of the severity of UI, and were more likely to refer to Continence Programmes (25%); all referrals by PCPs were to urologists [439]. An assessment strategy based on clinical evaluation, simple cystometry, and several criteria for referral was compared with urodynamic diagnosis. Approximately 25% of patients met criteria for referral, half of patients accepted urodynamic evaluation, yet urodynamics changed the treatment plan in only 12% of the patients who did not meet the a priori criteria for referral [440].

Practice patterns and adherence to US UI guidelines were evaluated by retrospective chart review of 300 consecutive patients aged >65y, seen by either an internist or geriatrician for UI at a tertiary care centre. Geriatricians ordered more testing, such as urodynamics, before referring patients to a surgical specialist [441]. Over-all, primary care practitioners rarely follow the US Agency for Healthcare Research and Quality UI guidelines, [442] and nursing home practitioners rarely follow the Federal guidance for UI care regarding recommended physical examination, PVR testing, urinalysis, and identification of potentially reversible causes [443]. Okamura and colleagues investigated the diagnosis and treatment of lower urinary tract symptoms (LUTS) by general practitioners (GPs) according to the "Practical manual for LUTS evaluation and treatment in the elderly for GPs (Japanese)" and found adherence to the manual, reinforced by educational and promotional activities resulted better treatment outcomes [444, 445]. A randomised trial of an electronic screening tool was useful in improving conversations about urinary incontinence in older women (not frail) [446].

A systematic review of articles identified only 5 studies meeting eligibility criteria, and all were in women. None of studies found sufficient diagnostic evidence (for different types of UI. The best was a general population study reporting the utility of history and examination for the diagnosis of SUI (positive and negative likelihood ratios 3.23 and 0.40, respectively) [447]. Adding a nurse practitioner to general practitioner care for adult patients with UI can reduce the impact of UI and has been proposed as a cost-effective model using the Netherlands as an example [448, 449].

3. COUGH STRESS TEST

We have found no additional evidence on the utility of the cough stress test since the 4th consultation. Utility of the cough stress test was studied in 97 incontinent female long-term care residents using blinded comparison with single channel cystometry. Of the 77% in whom single channel cystometry diagnosis was congruent with the stress test (i.e., urodynamic DO with negative cough test, no DO and positive cough test), all were correctly classified. No woman with SUI was missed nor were any with DO misclassified [450]. An analysis of 200 older women with UI found that provocative full-bladder cough test was as effective as radiographic or urodynamic pressure measurement in detecting SUI. Clinical diagnosis incorporating the cough test with leakage symptoms was 78% accurate, with only 6% false negatives for SUI, but was only 44% accurate with 45% false negatives for urgency UI [451].

4. POSTVOID RESIDUAL MEASUREMENT

We identified no new studies evaluating the impact of PVR measurement on clinical diagnosis and treatment outcomes. Readers are referred to previous consultations regarding the associated frailty state of older adults with raised PVR. Largely, the committee concurs with recommendations from the Urodynamic committee of the 7th ICI.

- PVR measurement is recommended in the evaluation of UUI in frail older adults with symptomatic voiding difficulty or a history of urinary retention. Assessment of prostate size and assessment of prolapse as well as of current use of all medications should be taken into account while considering PVR.
- PVR measurement is recommended before initiation of antimuscarinics in the frail older adult patient with UUI
- PVR measurement is recommended in the frail older adult patient with urgency UI prior to invasive therapy.

5. URODYNAMIC TESTING

Urodynamic testing is feasible and safe, even in frail nursing home residents [44]. There is no evidence, however, that urodynamic diagnosis changes the outcome of treatment. Expert guidelines, including those from this consultation, recommend urodynamic testing before surgical or minimally invasive UI treatment in women, but there remains debate about the utility of this approach in men.

Summary of evidence

- Active case finding and screening for UI in older adults because many do not spontaneously report their symptoms. **(LoE 1)**.
- Screening for frailty is possible with short screening instruments **(LoE 1)**.
- Current quality of primary care assessment of UI in frail older adults is poor **(LoE 2)**.
- Cough stress test has moderate accuracy in frail institutionalised women **(LoE 2)**.
- No recommendation is possible on the utility of PVR testing **(LoE 4)**.
- Urodynamic testing is feasible in frail older people **(LoE 1)**, but it is unlikely to change management or outcomes except, perhaps, in those considered for surgical treatment of UI **(LoE 4)**.

Recommendations for evaluation

The essential first step is to actively case find in the frail older adults, as both UI and FI are generally under-reported.

The second is to identify treatable, potentially reversible conditions and other factors (medications, environment) that can cause or contribute to incontinence. It is important to evaluate for such contributing factors because their amelioration may improve UI directly, make UI more amenable to other interventions, and overall improve the patient's (and caregiver's) quality of life [452]

The common, treatable, potentially reversible conditions that can contribute to UI in frail older people can be defined by the mnemonic DIPPERS ((Delirium, Infection [urinary tract), Pharmaceuticals, Psychological, Excess fluid (in/out), Restricted mobility, and Stool impaction [and constipation]). This is a useful aid to teach and remember these conditions [453]. Cognisance must be made of the potential to overtreat asymptomatic bacteriuria as apparent infection because of the risk of adverse outcome [454].

V. FACTORS IN MANAGEMENT OF THE FRAIL OLDER PERSON WITH URINARY INCONTINENCE

1. BACKGROUND

This section highlights some of the important issues that distinguish the management of incontinence in frail older adults from that in healthier older adults. Among these critical issues is an understanding of the roles of competing comorbidity, establishing the importance of patient-centred goals, incorporation of knowledge of remaining life expectancy, and the costs and benefits of care, both for the patient and for the caregiver. These factors contextualize continence care and should be incorporated into the management of all incontinent frail older adults, regardless of the choice of specific treatment.

2. ROLE OF COMORBIDITY IN MANAGEMENT DECISIONS

Many frail older adults have coexisting comorbidities, which can influence both the clinical presentation and assessment of UI, as well as responsiveness to interventions. Some examples of comorbidities that can affect the function of the urinary tract include diabetes mellitus, degenerative joint disease (resulting in lower limb weakness and dependency on walking aids), chronic obstructive pulmonary disease, congestive heart failure, lower extremity venous insufficiency, obstructive sleep apnoea, severe constipation and faecal impaction, and neurological and psychiatric conditions such as stroke, Parkinson's disease, dementia, and depression [455]. In part due to the presence of these comorbidities, frail older adults can also be at increased risk for poor treatment-related outcomes, such as fulminant *Clostridium difficile* colitis from antibiotics used to treat otherwise asymptomatic bacteriuria or constipation, dry mouth or even potential cognitive impairment resulting from anticholinergic medications used to treat overactive bladder. Reflexively, sometimes treatment of UI may result in improvement of comorbid conditions [452]. For example, topical oestrogen treatment for urogenital atrophy/genitourinary syndrome of menopause may also reduce risk of recurrent UTI), and a nursing home exercise programme for toileting can also improve physical function [409]. Treatment of comorbidities can also improve UI, as is the case with management of chronic cough from obstructive pulmonary disease, which may benefit stress urinary incontinence.

3. DEFINING OUTCOMES FROM TREATMENT

Outcome measures used in frail older adults must be fundamentally different from those used in healthy older persons. This is because of the heterogeneity of this frail population regarding comorbidity, remaining life expectancy (RLE), patient perceptions, personal values, and the involvement of caretakers and proxy decision makers. Unfortunately, intervention studies in frail older populations remain focused on objective disease related variables, and seldom consider these important factors. Subjective outcome goals and measures may be preferable study outcomes in this patient group. A review of care home residents' views on continence revealed that these individuals valued having independent bowel and bladder function, and that the effects of continence on QoL, self-esteem, and sense of value and autonomy were paramount [456].

Although quality of life (QoL) is a key concern for UI in all persons (see Committee 4, Initial Assessment), and has special relevance in frail older adults with limited RLE, there are few validated QoL outcome measures applicable to this population. Only one validated UI-related QoL measure is derived specifically from patient-based data among persons older than 65, and these subjects were community-dwelling and relatively healthy [457]. Only one ICI-endorsed UI-related QoL measures have been validated in the oldest-old or cognitively and/or functionally impaired persons, currently only available in German [429]. Traditional UI QoL domain—e.g., impact on IADLs, travel, sexual relations—are often not relevant to frail older adults, and there could be significant effects for social and functional domains. One alternative QoL domain for frail older adults is social interaction, especially for nursing home residents; [458] an analysis of cross sectional and longitudinal data from over 100,000 US nursing home residents found that prevalent and especially incident UI had a negative impact on social interactions, particularly among persons with moderate ADL impairment [458]. An analysis of older Medicare beneficiaries over 65 years of age, and including those over 85, found significant impairment of QoL, in accordance with that found in younger people [459].

The profound question when considering UI out- comes in frail older adults is, "Is complete cure possible?" In short, this depends on patient factors, specific treatment(s), and the target outcome. While no geriatrician endorses "ageism" or therapeutic nihilism, research evidence suggests that complete dryness is unlikely for certain frail older adults, particularly frail institutionalised adults with severe cognitive and functional impairment. Even "intractable" UI is amenable to interventions that may improve the individual's urinary and bowel function and QoL. The continence paradigm for frail older adults (Figure 3), which subsequently generalised for all persons with UI [460] remains valid. In this paradigm, people with "dependent continence" are dry due to ongoing assistance, behavioural treatment, and/or medications. UI would return if the interventions ceased, a situation analogous to chronic disease models [461] such as "controlled hypertension" or "controlled diabetes." Persons with "independent continence" are cured without the need for ongoing

treatment (e.g., dry after successful anti-incontinence surgery). For individuals who are unable to achieve independent or dependent continence, “contained incontinence” should be possible by use of appropriate products such pads, catheters, and appliances (See Chapter 19, Management Using Continence Products), thus providing “social continence” [462]. The balance between the degrees of continence achieved may vary as UI severity changes over time, and these states are dependent upon patient and caregiver preferences. outcomes encompass a common need: to be both realistic and hopeful about UI in frail older adults while avoiding nihilism and neglect; maintaining comfort and dignity and preventing avoidable complications of UI. The other consideration is that any comorbidities associated with frailty, e.g., dementia and Parkinsonism, are progressive conditions so that treatment goals may need to be re-evaluated as time progresses.

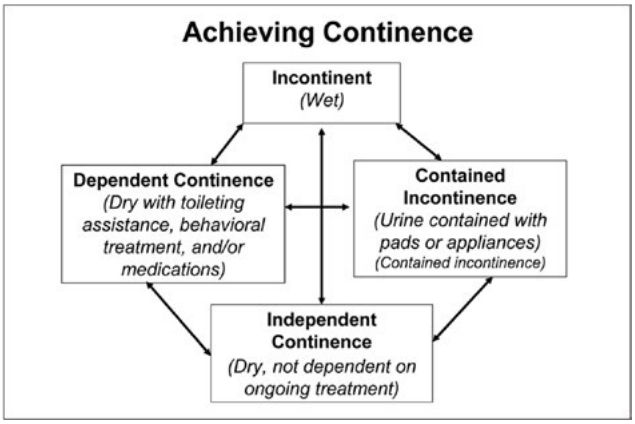

Figure 3. A paradigm for continence

4. ROLE OF REMAINING LIFE EXPECTANCY IN TREATMENT DECISIONS

Remaining life expectancy (RLE) is a key yet often misunderstood concept in treatment decisions for frail older people. RLE is not uniformly short in this population; moreover, there is a demographic trend of increasing RLE, with a smaller proportion of persons spending their remaining years living with disability [463]. Evidence shows that many health care professionals will underestimate life expectancy [464]. Reference to actuarial tables produced for insurance purposes is often enlightening. Comprehensive Geriatric Assessment can help estimate remaining life expectancy and can help predict treatment-related morbidity and mortality in older men with prostate cancer [465].

Walter and Covinsky [466] developed a graphical tool for estimating quintiles of RLE by age. Medical conditions most closely associated with shorter RLE are class III/IV congestive heart failure, end-stage renal disease, and oxygen-dependent chronic obstructive pulmonary disease. Estimates of RLE are significantly affected by frailty and cognitive impairment [467]. Functional status has a dramatic impact on life expectancy. For example, 75-year-old men and women without limitations have life expectancies 5 years longer than those with ADL limitation and more than 1 year longer than those limited in mobility [468]. Alzheimer’s dementia decreases RLE profoundly (by nearly 75%) among older persons who otherwise would be in the top quintile of RLE [469]. Compared to older adults with at most one IADL deficit, those with more deficits have significantly higher 5-year mortality (with two deficit, adjusted RR 1.46 [95% CI 1.20 – 1.78] ; with three or more deficits, adjusted RR 1.64 [1.26 – 2.14]) [466].

5. PREFERENCES FOR CARE

As multiple treatment options are available for frail older adults with UI, and individualised care should be emphasised, obtaining the preferences and goals of frail older adults and their caregivers is essential for quality care planning. This includes those persons living with cognitive impairment. It should not be assumed that persons with cognitive impairment are unable to make their care preferences known or participate in treatment decisions and all reasonable efforts to help them to do so should be made. Few studies have examined frail older adults and caregiver’s preferences. Four studies were identified in earlier editions. In a study of 111 nursing home residents with UI; residents preferred an average of 2 pad changes, 1.5 toilet assists, and 2 walking assists more than they received, yet even these levels were lower than guidelines recommendations, suggesting reduced expectations of residents [470]. In a study of family members of incontinent nursing home residents and facility nursing staff, participants were given definitions of and information about UI treatment options (indwelling catheter, prompted voiding, adult diapers, electrical stimulation, and medications). Residential care residents (n=70), who tend to be more independent and cognitively intact than nursing home residents, were proxy respondents and a small number of cognitively intact nursing home residents (n=9) were also included. [471]. Respondents rated preferences between pairs of treatment options Residents and family members were evenly divided between “definitely” and “probably” preferring prompted voiding versus diapers. Almost 80% of nursing staff, however, preferred prompted voiding to diapers. Families perceived staff members as unwilling to perform prompted voiding, and some thought prompted voiding was degrading and bothersome to the resident. A German study with 117 geriatric hospital patients (mean age 85; 43% with UI), 72 staff members, and 71 family members, found that most patients preferred diapers (79%), medications (78%), and scheduled toileting (79%) over urinary catheters, and 64% preferred scheduled toileting [472]. When choosing between diapers and medication, equal proportions preferred each option. Patients with greater functional dependence were more likely to prefer catheters, and those with experience with diapers were more likely to prefer medications and toileting. Spouses showed moderate to almost perfect agreement with patient preferences, but other family proxies had only slight to fair agreement. In a qualitative study of 25 women with pelvic floor dysfunction living in residential facilities, residents expressed a desire to live with their problem rather than undergo assessment and management, emphasizing the need to include the patient in management decisions at the outset [473].New evidence for preferences among frail older persons is scant. Only one retrospective study of women seeking care at a pelvic medicine clinic for pelvic organ prolapse and urinary incontinence was identified [474]. Women who preferred conservative treatment to surgical treatment at first visit tended to be older (mean age 64.5 ± 13.5 vs 59.0 ± 11.7 years), however no data were collected on cognitive or physical function, so whether they represented a frailer group is unknown.

6. COSTS AND BENEFITS OF TREATMENT OF UI IN FRAIL OLDER ADULTS

An overall discussion regarding UI-related costs is covered by Committee 21, Economics of Incontinence. The following discusses UI cost issues specific to frail older adults.

6.1. Estimating Costs

For most developed countries, the greatest increase in population is occurring in the oldest old, those > age 85. This group has the highest prevalence of UI, and accordingly the increased prevalence of lower urinary tract symptoms will result in higher UI care costs. Such an increase was observed between 1992 and 1998 amongst US women aged > 65 [475]. The costs of care for older persons has been estimated at dou-ble that for people under 65, but care for those older adults living in institutions was less than for community dwelling individuals [476]. Likewise, the cost of OAB in five European countries is estimated to rise by one billion Euros between 2000 and 2020 [477] and in the US it has been estimated that by 2030 the greatest increase in demand for UI care (81%) will be in older women aged 60-89 with OAB symptoms [478]. In one US study using of a community managed care population, the presence of OAB and comorbidity doubled the associated costs of UI care [479]. In South Korea, the estimated cost of treating overactive bladder was 117 billion Korean Won (KRW) in 2006 and 145 billion in 2007. The estimated total cost in treating stress urinary incontinence was 122 billion KRW in 2006 and 59 billion in 2007 [480].

Costs can be expressed as direct costs, indirect costs, and intangible costs [479]. Estimates have focused on diagnostic costs, treatment (including routine care and pads), and consequence costs (skin irritation, urinary tract infection, falls, fractures, additional nursing home and hospital admissions, longer hospital length of stay). Direct healthcare costs are most often estimated but there is a lack of meaningful research into indirect costs and those related to comorbidity in the frail older adults. Intangible costs have not been considered in these estimates because of their subjective nature and the methodological difficulty of collection and estimation. Much of the evidence for the cost of UI in older persons has been gathered from either epidemiological surveys or analyses of claims from insurance databases; these have often involved many assumptions or complicated formulae to calculate financial costs. There is a consistent theme that the cost of caring for older adults with UI will increase, but the estimated magnitude of this increase is variable.

For frail older adults, especially those in long term care, cost calculation is especially complex. The greatest costs for UI care in nursing homes are by far nursing labour costs [481]. Extrapolated costs for nursing home admission due to UI was $6 billion (2000 US dollars), with institutional costs of UI management and consequences of $5 billion (2000 U.S. dollars) [482]. In one small 6-month study, the mean daily cost of UI care, including direct nursing care, indirect nursing overhead, and supplies, was $9.09 (+/- $ 0.52) per resident (2003 U.S. dollars) [483]. The costs for UI pads alone in Dutch long-term care have been estimated at 160 million Euros [484]. In an Australian sub- acute care setting, the costs of daily UI care was AU $49, with most spent on staff wages [485]. In Canada, researchers found that 1% increase in UI prevalence was associated with an 11-12% increase in costs [486]. The extra nursing time needed to maintain toileting programmes contributes to high costs [487]. Routine garment and laundry costs may be lower than estimated because, in practice, residents are not changed as often as needed. In addition, for prompted voiding to remain effective, such things as regular refresher education programmes for staff or wet sensors may be necessary, and thus are rarely considered in cost estimates. Moreover, the time over which the costs and benefit are calculated needs to be explicit because both benefit and costs will change, and patient morbidity and mortality need to be considered. The costs of correcting functional and medical causes of UI are rarely considered. Also, the potential differential in costs across the span of cognitive and functional impairment has seldom been assessed, [204] despite evidence that UI care costs are closely related to the degree of functional impairment [205]. Some surveys suggest that the costs of care for younger community dwelling adults outweighs that associated with older persons, but there are wide variations of estimates depending upon the population studies [206].

Costs related to caregivers of frail persons with UI living in the community include lost wages, decreased productivity (both within and outside of the home), the additional number of caretaking hours when a frail person develops UI, [207] and the cumulative effect of increased strain and burden, along with any resultant illness. A qualitative study in Europe of spousal and adult child caregivers of older persons with incontinence identified effects on caregivers' quality of life, financial cost for products as well as mental and physical exhaustion [488]. Overall, there are still limited data on costs of UI treatment in other residential (such as assisted living or rest homes) and acute care settings [208], costs may vary by access to care. Frail older adults are often homebound or live in institutions without the same access to the UI therapies as other populations. Health care providers may be limited to primary care physicians, community nurses, and care assistants or aides with little to no expertise in UI management, and limited access to specialist consultation leading to a focus on behavioural management and/or containment products. An assessment of a multi-component intervention based upon absorbent products, a structured skin care regimen, and nursing advice on incontinence associated dermatitis revealed that incontinent residents used an average of 5.19 absorbent products, at a mean cost of € 1.79 per day. Following introduction of the intervention, the mean number of absorbent products consumed per day was € 2.02 per incontinent patient, at a mean cost of € 0.97 per day [209].

6.2. New studies identified

One US study using Medicare data for older adults in a single state identified that Lewy body dementia had higher costs that other types of dementia (e.g. Alzheimer's disease), which was explained in part by urinary incontinence or infection, as well as other co-occurring conditions including falls, depression, dehydration and delirium [489]. The authors suggest that dementia subtype may predict health care costs with potential mitigation through early identification and treatment. The influence of dementia type and the role urinary incontinence plays in costs needs further study.

Cost relates strongly to reimbursement, which varies considerably from country to country, depending not only on structure of the health system but special programmes for older persons and persons with UI. Within countries, there may be further variation based on insurance, co-insurance, drug versus procedure cover- age and incentives, access to care, programmes for vulnerable populations, and urban/rural differences.

6.3. Benefits and effectiveness of treatment

The ability to define the benefit of UI treatment in frail older people is highly dependent on the individual, their caregivers, and the health care system. Outcomes research indicates that patients value quality of life, which encompasses many domains beside

reduction in UI (See Committee 4, Symptom and Quality of Life Assessment). Even cognitively impaired people can still express treatment preferences [472, 490], so it is also possible to evaluate domains of quality of life (e.g., social interaction) [458] and assess treatment satisfaction directly or behaviourally. At the same time, we found no data on the value or utilities frail older adults, or their caregivers assign to varying degrees of UI (with or without treatment intervention) versus "dryness." Standard outcomes such as quality adjusted life years (QALYs) may overestimate effectiveness in older people, [491] not just because of potentially different utilities, but because of the altered importance of "years of life saved" in a population with variable and limited remaining life expectancy. However, studies continue to report QALYs. Future scenario cost analysis of implementing was used to assess a previously evaluated primary care continence nurse service in the community for older persons with urinary incontinence in the Netherlands. The authors found that while some costs increased (e.g. treatment costs and containment products paid by the insurer), reductions were found in both health care (formal home care) and social perspectives (informal care by family/friends, private home care costs and other out of pocket expenses) across four scenarios projected from 2014 to 2030 [492]. Overall, implementation was argued to have potential for large health gains and cost savings. A smaller study of nurse provided conservative treatment for older women in New Zealand rest homes reported a cost of $247.75 per participant for advisor time and travel cost, but costutility analysis was undertaken as no significant improvement in outcomes was found [427]. Larger well controlled studies of continence advisor services for older frail individuals that include cost-benefit analysis are needed.

Use of technology may shift the focus of assessment, and eventually outcomes of continence programs for older persons. A Canadian health technology study estimated the cost of a 72 hour continence assessment using an electronic monitoring system for residents in long term care facilities at $291.76 (CAD) resident, including the device, materials and development of a care plan [410]. They concluded that an electronic monitoring system had potential to health care system costs through savings in care workers time if the system improved incontinence care but expressed limited confidence in this due to the lack of certainty regarding how the electronic monitoring system would change management of incontinence. The economic benefits of pharmacological treatment of OAB in older persons is unclear, with few published studies found. A retrospective case-control study using medical and pharmacy claims from a US based healthcare network (mean age 73.32 years) found those with wet OAB had a significantly higher adjusted risk of experiencing falls/fractures and depression/anxiety after starting anticholinergic therapy than those without OAB, with total health total health care costs 33% higher for wet OAB [493] In contrast, Qin *et al.*, using a decision analytic cost model using data from a clinical trial of persons over 65 years with urgency urinary incontinence symptoms and a score ≥3 on the Vulnerable Elders Survey 13. They reported a decrease in healthcare cost in treating vulnerable older persons with the antimuscarinic agent fesoterodine compared to no treatment. Health Healthcare resource use included costs of inpatient hospitalization, outpatient visits, and physician office visits. This is one of the few studies that reported inclusion criteria that screened for frailty [494].

There is a continued need for novel and specific clinical and research outcomes related to care of incontinent frail older persons. Outcomes measured by single item tools of perceived benefit or satisfaction with treatment are unlikely to be generalisable across the heterogeneous older population. Perceived benefit of treatment cannot be measured with the same tools across cultures and health systems unless such tools are sensitive to differences in such things as reimbursement and provision of continence services and supplies. The association between expectations, preferences, and outcomes needs to be prospectively studied in relevant and representative populations. New approaches and tools to assess UI-specific quality of life in cognitively-impaired frail older adults are needed, as well as better understanding of the interaction between functional impairment and the impact of UI [458]. When QALYs are included as an outcome in UI treatment trials in older persons, they should be specifically analysed by age and health status.

Preferences for Care, Costs and Benefits of Treatment of UI in frail older adults

Summary of evidence

- Evidence for preferences for care among frail older adults is scant.
- There is beginning evidence on the potential cost saving of technology monitoring systems in long term care to support assessment of incontinence in frail older residents, but there remains lack of certainty on the effect of continence management. (**LoE 3**)
- Similarly, there is some evidence nurse led continence services for older adults in the community may be cost effective in term of formal and informal care providers, but treatment and containment costs may increase (**LoE 3**).
- The cost-effectiveness of pharmacological treatment of OAB in older persons in terms of health care system costs is uncertain (**LoE 3**).

Recommendations

- Future research on care preferences and cost benefit of treatments needs to acknowledge the heterogeneity within the population of older persons and differentiate between those older individuals who are robust and those that are frail, both in the community and long-term care.
- Future research studies need to include health system outcomes in cost-benefit analysis of using technology to assess incontinence in long term care residents, nurse led continence services in the community and pharmacological treatment of OAB in frail older persons.
- When QALYs are included as an outcome in UI treatment trials in older persons, they should be specifically analysed by age and health status.

7. ISSUES IN DRUG TREATMENT

7.1. Age related changes in pharmacology

Specific age-related changes in pharmacokinetics, alteration in drug absorption, distribution, metabolism and clearance, and their potential effect on UI drugs, are shown in Table 8. Age-related pharmacokinetic changes are rarely considered in planning the duration of time off previous UI medications, placebo run in periods, and wash-out periods in UI drug trials in older persons. Typically, a two-week washout from other drugs, three weeks for solifenacin and mirabegron, is planned, regardless of age. The numerous factors potentially affecting drug clearance in older, frail patients,

as well as previous and/or cross-over compounds, may confound observed drug effects. Age-related changes in pharmacodynamics have been described for benzodiazepines, beta-adrenergic agents, and opiates [495, 496] but there are few available data concerning change, even in these, other than for limited numbers of community dwelling older people, often with median age of around 65 years old.

7.1.1. Availability of low dose agents

One effect of the underrepresentation (if not exclusion) of frail older persons in UI drug studies is a lack of knowledge regarding minimal effective drug doses for this population. The age-related changes in pharmacology noted above suggest that some UI drugs may be effective at lower than standard doses in frail older adults with concomitant decreased adverse effects [497]. This issue is especially relevant for extended-release preparations, which cannot be divided into smaller doses. There are some data supporting the effective use of low dose oxybutynin in older adults [498, 499] with few adverse events reported. A single study has assessed low standard doses of trospium chloride and solifenacin in combination in older persons (not frail) of average age 69. 4 years in comparison to higher doses showing higher efficacy of combination lower dose therapy [500].

7.2. Polypharmacy

Accompanying the rise in multimorbidity, unsurprisingly, there has been a concomitant rise in the prevalence of polypharmacy in older adults reported across multiple countries [501-503]. The increase may be precipitated by adherence to disease specific clinical treatment guidelines [504-506]. As the number of prescribed medications increases, so does the risk of drug-drug and drug-disease interactions. Approximately 60% of people over age 65 take at least one prescribed medication, and about one-third take more than five prescribed drugs. There is evidence from some jurisdictions which suggests a reduction in potentially inappropriate medication exposure in older adults [506-509].

However, the rates of polypharmacy are highest in the oldest old, those in their ninth decade of life, frail older adults and those older adults living with dementia [510, 511]. There are also data suggesting under prescription of indicated medications in frail older adults suggesting that there remains a careful need to analyse the relative risks and benefits of disease treatment in this group [512].

Many older adults take over the counter (OTC), naturopathic or herbal agents and dietary supplements, with the rate of use varying across countries and cultures. In a Japanese cross-sectional study 32.5% of 729 patients aged ≥65 years with chronic diseases used such substances, Vitamins were the most commonly used dietary supplements. Female sex, higher education, and good economic status were identified as predictors for use. Concurrent use with more than 5 prescription medications was present in 12.2% of participants and 1:3 people had told their usual physician about their use [513]

In a population representative study of Canadians, females aged ≥71 years had the highest prevalence (67.8%; 95% CI = 64.1-71.5) of vitamin/mineral supplement use. Female gender, older age, higher education level, higher income, living in urban areas, having chronic conditions, having a normal body mass index (BMI), and being non-smoker were independent positive predictors of vitamin/mineral supplement use among adults. In the US, use of dietary supplements is high, with 29% of users regularly taking ≥4 DSs. There is a high concurrent usage with prescription medications. [514] A US study comparing changes in usage of OTC medications and supplements between 2005-2006 and 2010-2011 found increases in use and in 2010-2011, 15.1% of older adult users were at risk for a potential major drug-drug interaction compared with an estimated 8.4% in 2005-2006 [515]. In the Health Ageing and Body Composition Study of 3055 adults aged 70-79, over 1/3 had at least one potential drug-drug and drug-disease interaction [516]. Non-prescription medications (NPM) are also felt to be of low risk. In a Scottish study investigating this, just over half (57%) of the 927 respondents perceived NPM to be associated with low general risk. interestingly, those who judged NPM higher risk were less likely to disclose information during consultations than those with low-risk perception [517]. The likelihood of adverse drug reactions (ADEs) and drug interactions rises exponentially as the number of medications increases. This approach is relevant in geriatric UI, as UI may have been precipitated and/or worsened by medications (see Table 3). Changes to existing drug regimens should be considered in the management of UI in all frail older adults.

7.3. Adverse drug effects (ADE)

ADEs are extremely common in older persons, [518]. Although the prevalence of drug – drug and drug disease interactions in older persons is high, there are limited data on important clinical outcomes, largely due to the varying nature of the reporting of events [519]. In a systematic review of studies that examined drug-related hospital readmission, rates of readmissions due to drugs varied from 3% to 64% (median 21%, interquartile range (IQR) 14-23%) but generally were higher in older adults [520]. In an Australian study, adults aged between 65 and 84 years accounted for nearly half of ADR hospitalisations (45.6%). Over the period of comparison, 2001-2002 to 2012-2013, age-adjusted rates of ADR-related hospitalisations nearly doubled and increased by 5.8% (95% CI: 5.0-6.6%) per annum, with an in-hospital death rate increase of 2.4% (1.6-3.3%).

Table 8. Pharmacokinetic changes in older persons

Parameter	Age-associated Changes	UI Drugs Potentially affected
Absorption	Minimal quantitative change despite ↓ gastric motility, yet little known regarding effect on slow-release agents	Extended-release preparations
	↓ Skin thickness	Transdermal preparations
Distribution	Decrease in lean body mass leads to ↓ Vd / ↓ T½ for hydrophilic drugs and ↑ Vd/↑T½ for lipophilic agents	Lipophilic agents, tricyclic antidepressants
	Decreased protein binding in frail patients with low albumin, leading to higher concentration of free drug	Tolterodine
Hepatic metabolism	↓ Phase I reactions (oxidation/ reduction)	Tricyclic antidepressants
	No change in Phase II reactions (glycosylation)	
	↓ Hepatic blood flow and ↓ hepatic mass, leading to reduced clearance for agents with first-pass metabolism	Oxybutynin Tolterodine Solifenacin Darifenacin
	Stereoselective selectivity in metabolism (hypothetical)	Enantiomers
	Cytochrome P450	Oxybutynin Tolterodine Solifenacin Darifenacin Mirabegron 5HMT, (clearance only)
Clearance	Decrease in renal clearance	Tolterodine Fesoterodine (5-HMT)

Of particular interest are ADE related to antimuscarinic therapy because of age, and comorbidity-related changes in muscarinic receptor number and distribution, blood-brain barrier transport, and drug metabolism [521]. Whereas antimuscarinic ADEs in younger persons are bothersome, in frail older adults, they can result in serious morbidity such as sedation, heat intolerance, prolongation of delirium and use in some retrospective analyses is associated with an increased risk of dementia diagnosis [522].

Since the last consultation, a systematic review has examined the risk for AEs between older and non-older adults with OAB. Of the six included studies that made nine comparisons between older and non-older subjects, the AEs of dry mouth (46.7%), constipation (10.3%), and headache (7.7%) were most frequently reported. Older subjects were more likely to experience dry mouth (relative risk [RR] 1.09; 95% confidence interval [CI] 1.00-1.19), constipation (RR 1.92; 95% CI 1.52-2.43), dizziness (RR 2.37; 95% CI 1.21-4.62), and urinary retention (RR 4.17; 95% CI 1.76-9.89) than were non-older subjects. Treatment discontinuations due to AEs were more likely to occur in the older subjects (RR 1.59; 95% CI 1.20-2.11). In a separate review examining AEs and treatment discontinuations in adults 65 or older taking antimuscarinics for OAB, anticholinergic AEs were more common compared to placebo. Incidence of dizziness, dyspepsia, and urinary retention with fesoterodine, headache with darifenacin, and urinary tract infections with solifenacin were significantly higher compared to placebo. Treatment discontinuation due to AEs and dry mouth were higher in the antimuscarinics when compared to placebo in older adult [523]. No frail older adult data were available.

The evidence relating to individual AE are available in the 6th Consultation and are not repeated here. Readers are referred to the previous chapter.

7.3.1. Anticholinergic medication and cognitive impairment

A major antimuscarinic ADE of concern in frail adults is cognitive decline. There has, since the last consultation been several associative reports linking anticholinergic medication to cognitive impairment, an increase in incident dementia diagnosis and a possible increase in mortality [48, 522, 524, 525].

Medications with anticholinergic properties are commonly used by older adults and older adults living with dementia. For example, in a US retrospective, cross-sectional study of adults aged 65 years and older using 2012 American Geriatrics Society Beers Criteria, 9.56% (7.51 million) older adults used potentially inappropriate anticholinergic medications in 2009-2010; those aged 75-84 or ≥ 85 years did, however, have a decreased likelihood of receiving them [526]. Of 964 older persons attending an Australian memory clinic, potentially inappropriate medications affecting cognition were used by 206 (21.4%) patients. Anticholinergics and sedatives were the most common. One hundred and thirteen (11.7%) patients had a clinically significant anticholinergic burden score (≥3) [527]. As much as there is a reported increase in overall medication prescribing for older persons, temporal trends also reveal an increase in anticholinergic medication prescribing for older adults [528]. Due to the nature of the cohorts of persons studied, data on medications used for overactive bladder and urgency incontinence are limited to identifying immediate release oxybutynin as a consistent significant factor in exposure. In the study of Gray [49], over 10 years, those with the highest cumulative burden of oxybutynin exposure had a significant association with cognitive impairment. In a systematic literature review and meta-analysis aimed to assess the impact of ≥3 months of exposure to anticholinergics on the risk of dementia, mild cognitive impairment, and change in cognitive function, 21 studies underwent qualitative synthesis and 6 reported endpoints relevant for inclusion. The overall rate ratio for incident dementia was 1.46 (95% CI: 1.17-1.81; 95% PI: 0.70-3.04; n = 6). The risk of incident dementia increased with increasing exposure (n = 3). In addition, two studies from the meta-analysis reported an increased risk of dementia with ≥3 months of use of bladder antimuscarinics (adjusted odds ratios ranged from 1.21 to 1.65, depending on exposure category). This relationship was consistent in studies assessing overactive bladder medication [529]. In a retrospective cohort study of 71 688 Medicare claims, there appeared to be no difference in the strength of association between “bladder selective” and non-selective agents according to level of exposure, Odds ratios for non-selective use

were 0.97 (CI: 0.89-1.04) for the lowest quartile of exposure, 0.94 (CI: 0.83-1.06) for the 2nd quartile, 1.00 (CI: 0.87-1.16) for the third and 1.03 (CI: 0.88-1.20) for the highest. [530].

Cognitive effects may be under-detected because they are clinically subtle, neither asked about nor reported by the patient, or mistaken for age-related diseases and ageing [531, 532]. A 2014 systematic review of the effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality examined 46 studies including 60,944 participants; 77% of included studies evaluating cognitive function (n = 33) reported a significant decline in cognitive ability with increasing anticholinergic load. Four of five included studies reported no association with delirium and increasing anticholinergic drug load (P > 0.05). Five of the eight included studies reported a decline in physical function in users of anticholinergics (P < 0.05) [533]. A recent study investigating the association between anticholinergic medication use and neuroimaging biomarkers of brain metabolism and atrophy in 52 cognitively normal adults, mean [SD] age, 73.3 [6.6] years in the Alzheimer's Disease Neuroimaging Initiative and the Indiana Memory and Ageing Study found showed lower mean scores on Weschler Memory Scale-Revised Logical Memory Immediate Recall, Trail Making Test Part B and a lower executive function composite score in participants taking anticholinergic medications compared to those participants not taking such medications. Reduced total cortical volume, temporal lobe cortical thickness and greater lateral ventricle and inferior lateral ventricle volumes were also seen in the participants taking anticholinergic medications compared to those not taking such medications [534]. It is clear that duration of exposure and extent of exposure to medications with anticholinergic properties are significant factors in the observed associations with cognition. Many scales exist which purport to measure anticholinergic burden, each varies in its utility in identifying anticholinergic load. The clinical results in studies using these scales are different depending on the scale used and upon the different methods used in their development [535]. Persons with pre-existing cognitive impairment (especially from conditions known to affect central cholinergic pathways) may be at greater risk for cognitive impairment although there are also some data to suggest that those with established dementia may not experience cognitive decline following therapy with anticholinergic agents [50]. Additionally, a meta-analysis examined the relationship between serum anticholinergic activity and decline in cognitive performance, delirium, and functional impairment. The review included 4 RCTs, 5 prospective cohort studies, 3 longitudinal cohort studies, 17 cross-sectional studies, and 4 case-control studies. Twenty-four of the retrieved studies examined an association between SAA and cognitive outcomes, 2 studies examined an association with SAA and functional outcomes and 8 studies examined associations between SAA and both cognitive, and functional outcomes. The meta-analysis on 4 RCTs showed no association with higher SAA and cognitive performance however, the pooled data from 4 observational studies showed elevated SAA was associated with reduced cognitive performance (I2 = 0.00%, H2 = 3.37 and p-value = 0.34) [536]. For older adults living with dementia, use of non-selective antimuscarinics was associated with a 50% increase in mortality risk among older adults with dementia and OAB in a propensity matched retrospective new-user cohort study of 16,955 community dwelling Medicare claimants [537]. A related study found no effect on rate of falls or hospitalisation in older adults with dementia and OAB using nonselective and selective antimuscarinics [538].

7.4. Drug interactions

Because frail older adults take higher numbers of drugs and usually have several comorbid conditions, drug interactions are more common [539]. All antimuscarinic agents for UI will have additive side effects when combined with other anticholinergic agents.

Drug-drug interactions for oxybutynin, solifenacin, darifenacin, and tolterodine include potent CYP3A4 inhibitors (azole antifungals, macrolide antibiotics, cyclosporin, and vinblastine). Fesoterodine, a pro- drug that is converted to tolterodine by non-specific esterases, is also dependent upon CY3A4 for its excretion. There is one case report of interaction between tolterodine and warfarin in 2 older patients, which [540] has not been seen in healthy volunteers. Naturopathic/ herbal preparations should also be considered for potential interactions, especially in areas where these agents are frequently used. Potential drug-drug interactions with mirabegron, a beta-3-agonist for the treatment of overactive bladder have been evaluated in younger healthy subjects, between mirabegron and metformin, warfarin, digoxin, or a combination oral contraceptive. Changes in maximum concentration of metformin and digoxin were observed, but no dose adjustment of either drug is required when mirabegron is administered concomitantly with metformin, or warfarin. The authors suggested that patients receiving mirabegron with digoxin may require additional monitoring of digoxin concentrations with dose adjustments where needed [541].

Evidence regarding the co-prescription of bladder antimuscarinic agents and cholinesterase inhibitors (CEIs) used for dementia are of poor to moderate quality. There is evidence CEIs can cause or worsen UI from a case report [542] and also a case series of 216 consecutive patients with probable Alzheimer's disease attending a memory treatment centre [543], but this finding has not been replicated in a large Dutch dataset analysis [544]. In the case series, CEI treatment was overall associated with 7% risk of new UI: the highest risk was observed in patients with more behaviour problems, and lower risk in patients who demonstrated positive cognitive and/or behavioural response to CEI. Further evidence for an interaction between antimuscarinics and CEIs comes from a database study of nursing home residents in one US state [545]. Residents with dementia, newly treated with cholinesterase inhibitors, were more likely to then be prescribed a bladder antimuscarinic than those residents with dementia not given a cholinesterase inhibitor, an example of a geriatric "prescribing cascade", a finding replicated in a 2016 Finnish study. [546, 547]. In a cross-sectional survey to determine the proportion of nursing home residents with overactive bladder or urinary incontinence with potential contraindications to antimuscarinic treatment because of concomitant anticholinergic medications or acetylcholinesterase inhibitors (AChEIs) 71.3% received at least one anticholinergic medication. CEIs and antimuscarinic treatment were prescribed concurrently in 24% [548]. Concomitant use of antimuscarinics (extended-release oxybutynin and tolterodine) and cholinesterase inhibitors in nursing home residents was associated with a decline in ADL function in the most functionally able residents but there was no worsening of cognition, probably because the cognitive measure (MDS-COG) was inadequately sensitive. More importantly, there was no case of delirium observed [549]. In a study in which the primary objective was to assess the cognitive impact of trospium chloride in older people with dementia treated with galantamine over a six-month period, 46 subjects with UI and dementia were enrolled, 10 withdrew from the study. No effect on cognition or activities of daily living was detected over the duration of the study. A within group analysis demonstrated an improvement in nocturia and reduction in pad use in this combination group [550]. A small study reported some positive effect of the treatment of UI with propiverine in subjects with probable AD taking cholinesterase inhibitors [551]. The practice appears to be common in Finland [552]. Although intuitively illogical, given the opposing pharmacological actions, there seems to be no reason

not to use bladder antimuscarinics for older people with dementia, ensuring that the cholinesterase inhibitor is warranted and effective, that the incontinence is sufficiently bothersome to warrant treatment and that the patient (where possible), and the caregiver are fully informed. The current weight of evidence appears to be that a positive outcome in terms of bladder control can be achieved without a significant detriment in either cognition of activities of daily living.

7.5. Potentially inappropriate drugs for older adults

Efforts at quality improvement for older populations have led to the development in several countries of expert consensus guidelines regarding inappropriate drugs for older persons, although the continuing relevance of these guidelines has been questioned and alternative systems suggested. A revised Beers criteria was published in 2019 [553] These guidelines focus on drugs with lower risk-benefit ratios and higher potential for drug-drug and drug-disease interactions, and are used for nursing home regulation and quality performance measurement. All bladder antimuscarinics are included with respect to their anticholinergic properties. The Fit fOr The Aged (FORTA) criteria with respect to drugs for lower urinary tract symptoms systematically review available evidence for the use of medications adults >65y with multimorbidity and assign levels of appropriateness according to the available data. A Delphi process is used to assign drugs into A, Absolutely, B, Beneficial, C, Caution and D, Don't criteria. Of all lower urinary tract drugs, fesoterodine achieved a Beneficial grade. Most drugs were placed into the Caution category, reflecting either deficiencies in, or absence of, available data [554].

8. SPECIAL ISSUES IN FRAIL OLDER MEN

Although their ranks thin into the ninth decade, men still comprise a significant portion of frail older adults. The prevalence of UI increases in men after age 80, going from about one-third of the rate in women to become equivalent. At the same time, frail older men are under-represented in UI treatment trials, whether behavioural, pharmacological, or surgical (see also Committee 10: Surgery for Urinary Incontinence in Men). This under representation is unfortunate, because results from treatment trials in frail women cannot be directly extrapolated to men for several reasons:

8.1. Differences in comorbidity

Frail older women have higher rates of functional impairment, chronic disease and geriatric syndromes [555] which may mean that frail older men may be more likely to respond to behavioural intervention. For older adults who become incontinent, a composite measure of physical performance (rising from a chair, walking, balance) is a better predictor of UI incidence in men than in women [556].

8.2. Differences in caregivers

More older men have living spouses who can provide care, with a potential impact on the risk and type of caregiver burden associated with UI management.

8.3. Prostate cancer

Nearly all men in their ninth decade have histological evidence of prostate cancer. However, it is not clear that frail older men have an increased risk of prostate cancer-specific mortality, especially given that their remaining life expectancy (RLE) is primarily affected by comorbid conditions. The need to screen for and treat prostate cancer diminishes with functional status, comorbidity, and RLE [557]. At the same time, more men are living with the sequelae of prostate cancer treatment, particularly stress UI after radical surgery. In several studies and metanalyses different techniques are discussed with a primary focus on a possible improvement through robotic assisted radical prostatectomy (RARP) [558, 559, 560]. None of these studies analyzed specific risk factors for older or frail older. Physicians tend to underestimate the incidence of urinary incontinence following radical prostatectomy and age seems to increase the magnitude of this underestimate [561].

8.4. Benign prostate disease

The prevalence of histological BPH, BPE, and BOO increase with age, and is associated with LUTS, UI, and DO. In a urodynamic study of older adults, 29% of men had BOO and 59% had DO as the predominant cause of UI, versus 4% BOO and 61% DO in [44]. Bortnik *et al.* give an overview of modern best practice in the management of BPE. They state that often medical therapy for BPH has been thought to be both safe and effective, however, newer studies sow a seed of doubt [562]. Antimuscarinics and alpha-blockers are associated with AE which might outweigh the benefit of treating older men with these drugs [554]. That the major trials studying the efficacy of these medications are limited as they did not focus on older men and were not of sufficient duration to make meaningful conclusions regarding long-term side effects. Surgical treatment for BPH might be an alternative. There has been a push for minimally invasive, office-based procedures which can be performed without general anesthesia. However, AUA recommendations on minimally invasive techniques such as the use of Prostatic UroLift®, RezümTM or Aqua Ablation are based on prostate size and not on comorbidities [563, 564]. A systematic review and meta-analysis comparing endoscopic enucleation vs endoscopic vaporization and laser enucleation procedures vs laser vaporization procedures included 16 studies with 4907 patients. Endoscopic enucleation and laser enucleation procedures were favoured regarding perioperative factors, rate of complications, and functional outcome. The authors stated that the clinical significance of their findings remained unclear and did not evaluate data in relation to risk factors common in frail older men. However, photoselective vaporization and enucleation of prostate might be beneficient for frail older men due to the better control of bleeding [565]. European Association of Urology (EAU) guidelines recommend laser vaporization and enucleation for anticoagulated patients while HoLEP, PVP, and ThuLEP are recommended by the American Urology Association (AUA) Guidelines [566, 567]. Prostatic stenting – either temporary or permanent is not mentioned in the AUA guidelines. The EAU recommends the use of prostatic stents as an alternative to catheterization -although the use of prostatic stents is rare due to the associated rate of complications. New types of prostatic stents are in clinical trials and, if approved, might add to the therapeutic armamentarium, especially for frail older men.

8.5. Risk of urinary retention

Because of age-related decrease in detrusor contractile function and increased likelihood of BPE and BOO, it is often assumed that frail older men have a higher prevalence and risk of urinary retention. However, this has never been demonstrated. Among NH residents with UI, the prevalence of underactive detrusor was similar in women and men (38% and 41%, respectively), despite the higher prevalence of BOO in men [44] [44, 88].Ahmadi *et al* demonstrated in a single centre RCT with 172 patients that condom sheet placement to prevent postoperative urinary retention showed no benefit [568].

8.6. Differences in device usage
A nationally representative survey of adults in the US showed that older men were nearly three times less likely than older women to use pads to contain leakage (15% vs. 45%) [569]. Data from Scandinavia, where some countries provide absorptive pads as part of the health care benefit, showed that this gap might be narrowing (22% vs. 48%), and that increased functional impairment was associated with greater pad usage [570]. In a survey of patients recruited from family practice clinics in the Netherlands, the sex difference for pad usage by older adults with UI was even higher, with 4 out of 5 women using pads versus 1 of 9 men using pads [571]. Men are also more likely to be users of indwelling catheters, both in the long-term care setting [371] [572]. There remain few data and little guidance on use in men.

8.7. Differences in medical treatments
There are medications that might be used by only one sex or might have distinct side effect profiles. For example, alpha-adrenergic antagonists, in particular, should be cautiously considered in men due to their potential side effect of causing orthostatic hypotension. The interactions of UI and other conditions with regards to orthostatic hypotension and risk of falls merits attention. In a German registry of 3,414 patients with Parkinson's disease, for those with urinary incontinence (716; 21%), orthostatic hypotension was reported for 14% of the men, yet only 9% of the women [573]. On the other hand, for women and men who had strokes and urinary incontinence, both were equally more likely to sustain a fall after stroke, though women were more likely to sustain an injury (OR 1.5) than were men [574]. The use of tamsulosin has been associated with an increased risk of cognitive impairment in older men a single study [575] although this finding has not been replicated by others [576].

8.8. Differences in surgical treatments
There are gender-specific devices and surgical approaches that do require active management on the part of the patient. In particular, certain frail older men might not be appropriate for placement of an artificial urinary sphincter due to co-morbidity, medications and cognitive and/or functional impairment. This would not allow for the individual to manage the device on his own (Grade C) [577].

Despite these issues, evaluation and management of UI in most frail older men follows the same roadmap as for women (see Algorithm).

Summary of the evidence

Age-related changes in pharmacokinetics affect antimuscarinic drugs for UI and should be incorporated into treatment planning. **(LoE 1-2)**

Drugs may be effective at lower doses in frailer compared with healthier older adults **(Level 3)**

Polypharmacy increases the chance of adverse reactions to drug therapy. **(LoE 1)**

Adverse drug events are more common in frail older adults. **(LoE 2)**

Drug-drug and drug-disease interactions are common in frail older adults **(LoE 1-3).**

Antimuscarinics for treatment of overactive bladder remain as potentially inappropriate medications for frail older adults according to the Beer's criteria **(LoE 3-4)**

Specific guidance for drugs for LUTS in older people exists, this may, with caveats, guide practice **(LoE 3).**

VI. TREATMENT OF URINARY INCONTINENCE IN FRAIL OLDER ADULTS

1. LIFESTYLE INTERVENTIONS

Lifestyle interventions are recommended in clinical practice guidelines to treat UI [578-583], and in the 6th ICI management recommendations for women, men, and frail older adults. New systematic reviews were published on weight loss interventions in overweight and obese women [584]; non-antimuscarinic treatment for overactive bladder in adults [585]; and nonsurgical interventions for UI in women [586]. Trials reported in these reviews and recent studies on individual lifestyle interventions were predominantly conducted in healthier younger and older adults (See Committee 8, Adult Conservative Management. No new studies on lifestyle interventions in frail older adults were published.

Weight loss has the strongest evidence for improving stress UI and overall UI in obese or overweight women and men (See Committee 8, Adult Conservative Management; [584]. However, weight loss interventions may be inappropriate for or impractical to use in frail older adults. Caution should be exercised in recommending fluid restrictions as inadequate fluid intake and dehydration are common in long-term care residents [587, 588], assisted living memory care residents [589], and newly admitted frail older hospitalized patients [590]. Dehydration may increase the risk of UI and its severity in frail older adults because of its significant association with constipation and delirium, both known risk factors for UI [591, 592]. The 6th ICI found limited evidence that increased hydration for incontinent frail older adults may decrease UI.

1.1. Recommendation
In the absence of trials in frail older adults, no recommendation can be made about any individual lifestyle intervention for prevention or treatment of UI. If modifiable lifestyle factors are established as risk factors for UI, these could be targeted for treatment if assessment warrants this. There remains a need for rigorous studies to evaluate lifestyle interventions in the prevention and management of UI in frail older adults.

2. BEHAVIOURAL INTERVENTIONS

2.1. Voiding programmes
Voiding programmes are used predominantly with frail older adults, some who require active caregiver participation. Voiding programmes can be used for older adults with cognitive and physical impairments who have difficulty learning new behaviours or difficulty actively participating in self-care activities, as well as in frail older adults without these impairments. They include:

- **Prompted voiding (PV)**, involving prompts to toilet with contingent social approval, is designed to increase patient requests for toileting and self-initiated toileting, and decrease the number of UI episodes. It has been used for older adults in long-term care settings and homebound older adults [593, 594].

- **Habit training** requires the identification of the incontinent person's individual toileting pattern, including UI episodes, usually by means of a bladder diary. A toileting schedule is then devised to pre-empt UI episodes; no attempt is made to alter an individual's voiding pattern [595].
- **Timed voiding** involves toileting an individual at fixed intervals, such as every 2-3 hours. This is considered a passive toileting programme; no attempts are made at patient education or reinforcement of behaviours, or to re-establish a voiding pattern. Other terms used to describe timed voiding are scheduled toileting, routine toileting, and fixed toileting [595].
- **Bladder training (or bladder retraining)** involves a progressive voiding schedule in combination with patient education that incorporates teaching of strategies for suppressing urgency and delaying voiding. This intervention is used in motivated individuals who do not have cognitive or physical impairments [596].

2.2. Summary

Prior ICI reviews found limited evidence that supported the short-term effectiveness of PV alone or in combination with functional exercise training to improve mobility and toileting skills. Since the last review, three RCTs on PV in nursing home populations were published [Table 9]. A RCT testing a staff-implemented PV protocol in 52 residents from five Hong Kong nursing homes found statistically significant improvements in wet episodes/day, incontinence rate/day, and total continent toileting/day but not self-initiated toiletings at 6 months, suggesting the effects can be sustained [413]. Overall, there was a 9.1% decrease in the incontinence rate. In 28-day trial of a PV protocol conducted by researchers with staff assistance with 12 nursing home residents in Indonesia, there were statistically significant improvements in Incontinence Severity Index scores [597]. In an 8-week cluster RCT, ultrasound-assisted PV resulted in a statistically significant reduction in daytime urine loss measured by pad weights in 80 residents from 13 Japanese nursing homes compared to a conventional PV [414]. There were no differences in residents' generic quality-of-life scores nor staff's burden scores; however, within group staff burden scores were significantly worse in the conventional PV group. This new trial, along with prior evidence, indicates that ultrasound-assisted PV may be superior to conventional PV.

Earlier studies used research staff to implement PV; however, the new studies indicate that it may be feasible when administered by nursing home staff, although this might be country specific. The 6th ICI identified that treatment response could be predicted by a three-day PV trial prior to actual implementation. Predictors included: appropriate toileting rate greater than 66%, a wet check rate less than 20%, ability to pass a simple cognitive screening procedure of a one-step command, and the ability to transfer without human assistance. This approach was not incorporated in recent PV trials and may have affected UI outcomes. PV studies continue to be limited by sample size, methodological weaknesses, including lack of staff adherence measures, and use of different outcome measures making comparisons across studies difficult.

No new studies were published on habit training, timed voiding, or bladder training since the last review. The 6th ICI found bladder training was effective in the short-term for older women, some of whom may be frail.

2.3. Recommendation

PV with and without exercises to improve mobility and toileting results in modest short-term improvements in daytime wetness rates and UI and is recommended for nursing home residents and home care clients (**LoE 1**). Ultrasound-assisted PV may offer greater benefit for nursing home residents than conventional PV (**LoE 2**). A 3-day PV trial is recommended to predict which frail older adults can benefit from PV (**LoE 1**).

Based on limited evidence, no recommendations can be made about the other voiding programmes. Habit training and timed voiding may be effective in frail older adults (**LoE 4**). Bladder training may be effective in motivated frail older women who are cognitively and physically intact (**LoE 4**).

Future research involving rigorous designs are needed to determine the effects of voiding programmes in frail older adults. Trials on voiding programmes in long-term care settings should include care process measures, staff and resident outcomes, and costs.

2.4. Pelvic Floor Muscle Training (PFMT).

PFMT has been extensively studied in adults and some older people, primarily women and men undergoing prostatectomy; however, it has had limited study in frail older adults.

2.5. Summary

Evidence from prior ICIs indicates that PFMT as a stand-alone therapy is effective for improving UI in healthy adults and non-frail older adults, and that biofeedback-assisted PFMT improved UI in homebound older adults. One quasi-experimental, 2-arm study was published that tested a 12-week programme of PFMT in 38 homebound male and female stroke patients in Turkey. Statistically significant within treatment group changes in ICIQ-SF and quality of life scores, reduced pad test weights, UI episodes, and self-efficacy scores were found [598] [Table 9].

2.6. Recommendation

PFMT should be offered to frail older adults with sufficient cognition and motivation to participate (**LoE 1**). Future research is needed to determine the most effective methods of teaching PFMT, the training regimen, and supervision needed to optimize outcomes in frail older populations.

3. MULTICOMPONENT BEHAVIOURAL INTERVENTIONS

An increasing number of trials investigate a combination of one or more behavioural interventions in the prevention and treatment of UI in long-term care and community-residing populations, predominantly in women and non-frail older women.

3.1. Prevention Trials Using Multicomponent Behavioural Interventions

Summary

Prevention trials for UI have tested interventions that combine PFMT with bladder training, the Knack (preventive pelvic muscle contraction), and/or lifestyle modifications and exercise using a variety of teaching formats (Committee 8: Adult Conservative Management). Prior research and two new RCTs [599, 600]. found that these interventions were effective in preventing UI in community-dwelling non-frail older women. There have been no published trials on prevention of UI in frail older adults.

3.2. Recommendation

Given the lack of evidence, no recommendation on multicomponent behavioural interventions to prevent UI in frail older adults can be

made. Evidence in non-frail older women suggests that multicomponent behavioural interventions that include PFMT may be effective in preventing UI in frail older women (**LoE 4**). Future RCTs are needed that test prevention strategies in continent frail older adults.

3.3. Treatment trials using multicomponent interventions

The 6th ICI found limited evidence on the effectiveness of multicomponent behavioural interventions. Five new studies were located, including one RCT in a community setting with non-frail older women [601], two RCTs with frail older adults, one in a long-term care setting with older men [602], and one in a community setting with frail older women [603] and two uncontrolled studies with older women residing in the community [604] and rest homes [427].

A RCT of an 8-week self-care programme (e.g., lifestyle modifications, PFMT, bladder training, balance and strength exercises) involving weekly group-based sessions and individual visits with research staff conducted in 61 male nursing home residents in Iran [602]. Findings indicate statistically significant improvements in ICIQ-SF scores, change in ICIQ-SF severity category (6.7% to 0% very severe, 93.3% to 10% in severe and 0% to 90% in moderate categories), and improvement in self-esteem scores were found 4 weeks post-intervention. A RCT evaluating a 12-week programme involving PFMT and tailored behavioural interventions provided by a gerontological nurse practitioner, along with weekly walking (150 minutes) and group-based strength exercises in 42 community-residing, cognitively intact, frail older women in the United States [603] found a statistically significant reduction in daily UI episodes (50%), and a higher percentage of participants perceiving improvement (81%). Although toileting skills were improved, these changes were not significant. A two-group pretest-posttest study evaluating the long-term effects of a self-management educational programme involving PFMT, lifestyle modifications, and action plans in 26 older women in rural Korea found statistically significant improvements in ICIQ-SF scores at 12-months but no difference in UI knowledge or attitude scores [604]. An uncontrolled study evaluating a 12-week programme of tailored conservative treatment (e.g., lifestyle changes, physical activity, PFMT, bladder training, and urgency suppression techniques) provided by a continence advisor nurse to 68 older female rest home residents in New Zealand found significant reductions in leakage (mean reduction 60 ml/24 hr and 4 less pads/week) and improvements in overall ICIQ-SF and perceived bother item scores, with the mean cost of $247.74 NZ/participant [427]. There was a small, but minimal clinically significant change in function, and no change in daytime frequency, nocturia, or quality of life scores.

There continues to be a lack of evidence on multicomponent behavioural interventions in the prevention UI in frail older populations. There is increasing evidence, although insufficient, that multicomponent behavioural interventions that include PFMT with and without exercise are effective in frail older adults. Studies are limited by small samples; high risk of bias; varied outcome measures; inconsistent definitions and measurement of frailty; limited racial or ethnic diversity or men in samples; little focus on nighttime UI; limited measurement on caregiver burden and intervention costs; and no long-term follow-up. The increasing number of trials incorporating the ICIQ-SF as a primary outcome measure is a positive development in being able to compare outcomes across studies.

3.4. Recommendation

Multicomponent behavioural interventions that incorporate PFMT with and other behavioural interventions should be offered to frail older populations (**LoE 2**).

Future high-quality RCTs with larger samples of frail older adults residing in long-term care and community settings, with evidence on their effectiveness in reducing UI, improving quality of life, impact on caregiver burden, their costs, and long-term benefit are needed.

4. INTERVENTIONS TO MANAGE NIGHT-TIME INCONTINENCE IN LONG-TERM CARE SETTINGS

Nighttime sleep in long-term care residents is often fragmented and disrupted, with much of this sleep disruption caused by noise, light, and incontinence care routines.

The 6th ICI found some evidence on interventions that enhance the quality and duration of sleep for long-term care residents with UI. Interventions tested include a daytime physical activity programme alone or with a night staff behaviour programme aimed at reducing noise, light, and sleep-disruptive care practices; a 2–4-hour PV schedule based on an individualised assessment of each resident's skin health; an individualised UI care routine combined with feedback to staff about methods to reduce noise levels; and 4-8 hourly pad changing regimen based on an individualised assessment of each resident's skin health. The ICI recommended that nighttime continence care in long-term care settings should be individualised based on an assessment of residents' skin health; their ability to spontaneously move in bed; their sleep/wake status, the frequency, severity, and type of the UI, and residents' preferences. Few trials on behavioural interventions in long-term care populations include nighttime frequency as an outcome. Since the last review, no new studies were located on behavioural interventions to improve nighttime UI in long-term care residents.

4.1. Recommendation

Given the limited evidence available, no recommendation can be made on a particular behavioural intervention for nighttime UI in long-term care residents. Nighttime continence care should be individualised to the residents' needs, UI and health status, functional abilities, and preferences (**LoE 4**).

Further research to guide practice is needed on residents' preferences for nighttime continence care, the frequency of nighttime pad changing regimes, as well as their impact on skin health. Well-designed behavioural trials that include outcomes on nighttime urinary frequencies and U are needed.

5. INTERVENTIONS FOR NURSING STAFF IN LONG-TERM AND ACUTE CARE SETTINGS

The 6th ICI found that nurses across all care settings (home care, acute care, and long-term care) provide urine containment interventions rather than promoting continence, and that assessment processes are inconsistently used. Nursing staff preferences for UI management (toileting) often conflict with those of residents and their families' treatment preferences (medications and absorbent products) in long-term care and acute care settings. A recent secondary analysis from the Dutch annual independent Prevalence Measure of Quality of Care found that the most common approach in care homes was a combination of absorbent products and toileting times on a set basis [605].

The previous ICI noted multiple challenges reported in conducting research in long-term care and other practice settings which include staffing ratios, staff turnover, suboptimal staff attendance at trainings, staff adherence to implementing behavioural interventions, administrative and regulatory issues, and resident/patient turnover. Because of the limited RCTs in practice settings, this current ICI review includes evidence from implementation studies that have been conducted in long-term and acute care settings [606].

6. INTERVENTIONS WITH LONG-TERM CARE STAFF

Frail older residents in long-term care settings rely on nursing staff for toileting assistance and personal care. Prior ICIs have noted barriers to implementing voiding programmes in nursing homes which include poor communication, inadequate staffing, staff workload, turnover, absenteeism, lack of UI education programmes, and the need for staff monitoring. Other barriers include the belief by nursing assistants that UI is a normal part of ageing and that nothing could be done for it or that use of incontinence pads protect and dignify residents [309]. The 6th ICI identified the need for changes at resource and policy levels to address the disincentive inherent to toileting assistance programmes that require significantly more staff time than the practice of checking and changing residents' pads.

As reduced mobility is a major risk factor for UI, interventions that can increase residents' functional skills or at the very least, minimise their physical decline may be beneficial in preventing and treating UI. A recent scoping review on toileting disability (i.e., the need for assistance to use the bathroom) in older adults residing in long-term care or assisted living facilities found limited evidence on its epidemiology, contributing factors, and validated instruments for measuring toileting disability [346]. Future research is needed to develop toileting disability measures and test multicomponent and multidisciplinary approaches on the prevention and management of toileting disability which then may result in reduced UI rates. Interventions for continence care in frail older adults should also minimize the incidence of incontinence-associated dermatitis (IAD) (See Committee 19: Management Using Continence Products).

6.1. Summary

The 6th ICI noted that education alone does not change staff behaviour and improve UI rates in care settings. Important factors in optimizing uptake of evidence into continence care practices include managerial support; sufficient resources to implement new learning; the learner's belief in the practicality of training; integration of the learning into ongoing practice; staff feeling valued; on-the-job reinforcement of learning; knowing change of practice is supported; seeing benefits of new approaches; and attitudes toward older people. Interventions tested for increasing staff knowledge of UI and improving continence care delivery in subacute and long-term care settings included a clinical leadership model involving staff empowerment and mentorship for implementing practice-based changes for continence care, and a staff training programme involving distance learning and coaching for motivating nursing home staff to adopt a best practice toileting programme.

One new systematic review was published on the effects of education about UI on nurses' and nursing assistants' knowledge, attitudes, continence care practices and patient outcomes [418]. This review noted that positive effects of education found in non-randomised and pretest-posttest studies were not confirmed in RCTs. Education combined with facilitation and/or audits and feedback did not consistently produce statistically significant differences in patient-related outcomes. Study differences were attributed to variable methodological quality; the strength and quality of the educational interventions; limitations of education in achieving behavioural and organisational change; and limitations in outcome measures that focus on UI cure or reduction. This review noted the importance of evaluating measures of care as well as cure in a population where continence restoration is not possible.

Five new studies on staff interventions in semi-acute and long-term care settings were published [Table 10], including three RCTs [65, 348, 426] and two uncontrolled studies [419, 607]. One study employing a stepped-wedged design with four clusters evaluated the effects of a 4-hour educational session and six unit-based care conferences in seven Switzerland nursing homes [65]. Pad test weights decreased in some clusters or was approximately equal at baseline, and residents had significant improvements in 7 out of 9 quality of life subscale scores. A large, pragmatic clustered 3-arm RCT involving 24 long-term care sites in four European countries investigated different facilitator development programmes that varied in the days allocated to facilitator training, months to work on unit-based implementation and evaluation, self-study, and virtual support (e.g., monthly teleconferences and email communications [426]. All arms received written UI recommendations and a slide presentation on implementation strategies. No differences were found among groups in documented compliance with UI screening recommendations, detailed assessments, individualised treatment plans, and specialist referrals. A 2-arm clustered RCT evaluated an education and training programme along with implementation strategies in three Swedish residential care facilities. The education programme consisted of five sessions that focused on implementing a person-centred approach that involved tailoring UI care plans to individual residents. Statistically significant increases in documented UI assessments and number of person-centred care actions (e.g., toilet assistance) and decreased use of incontinence products were found. Residents' quality of life scores also significantly increased [348]. A one group, pretest-posttest design of a 6-month intervention involving education, unit-based continence champions, team huddles and PV in a Canadian inpatient geriatric rehabilitation unit found significant changes in nurses' attitudes, confidence, with an 80% completion of continence assessments [607]. A 6-month implementation study to improve continence care practices using pretest-posttest chart audits in a Spanish medium-to-long stay rehabilitation ward found 100% compliance in staff documentation of UI including UI type, continence products changed as required, and completed UI discharge assessments. However, there was only a slight increase in use of PV [419].

6.2. Recommendation

Staff education alone is insufficient for improving continence care practices in long-term care. Staff education that incorporates implementation strategies may improve continence care processes (**LoE 3**). Based on limited data and mixed findings, no recommendation can be made on the type and format of staff-based interventions and implementation strategies that are most effective. The specific implementation approach may be unique to each setting. Future well-designed controlled studies are needed that evaluate care processes, staff burden, resident outcomes, and costs. Attention should be given to incorporating residents' treatment preferences into care plans.

7. INTERVENTION STUDIES WITH ACUTE CARE STAFF

Summary
Four new uncontrolled studies were published that evaluated staff-based interventions for older hospitalised patients {Table 10). A study using pretest-posttest chart audits evaluating education workshops and teleconferences for older patients undergoing hip surgery in two orthopaedic units in Swedish hospitals found that only one unit increased their UI documentation [383]. A 14-month quality improvement project in an Australian acute care hospital used pretest-posttest chart audits to evaluate an education session on a formalised continence pathway in combination with continence tools in four medical and surgical units. Increased staff compliance on all audit criteria was found with notable improvements in UI assessments, specialist referrals, and patient receipt of tailored interventions [608]. A large 1-year study with pretest-posttest chart audits implemented in the Spanish National Health Service evaluated education, use of internal facilitators, clinical audits, and feedback on continence care processes [609]. Audits in 17 participating medical, surgical, primary care/outpatient care, and nursing home units found statistically significant increases documentation of UI assessments, with a non-significant increase in care plans and patient education. Staff-based intervention and implementation studies were limited by methodological issues including lack of a comparison group, small samples, no fidelity measures, and lack of patient-based UI outcomes.

7.1. Recommendation

Education in combination with implementation strategies may be effective in improving continence care practices in acute care settings (**LoE 3**). Because of limited studies and inconsistent results, no recommendations can be made on the format and type of implementation strategies that are the most effective.

Future well-controlled studies are needed that can assess different types and formats for education as well as implementation strategies on continence care processes, staff and patient outcomes, and costs.

7.2. Interventions with family caregivers

Family caregivers of frail older adults with UI report a high level of physical and psychological exhaustion, burden, embarrassment, and social isolation [610]. This is particularly so for family caregivers of individuals with UI and dementia, especially if the care recipient has responsive behaviours. A review on qualitative studies on continence care of community-dwelling people with dementia in Europe found that the main difficulties and challenges in caregiving were personal perceptions of incontinence, availability/provision of support and care, financial cost, mobility and the environment, relationships and social inclusion, and emotional issue [611]. This and a recent study on the burdens and educational needs of family caregivers of older adults in the United States [612] indicate that family caregivers need information on UI treatment strategies, resources, and guidance to select appropriate supplies.

7.3. Summary

The 6th ICI identified that limited intervention studies have been conducted with family caregivers of frail older adults with UI. Two systematic reviews of dementia caregiver training programmes indicate these programmes primarily focuses on dementia education, management of behavioural and neuropsychological symptoms, and caregiver support, with content on UI rarely included [613] [614]. Since the last ICI, no RCTs or uncontrolled studies on UI caregiver interventions were located. One small study using a single group, pre-post design was published that described the development and preliminary feasibility testing of a 6-week multicomponent behavioural intervention involving education, PV, and social support delivered by tablet computer and weekly telephone calls with a specialist nurse practitioner [594]. This intervention involved six interactive video modules that focused on UI in frail older adults, practical help to promote toileting, PV techniques, fluid management, and skin care and UI costs, along with a 3-day PV diary. Evidence from an evaluation with three family caregivers indicated the intervention was feasible and acceptable. Technology-based interventions have the potential to increase the reach and access of family caregivers to UI education and support interventions.

7.4. Recommendation

Technology-assisted skill-based education, information, and support may be an effective approach as a family caregiver intervention (**LoE 4**).

There is a major gap in the evidence base related to family caregiver interventions for UI which offers an opportunity for future research. Well-designed RCTs are needed that address caregivers' needs for education, skill training, information on resources and UI products, and support. Intervention studies should include caregiver outcomes on burden, quality of life, and satisfaction as well as care recipients' outcomes related to UI.

7.5. What is new?

1. Several small studies on multicomponent behavioural interventions in frail older adults indicate that these may be effective.
2. Increasing use of the ICIQ-SF as a primary outcome measure in behavioural intervention studies with frail older adults enables the comparison of interventions across studies.
3. The inclusion of implementation studies of staff-based interventions that include education and implementation strategies offer a pragmatic approach for improving the quality of continence care in long-term and acute care settings.
4. The development of a feasible technology-based, educational and social support intervention for family caregivers can increase the reach and improve UI care for frail older adults.

Table 9. Behavioural intervention trials in frail older adults

Author, Year	Intervention	Study Design	Sample	Methods	Results
Voiding Programmes					
Lai *et al.*, 2017	PV	2-arm RCT3	52 male and female residents (mean age 85.4 years) from 5 Hong Kong nursing homes	6-month intervention delivered by nursing home staff with prompting q 2-2.5 hours for 12 hours/day; control group received usual care	• Intervention group had statistically significant improvements in wet episodes/day, incontinence rate/day, and total continent toileting/day • No change in self-initiated voiding
Siswoyo *et al.*, 2020	PV	2-arm RCT	12 residents (mean age 72.7 years) from Indonesian nursing homes	28-day intervention delivered by nursing staff with prompting q 2-2.5 hours over 24 hours; control group received usual care	• Intervention group had statistically significant within group improvement of ISI scores
Suzuki *et al.*, 2018	PV	2-arm RCT	80 residents (median age 85 years) from 13 Japanese nursing homes	8-week intervention delivered by nursing staff; Arm A received prompting q 2-3 hours; Arm B received prompting based on ultrasound-assessed residual urine volume at 75% of individual predetermined bladder capacity q 2-3 hours	• Ultrasound-assisted PV group had statistically significant greater reduction of daytime urine loss compared to conventional PV • No within group differences in generic quality-of-life, depression, or activities of daily living scores • No change in care burden scale scores in ultrasound-assisted PV group, whereas conventional PV scores significantly worsened
Pelvic Floor Muscle Training					
Arkan *et al.*, 2019	PFMT	2-arm quasi-experimental	38 community-residing male and female stroke patients (mean age 65.1 years) in Turkey	12-week intervention of PFMT with 4 home visits; control group received no treatment	• ntervention group had statistically significant within group changes in ICIQ-SF and quality of life scores, reduced pad test weights, UI episodes, and self-efficacy scores, whereas the control group had no significant within group changes
Multicomponent Behavioral Interventions					
Arnold *et al.*, 2016	Tailored behavioural treatments and drug management	One group, pre-test, post-test design	68 older women (mean age 85.3 years) in 26 New Zealand rest homes	12-week intervention with visits by a continence nurse advisor q 2-4 weeks; tailored behavioural interventions (e.g., lifestyle interventions, PFMT, bladder training with urgency suppression, or prompted voiding), drug deprescribing or drug therapy with anticholinergics and/or oestrogen cream)	• Intervention led to statistically significant improvements in overall ICIQ-SF and bother scores, reduced leakage and pad use and costs • Modest improvement in function, but not clinically significant • No change in daytime frequency, nocturia, or EQ-5D scores • Costs were $247.75 (NZ) per participant

Author, Year	Intervention	Study Design	Sample	Methods	Results
Voiding Programmes					
Azizi, *et al.*, 2020	Education, PFMT, bladder training, and strength exercise	2-arm RCT	61 male residents (mean age 68.2 years) in two Iranian nursing homes	8-week self-care education programme with weekly group-based education sessions, lifestyle modifications, PFMT, bladder training, and balance and strength exercises, with visits every other day by researchers; control group received no treatment	• Intervention group had statistically significant improved overall ICIQ-SF and ICIQ-SF severity category scores and improved self-esteem scores at 12-week follow-up compared to control group
Brown *et al.*, 2019	Education, PFMT, fibre and fluid modifications, bladder training	2-arm RCT with wait-list control group	121 community-residing older women with urinary or faecal incontinence, or both (mean age 75 years) in United States	4-month intervention involving small group-based education, behavioural interventions (PFMT, bladder training, lifestyle fibre and fluid modifications), personalized goal setting, and action planning delivered by trained facilitators. Control group: no intervention	• Intervention group had statistically significant improvement in ICIQ-SF, perceived percent improvement, quality of life, and self-efficacy scores • No difference in depression or care-seeking
So *et al.*, 2019	Education, PFMT, action plans	Quasi-experimental, two group, pretest, posttest	26 community-residing older women (mean age 72.7 years) in rural South Korea	5-week intervention with weekly 90 minute education sessions delivered by community health practitioner and investigators, PFMT, daily diary. Comparison group: no intervention	• Intervention group had statistically significant improved ICIQ-SF scores over 12-months • No difference in UI knowledge and attitude scores • Intervention group had statistically significant improved UI attitudes scores at 5-weeks, but scores declined lower than baseline score
Talley *et al.*, 2017	PFMT, tailored behavioural treatments, and exercise	2-arm RCT	42 community-residing, frail older women (mean age 84.9 years) in the United States	12-week intervention with 4 home visits by a gerontological nurse practitioner; PFMT, tailored behavioural interventions (e.g., lifestyle interventions, bladder training, urge suppression, medication education), walking 150 minutes/week of walking and twice weekly strength exercises; control group received no treatment	• Intervention group had statistically significantly reduced daily leaks, reported greater satisfaction and perceived improvement compared to control group • No difference in total ICIQ or quality of life scores • Toileting skills were improved in intervention group but not significantly compared to control group who declined

PMFT= pelvic floor muscle training; PV= prompted voiding

Table 10. Staff-Based Interventions in Long-Term and Acute Care Settings

Author, Year	Intervention	Study Design	Sample	Methods	Results
Systematic Reviews					
Ostaszkiewicz *et al.*, 2020	Education	Systematic review on the effects of UI education on nurses' and nursing assistants' knowledge, attitudes, continence care practices, and patient outcomes	19 studies of UI educational programs to nurses and nursing assistants (N=1301)	Literature review using PRISMA guidelines; included RCTs and uncontrolled studies	• Education improved nurses' and nursing assistants' knowledge, but most effective forms of education are not known • Lack of statistically significant changes in practices and patient-related outcomes in 3 RCTs, whereas 5 uncontrolled studies reported positive outcomes
Individual Studies—Long-Term Care Settings					
Kohler *et al.*, 2018	Education and case conferences	Clustered, stepped-wedge design with 2-arms	140 residents with dementia from 7 Switzerland nursing homes	13-month project involving one 4-hour education session (dementia symptoms and UI care), with 6 unit-based case conferences (1 hour each); control clusters nursing homes in control clusters received no intervention	• UI (pad weights) decreased in some clusters or were approximately equal to initial measurement • Significant improvements in 7 of 9 quality of life subscale scores
Lappen *et al.*, 2016	Education, implementation strategies, and PV	One group, pre-post intervention	21 nurses and 12 interdisciplinary team members on a Canadian inpatient geriatric rehabilitation unit	6-month continence care protocol involving education, unit-based continence champions, team huddles, and prompted voiding	• Significant changes in nurses' attitudes, confidence, and completion of admission continence assessments (80%) • No difference in nurses' responses on sufficient team communication and whether patients and families were informed of discharge continence care plans • No change in interdisciplinary team's responses on use of a multidisciplinary approach for managing continence, sufficient team communication, and whether patients and families were well-informed about discharge continence care plans
Martín-Losada *et al.*, 2020	Education, PV, and implementation strategies	Pre-post implementation chart audit using JBI's PACES and GRIP tools	140 nurses and nursing assistants and 60 patients (mean age74- 80 years) from a medium-to-long stay rehabilitation ward in Spain	6-month implementation involving short educational sessions (20 mins), UI champions, and PV	• Improved compliance on all audit criteria • 100% compliance in documentation of UI assessment including UI type, continence products changed as required, and UI discharge assessment • Slight increase in documented use of PV

Author, Year	Intervention	Study Design	Sample	Methods	Results
Systematic Reviews					
Seers *et al.*, 2018	Education, implementation strategies, and virtual support	Pragmatic clustered 3-arm RCT	346 male and female residents (mean age 82-87 years) from 24 long-term care sites in 4 European countries (England, Sweden, Netherlands, Republic of Ireland)	12-24-month project with dissemination of written UI recommendations and presentation on implementation strategies, facilitator development program with virtual support (monthly telephone group supervision and email communications); Type A arm (12 months): facilitators received a 3-day program, followed by 10 days over 12 months to work locally on implementation and evaluation, 12 half-days for monthly teleconferences and self-study. Type B arm (24 months): facilitators attended a 5-day program, 20 days to work on local implementation and evaluation, 24 half-day learning groups via teleconference and 24-half days for self-directed study	• No significant differences among groups in documented percentage compliance with recommendations for UI screening, detailed assessment, individualized treatment plans, and specialist referrals
Wiljk *et al.*, 2018	Education and implementation strategies	2-arm cluster RCT with matched control	54 residents with cognitive decline and 20 health care workers in three Swedish residential care facilities	10-month project implementing a person-centred approach involving 5 training sessions, staff facilitators, and tailored incontinence care plans; control group received usual care	• Statistically significant increase in UI assessments, person-centered caring actions (e.g., toilet assistance) during and 6 months after implementation • Fewer incontinence products needed to manage UI • Statistically significant increases in residents' quality of life scores
Individual Studies--Acute Care Settings					
Martínez-Gimeno *et al.*, 2021	Education and implementation strategies	Secondary analysis using pre-post implementation chart audit using JBI's GRIP tools	2492 patients from 17 medical, surgical, primary care/outpatient care, maternal care, and nursing homes in Spain	1-year project implementing UI recommendations with training, facilitators, clinical audits, and feedback	• Statistically significant increases in frequency of UI assessments • Increased frequency in care plan, and patient education
Nyman *et al.*, 2017	Education and implementation strategies	Pre-post implementation chart audit	271 nursing and rehabilitation staff in 2 orthopaedic units in Swedish hospitals	3-month intervention consisting of workshops and teleconferences on bladder function, UI, and knowledge translation. Unit-based multidisciplinary teams (nurses, physiotherapists or occupational therapists) supported by external facilitators	• Chart audits indicated increased documentation of UI and urinary problems in one unit
Trad *et al.*, 2019	Education and implementation strategies	Pre-post implementation with chart audits using JBI's PACES and GRIP tools	131 nurses and 100 adult medical and surgical patients from 4 acute care hospital wards in Australia	14-month quality improvement project. Education session (60 minutes) of a formalized continence pathway supported by continence tools (e.g., step-by-step flowchart, assessment and management guides, and pad selection guide); education facilitated by ward nurse unit managers, and clinical nurse educators	• Increased staff compliance with all audit criteria with notable improvements in UI assessments, specialist referrals, and patient receipt of tailored conservative interventions

VII. PHARMACOLOGICAL TREATMENT

1. BACKGROUND

This section deals with the management of frail older adults. The pharmacological management of UI in robust older men and women is discussed in Chapter 9, Pharmacology. Specific treatments for bladder outlet obstruction and associated LUTS in frail older men are outside the scope of this chapter; special matters relevant to the care of frail older men with UI are discussed above. For frail older men and women in nursing homes, urinary incontinence and overactive bladder appears to be associated with an excess of concomitant co-morbid conditions compared to continent residents [615] thus frail older adults with UI should undergo a comprehensive evaluation of remediable causative factors and, if practical, have had a trial of behavioural and lifestyle interventions prior to initiating pharmacological therapy. Drug treatment should not generally be used for persons who make no attempt to toilet when aided, become agitated with toileting, or are so functionally and cognitively impaired that there is no prospect of meaningful benefit.

Data for the use of pharmacotherapy for OAB in frail older people remain sparse. A systematic review in 2015, largely encompassing data published in the period covered by the 6th ICI, concluded that anticholinergics have a small, but significant, effect on urinary leakage in older adults with UUI and that "treatment with drugs for UUI in the frail elderly is not evidence based" [616]. This analysis only considered anticholinergic agents, and the beta-3 agonists mirabegron and vibegron were not included in this analysis. No new trials of pharmacotherapy for OAB in frail older adults were identified during the period of the 7th ICI. Readers are referred to previous editions of the ICI for trial data up until 2016.

2. NEW TRIALS OF SPECIFIC AGENTS IN OLDER ADULTS

2.1. Topical Oestrogens

In a small uncontrolled and unblinded trial, treatment with topical oestrogens in post-menopausal women for 12 weeks was associated with increased lactobacillus levels in the bladder and a small decrease in OAB symptoms, as measured with the 33-point overactive bladder questionnaire, OAB-q [617].

2.2. Mirabegron

The PILLAR trial compared mirabegron to placebo in 888 people aged 65 and over with OAB-wet. The participants were community-dwelling and frailty was not formally assessed. Following placebo run-in, participants were randomised to either placebo or mirabegron 25mg, increasing to 50mg at week 4 or 8 at participant or investigator discretion. At 12 weeks follow up, those in the mirabegron treated group had, on average, 2.3 fever micututions/24 hours, compared to 1.7 fewer with placebo ($p<0.001$) and 2 fewer episodes of incontinence/24 hours, compared to 1.5 fewer in the placebo group ($p<0.001$). Statistically significantly more people in the mirabegron group achieved a 50% decrease in incontinence episodes/24h and complete dryness than the placebo group (72% vs 60% and 38% vs 30% respectively) [618].

Safety and tolerability data in the PILLAR trial were also reported. TEAEs were reported in 39.4% of the placebo treated group and in 44.2% and 49.8% of those receiving mirabegron 25mg and 50mg respectively. There were slightly more TEAEs in those aged over 75 years, and no clinically significant changes to vital signs or cognitive function, measured with the MoCA and reported separately, with the change in adjusted mean (SE) MoCA total score from baseline to end of treatment in the mirabegron group being -0.2 and -0.1 in the placebo group (NS). [619, 620]

A pre-specified subgroup analysis of older people in the BESIDE study, a randomised, blinded trial studying the effects of solifenacin and mirabegron in combination. Patients remaining incontinent following 4 week run in with solifenacin 5mg daily were randomised to receive either solifenacin 5mg, solifenacin 10mg, or solifenacin 5mg with mirabegron 25mg increasing to 50mg at week 4. There were no significant differences in efficacy and safety data in the >65 year and >75-year age groups compared to those <65 years of age. The participants were community-dwelling older people, and no measurement of frailty was performed [621].

3. SAFETY CONCERNS WITH PHARMACOLOGICAL TREATMENT OF OAB IN OLDER ADULTS

A network meta-analysis of 21 RCTs of pharmacotherapy for OAB in older adults (aged ≥65 years) examined five efficacy and five safety endpoints found that mirabegron was not associated with increased odds of dry mouth (OR 0.76 (95%CI 0.26-2.37) or constipation (OR 1.08 (0.39-3.02) relative to placebo, whereas anticholinergics were associated with these anticholinergic effects (95%CI of OR 3.78-7.85 and 2.12-4.66, respectively). The overall rates of treatment emergent adverse events were similar between the groups, with antimuscarinics having slightly higher TEAE rates than mirabegron (OR vs placebo 1.46 [1.05-2.05] and 1.32 [0.78 – 2.27]) respectively [622].

4. ANTIMUSCARINIC TREATMENT AND COGNITION

There has been increasing concern in the literature around the associated risk of receiving a dementia diagnosis and cognitive decline in older people treated with drugs with anticholinergic properties, including those used for treating OAB.

A retrospective cohort study in Canada used propensity- matching to compare rates of dementia diagnoses in those treated with anticholinergic agents, most commonly tolterodine (40%), oxybutynin (29%) and solifenacin (26%) to rates in people prescribed mirabegron. There was an increased risk of dementia among anticholinergic users compared to beta-3 agonist users (hazard ratio 1.23, 95% confidence interval 1.12–1.35). There was a significant effect modification based on both sex and age; men and those aged ≤75 years on anticholinergics had the highest risk of dementia relative to similar beta-3 agonist users [522].

A prospective cohort study assessed cognition in 106 older women. Using the Montreal Cognitive Assessment score (MoCA), the authors compared changes in cognition over 12 months in people with OAB treated with anticholinergics, specifically oxybutynin and tropism chloride, and those attending for "routine gynaecological care" who did not receive anticholinergics. They found no difference between the groups, with the anticholinergic treated group and the

non-anticholinergic group both having changes of less than one point in the MoCA at 12 months [623].

A nested case-control study of 284,343 participants studied 6,864 cases prescribed bladder antimuscarinics with 18,778 controls, finding that those prescribed bladder antimuscarinics had higher odds of incident dementia with OR 1.65 (95%CI 1.56 – 1.75). Anticholinergics for OAB were treated as homogenous group with no distinction made between those anticholinergics with demonstrated cognitive effects and those without [624].

Concerns have been raised around a possible link between the use of anticholinergics for OAB and depression in older people. A retrospective cohort study using the Taiwan Longitudinal Health Insurance Database studied 1952 women with OAB, finding that those treated with antimuscarinics were more likely to be diagnosed with a depressive disorder than those treated with conservative treatment (HR 1.38, 95CI 1.15-1.64) over three years of follow up. However, no control for severity of OAB was in included, and a larger study using administrative data in Ontario, Canada compared rates of depression in older adults with OAB, being treated with antimuscarinics and the β3 agonist mirabegron. 23,622 mirabegron users and 47324 anticholinergic-treated patients. No differences in the rates of depression were found between the groups, HR 1.08, 95% CI 0.92-1.28 [625].

Asparu and colleagues studied the discontinuation of antimuscarinics in older adults living in nursing homes in the USA. In their analysis of 11,912 people, mean age 81.6 years, two thirds of people had their antimuscarinics discontinued during their time in long term care, with solifenacin and fesoterodine the least likely to be discontinued [626].

A small randomised controlled trial of fesoterodine vs placebo in older people with Parkinson's disease, with a mean age of 67, found a reduction in 24-hour micturition frequency, urgency scores, and nocturia over four weeks of placebo control and four weeks of open-label extension, with no deterioration in cognitive function over four weeks, as measured with the mini-mental state examination score [627].

Table 11. evaluable drug trials in frail older adults

Author	Population	Intervention	Outcome measure	Result	PMID
Thomas-White K *et al*	Postmenopausal women with OAB symptoms	Vaginal oestrogen twice weekly for 12 weeks	OAB-q	Improvement in OAB symptoms	32791124 [617]
Wagg A *et al*	Community dwelling older adults with OAB >12 weeks	Mirabegron 25mg, increasing to 50mg at week 4 or 8, vs placebo	Change from baseline to end of treatment (EOT) in the mean numbers of micturitions/24 h and incontinence episodes/24 h. Secondary endpoints: change from baseline to EOT in the mean volume voided/micturition, mean number of urgency episodes/24 h, and mean number of urgency incontinence episodes/24 h.	Statistically significant improvements were observed for mirabegron versus placebo in change from baseline to EOT in the mean number of micturitions/24 h, mean number of incontinence episodes/24 h, mean volume voided/micturition, mean number of urgency episodes/24 h, and mean number of urgency incontinence episodes/24 h.	31733990 [628]
Herschorn *et al*	Community dwelling older adults with OAB >12 weeks	Mirabegron 25mg, increasing to 50mg at week 4 or 8, vs placebo		Treatment-emergent AEs (TEAEs), the majority mild or moderate in severity, were reported in 39.4% of placebo patients and 44.2 and 49.8% of those who received mirabegron 25 mg or 50 mg, respectively. The most common TEAEs in mirabegron-treated patients were urinary tract infection, headache, and diarrhoea. The incidence of TEAEs was slightly higher in mirabegron patients aged ≥ 75 years than in those aged < 75 years. There were no clinically meaningful differences in changes in vital signs from baseline to end of treatment for any treatment group, and no differences were observed between mirabegron and placebo treatment groups. TEAEs tended to occur early post exposure and were not dose related.	32725584 [619]
Griebling *et al*	Community dwelling older adults with OAB >12 weeks	Mirabegron 25mg, increasing to 50mg at week 4 or 8, vs placebo	MoCA scores at baseline and week 12	No statistically significant change in adjusted mean (SE) MoCA total score from baseline to EoT in the mirabegron group (-0.2 [0.1]) or the placebo group (-0.1 [0.1]).	32183741 [620]
Gibson W *et al*	Community dwelling older adults age >65 with OAB, remaining incontinent (≥1 episode during 3-d diary) following 4-week single-blind daily solifenacin 5mg	solifenacin 5mg and mirabegron 25mg, increased to 50mg at week 4, solifenacin 5mg or 10mg for 12 weeks	change from baseline to end of treatment in average daily incontinence (primary) and micturition frequency (key secondary), number of incontinence episodes during the 3-d diary (key secondary) and change from baseline in average daily urgency and urgency incontinence episodes. Safety included treatment-emergent adverse events and vital signs.	Full analysis set included 2110 patients: 30.9% aged ≥65 yr and 8.9% aged ≥75 yr. At the end of treatment, daily, and 3-d incontinence daily micturitions, urgency, and urgency incontinence, were improved in each treatment group and age group; the largest reductions were observed with combination in each age cohort. There were no notable differences in vital signs or the incidence of treatment-emergent adverse events between treatment and age groups, with the exception of dry mouth, which was highest with solifenacin 10mg.	28916436 [621]

Author	Population	Intervention	Outcome measure	Result	PMID
Lozano-Ortega, G *et al*	Twenty articles reporting on 21 randomized controlled trials were eligible for data extraction and synthesis. NB – all these trials were in the 6th ICI			Mirabegron was not associated with an increased odds of dry mouth (odds ratio 95% credible interval 0.76 [0.26-2.37]) or constipation (1.08 [0.39-3.02]) relative to placebo, whereas antimuscarinics were strongly associated with these events (odds ratio range 3.78-7.85 and 2.12-4.66, respectively) No increased odds of experiencing overall treatment-emergent adverse events was observed for mirabegron or antimuscarinics (odds ratio range 1.25-1.55), apart from fesoterodine (2.23 [1.37-3.37]) a similar treatment effect was observed across all efficacy endpoints between mirabegron and antimuscarinics in this older population.	32960422 [622]
Welk B, McArthur E	Population-based, retrospective, matched cohort study using linked administrative data from Ontario, Canada from 2010 to 2018.	47324 new users of anticholinergic medications (oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine, trospium) to 23662 new users of mirabegron		There was an increased risk of dementia among anticholinergic users compared to beta-3 agonist users (hazard ratio 1.23, 95% confidence interval 1.12-1.35). There was a significant effect modification based on both gender and age; men and those aged ≤75 years on anticholinergics had the highest risk of dementia relative to similar beta-3 agonist users.	32167223 [522]
Iyer S *et al*	prospective cohort study assessing changes in cognition in women seen in a referral urogynaecology practice.	Women who started anticholinergic OAB medications with women not on anticholinergic OAB medications (receiving routine gynaecological care so not OAB)	106 women were enrolled, 60 in the OAB medication group (Trospium and oxybutynin) and 46 in the control	Over time there was no difference in change of MOCA score between the OAB and control groups when controlling for age, GDS score, and ACB score (p = 0.78). This association did not change when women with a neurological diagnosis were excluded (n = 6). On average MOCA scores for the OAB group increased by 0.76 over 12 months and the control group increased 0.39, with no difference between the groups (p = 0.53).	31813036 [623]
Coupland *et al*	nested case-control study took place in general practices in England that contributed to the Research primary care database. The study evaluated whether exposure to anticholinergic drugs was associated with dementia risk in 58 769 patients with a diagnosis of dementia and 225 574 controls 55 years or older matched by age, sex, general practice, and calendar time			Increased odd ratio for dementia with exposure to bladder antimuscarinic drugs (AOR, 1.65; 95% CI, 1.56-1.75	31233095 [624]

Author	Population	Intervention	Outcome measure	Result	PMID
Chung SD *et al*	retrospective cohort study examined the association between antimuscarinic use and the subsequent risk of depressive disorder using a population-based data set in Taiwan	1952 OAB women who received antimuscarinics as the study cohort and 9760 OAB women who did not receive antimuscarinics as the comparison cohort. Each subject was tracked for 3 years mean ages of the study cohort and comparison cohort were 51.5 ± 16.7 (Rx) and 51.5 ± 16.9 years (no Rx)		Adjusted hazard ratio (HR) for depressive disorder in OAB women who received antimuscarinics was 1.38 (95% confidence interval [CI], 1.15-1.64) compared with those OAB women who did not receive antimuscarinics. In addition, the adjusted HRs for subsequent depressive disorder for OAB women aged 18-39, 40-59, and ≥60 years who received antimuscarinics were 1.83 (95%CI, 1.27-2.64), 1.36 (95%CI, 1.03-1.81), and 1.16 (95%CI, 0.86-1.56), respectively, compared with those OAB women who did not receive antimuscarinics.	28378881 [629]
Welk, B McArthur A	Retrospective cohort study with administrative data	23 622 beta-3 agonist users (mirabegron) to 47 324 anticholinergic users (most commonly tolterodine, oxybutynin, and solifenacin).		The rate of depression was similar among beta-3 agonist users (11.2 per 1000 patient-years) and anticholinergic users (11.9 per 1000 patient-years). In our primary analysis, the risk of depression among anticholinergic users was not significantly different compared to beta-3 agonist users (HR 1.08 [95% CI 0.92-1.28, P = .35])	33015899 [625]
Aparasu R *et al*	Cohort study in long-term care, examining people with LOS >101 in LTC. Mean age 81.6	Discontinuation rates of anticholinergics for OAB		About two-thirds of LTNH residents with OAB discontinued their index antimuscarinic during their nursing home stay. There was significant variation in discontinuation based on the index antimuscarinic agent with lowest risk of discontinuation with solifenacin and fesoterodine.	32638205 [626]
Yonguc *et al*	63 Older adults with PD, mean age 69/6 (placebo) 65.5 (intervention) (p=0.97) H&Y score no difference between groups	Fesoterodine 4m vs placebo for 4 weeks followed by 4 weeks open label	Micturitions per day, MMSE	The number of micturition episodes per 24 h period significantly improved with the use of fesoterodine fumarate in the double-blind phase ($p < 0.001$). Also, the mean number of nocturia and urgency episodes decreased in the fesoterodine group. In the open-label phase, the mean number of micturition, urgency and urgency urinary incontinence episodes were improved significantly. The number of nocturia episodes did not change in the open-label phase. Cognitive functions were stable after 4 weeks of fesoterodine 4 mg treatment.	31642953 [627]

5. BLADDER ANTIMUSCARINICS AND DELIRIUM

Since the 6th ICI, there have been no further studies reporting on the occurrence of delirium and OAB antimuscarinics. Delirium remains a rare adverse event from bladder antimuscarinics at therapeutic doses and, apart from a general recommendation to reduce anticholinergic load in cases of delirium, as they may prolong delirium. There appears to be no reason to exclude even frial older adults from treatment based on presumed risk of delirium. (**LoE 4**)

6. CHOLINESTERASE INHIBITORS AND BLADDER ANTIMUSCARINICS

There is evidence cholinesterase inhibitors can cause or worsen UUI. Evidence of this association is discussed in depth in the previous chapter. Since the last ICI, we located one cohort study which examined the association between individual cholinesterase inhibitor (AChEI) use and antimuscarinic usage in older adults with dementia. The study included 47,059 older adults who were incident users of AChEIs. Most of these patients were initiated with donepezil (83.1%), followed by rivastigmine (12.3%) and galantamine (4.6%). Overall, 8.16% of the study cohort had incident OAB diagnosis or an antimuscarinic prescription. Antimuscarinics were initiated by 1725 (3.7%) older adults with dementia within 6 months of AChEI prescription, this varied widely across individual agents-donepezil (3.9%), rivastigmine (2.6%), and galantamine (2.9%). Cox proportional hazard analyses revealed that donepezil users had an increased risk of receiving antimuscarinics (adjusted hazard ratio 1.55, 95% confidence interval 1.31-1.83) compared with rivastigmine. The findings were consistent in sensitivity analyses. Donepezil use was more likely to lead to antimuscarinic cascade than rivastigmine [630].

There have been no further trials reporting on UI outcomes in older adults living with dementia taking cholinesterase inhibitors. Based upon limited evidence, there remains no reason not to use bladder antimuscarinics for older people with dementia on AChEI with UUI. The current weight of evidence appears to be that a positive outcome in terms of bladder control can be achieved without a significant detriment in either cognition of activities of daily living (**LoE 3**).

7. NON - ANTIMUSCARINIC AGENTS

There are no data on frail older adults or those with a dementia diagnosis. However, a prospective randomised study examining the neurological safety and clinical efficacy of darifenacin and mirabegron in patients with a history of cerebrovascular accident (CVA) who had overactive bladder was located. In 60 patients, 30 per arm, after 3 months of treatment with darifenacin or mirabegron, ICIQ bladder diary parameters improved and there was no deterioration in cognitive function measured with MoCA-B score in either of the arms. The mean change in bladder diary parameters and the MoCA-B scores was similar between the two groups. The sample size was small, frailty status was not described [631].

Patients that might be at risk of impaired cognition have been well described [632] and consist of those with mild cognitive impairment, long-standing type II diabetes, poorly controlled hypertension, alcohol misuse, dementia, Parkinson's disease and the other akinetic-rigid syndromes. Those with Parkinson's disease may be exquisitely sensitive to the cognitive adverse effects of antimuscarinics [633]. These individuals will need to be carefully assessed, both prior to, and shortly after, initiation of treatment with bladder antimuscarinics. Treatment may necessarily depend upon a global assessment of cognition during the clinical assessment and, if possible, a carer's impression of change. In addition to the of likely benefit from drug treatment, considering the life expectancy and wishes of the patient, account should be taken of total anticholinergic load, as this clearly increases the likelihood of cognitive impairment. There is evidence of the short-term cognitive safety of bladder antimuscarinics, with the exception of immediate release oxybutynin, for the most part in cognitively intact older adults, and therefore, prescribing bladder antimuscarinics as single agents is, on the whole, probably safe.

Those studies using high doses (20mg) of oxybutynin are associated with an increased likelihood of causing cognitive impairment, which may not be apparent to either the patient or the clinician [634]. This drug should probably be avoided in the elderly at high dose, and in those at cognitive risk, in any case. The other antimuscarinics should be initiated carefully, at the lowest dose for tolerability, with dose increases where indicated for efficacy, and reviewed early.

Summary of the evidence

There remains insufficient evidence to determine the efficacy, tolerability, and safety of OAB drugs in frail older adults **(Level 4)**:

VIII. SURGICAL TREATMENT IN FRAIL OLDER ADULTS

1. INCONTINENCE SURGERY IN FRAIL OLDER WOMEN

Surgical intervention, mainly the midurethral sling, is the most effective and durable treatment for SUI in women. Due to the minimally invasive nature of these procedures, the number of older women undergoing midurethral slings is increasing.

Multiple retrospective and prospective cohort studies report favourable outcomes for older women undergoing these procedures. One single institution case series reported excellent surgical results with well-selected older women >/=70 years of age compared to women <70 years of age undergoing surgeries for incontinence and other pelvic floor disorders [635]. These older women were shown to do well with anti-incontinence surgery and to have significant gains in QOL, that did not significantly differ compared to the younger cohort. Another study of 76 women >/=70 years of age who underwent tension-free vaginal tape (TVT) procedures also demonstrated good outcomes, with a 67% cure rate and no serious complications, either intra- or post-operatively [636].

However, the literature on this topic is somewhat mixed and not all studies demonstrate as favourable outcomes. A large secondary analysis of the National Health and Nutrition Examination study showed that the risk of perioperative complications from midurethral slings was higher among women ages 80 years or older,

compared to those who were younger (odds ratio [OR], 1.4; 95% CI, 1.3–1.5) [637]. Outcomes of a subgroup of women enrolled in the Stress Incontinence Surgical Treatment Efficacy (SISTEr) trial demonstrated that age was one of the preoperative baseline factors that was associated with recurrent urinary incontinence seven years following surgery [638].

A more recent retrospective study of 688 older women undergoing three different types of midurethral sling surgery [i.e., single incision slings, transobturator tape (TOT), and retropubic transvaginal tape (TVT)], also demonstrated inferior outcomes in older women. In this study, women were stratified by age according to three categories: <64 years (young), 65-74 years (elderly), and >75 years (old). Objective and subjective cure rates for young, elderly, and older women were 91.0%, 80.6%, 66.7% and 89.2%, 77.6%, 58.3%, respectively. There were no differences in operative time, perioperative complications, or hospital length of stay between the different age groups. Findings from this study may not be generalisable due to possible positive selection bias of the retrospective study design, whereby procedures were likely mostly selected to be done among healthier individuals [639].

The above studies, and most of the literature, use age as a binary predictor, and fail to consider any other important factors that account for the phenotypic heterogeneity demonstrated in older adults, including multimorbidity, frailty, or physical or functional impairment. Unfortunately, these omissions lead to major gaps in our knowledge regarding which older individuals may benefit from surgical treatment for their stress urinary incontinence, and which may not. Research inclusive of these important factors is critically needed to help identify which treatments for stress incontinence are most appropriate in which older women.

To this end, one study specifically looked at the association of frailty with postoperative outcomes in older adults undergoing sling surgery using the American College of Surgeons National Surgical Quality Improvement Project (ACS-NSQIP) data from 2013-2016. Approximately 10% of individuals undergoing sling surgery (with or without concurrent prolapse repair) were identified to be frail and frailty was associated with increased hospital length of stay (OR 1.2, 95% CI 1.1-1.4) and 30-day hospital readmission (OR 1.7, 95% CI 1.1-2.5) in this cohort [640].

Another study evaluated nursing home residents, a cohort characterised by frailty and physical and cognitive impairment, undergoing female pelvic surgery (inclusive of both sling and pelvic organ prolapse surgery). Residents were propensity score matched to community-dwelling older adults based on procedure type, age, comorbidity, race and calendar year. Among this cohort, 34% demonstrated 30-day complications and 1-year mortality was 7%. The relative risk of each outcome was higher among the nursing home residents, compared to matched community-dwelling older adults, highlighting that factors other than age and comorbidity (such as frailty and physical and cognitive impairment) may account for these inferior outcomes [641].

No further studies investigating the utility of onabotulinumtoxinA in older women with frailty were identified since the 6th ICI. A review article has noted the absence of evidence for the therapy in older adults [642]

2. INCONTINENCE SURGERY IN FRAIL OLDER MEN

As noted in the 6th ICI, no specific conclusions can be drawn regarding surgical treatment of UI in frail men. Since the last chapter, one cohort study described the health characteristics and treatment choices of male stress urinary incontinence (mSUI) patients to inform patient-centred decision-making. Of 130 participants (mean age 75) and moderately bothersome incontinence, nearly 80% had significant morbidity, three-quarters had >50% 10-year mortality risk, 10% needed help with 1 + ADL and 22% had an impaired Timed Up and Go test >10 seconds. Only incontinence characteristics, rather than any other considerations were statistically significantly associated with conservative vs surgical treatment choice [643]. Typical studies of anti-UI surgery in elderly men are very small or fail to stratify results by age and/or comorbidity [644]. One small study (n=46) found that advanced age was not a risk factor for poor outcome after collagen injection for post-prostatectomy UI [645], while another (n=12, mean age 80 years) of transurethral resection prostatectomy (TURP) for obstruction-associated urgency UI concluded that cognitively impaired men demonstrated the greatest UI improvement [646]. In a single institution case series of men aged > 80 years old undergoing TURP (68% of whom had urinary retention), 80% were satisfied with their outcome. Of the men with retention, 80% were able to void with a small PVR by six weeks. Complication rates were 41% (early) and 22% (late) age was not a risk factor for poor outcome after collagen injection for post-prostatectomy UI [647]. A retrospective cohort study of men undergoing AUS placement and removal procedures using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) (2006 to 2013) quantified frailty using the NSQIP-FI (frailty index) and was applied to logistic regression models predicting 30-day complications (overall, major, and minor) and the odds of having an AUS removal procedure (over an AUS placement procedure. 624 and 147men undergoing AUS placement and removal procedures, respectively were identified. NSQIP-FI of ≥0.27, but not age, was associated with major complications (aOR 3.5, 95% confidence interval 1.2-9.9), while age ≥85 years, but not NSQIP-FI, was associated with minor complications (aOR 7.9, 95% confidence interval 1.4-45.6). Men undergoing AUS removal procedures tended to be frailer compared to men undergoing AUS placement procedures (12.9% vs 6.1% had NSQIP-FI of ≥0.27, P<.01) [648]. There has been a push for minimally invasive, office-based procedures which can be performed without general anaesthesia. However, AUA recommendations on minimal invasive techniques such as the use of Prostatic UroLift®, RezümTM or Aqua Ablation are based on prostate size and not on comorbidities [563]. A systematic review and meta-analysis comparing endoscopic enucleation vs endoscopic vaporisation and laser enucleation procedures vs laser vaporisation procedures has been done by Xinbao *et al.* including 16 studies with 4907 patients [649]. Endoscopic enucleation and laser enucleation procedures favoured in perioperative data, rate of complications, and functional outcome. The clinical significance of the findings remained unclear and there was no consideration of risk factors common in frail older men. However, photoselective vaporisation and enucleation of prostate might be beneficial due to the better control of bleeding [565]. Prostatic stenting – either temporary or permanent is not mentioned in the AUA guidelines. The EAU recommends the use of prostatic stents as an alternative to catheterisation although the use of prostatic stents is due to complications still rare [566].

3. SURGERY FOR IDIOPATHIC OR NEUROGENIC DETRUSOR OVERACTIVITY

There remains only one study examining onabotulinumtoxin A therapy in frail older men [650]. The authors concluded that safety and efficacy were similar between older men without frailty and younger patients. However, an increased risk of finding a large post-void residual urine volume and a lower long-term success rate in frail patients were noted.

4. GENERAL ISSUES IN THE SURGICAL CARE OF FRAIL OLDER ADULTS

Frailty is becoming increasingly recognised as an important prognostic factor in surgical outcomes. However, measured, the presence of frailty is associated with an increased likelihood of surgical complications, increased lengths of hospital stay and a greater probability of requiring an increased level of care following hospital discharge [644, 651, 652]. Important factors in the surgical care of frail patients include: preoperative risk stratification (e.g., American Society of Anaesthesiology class, Charlson index, Modified Cardiac Risk Index, Burden of Illness Score) [653]; ensuring adequate nutrition, especially when patients cannot take oral feeding or become delirious; proactive management of comorbid heart disease, diabetes, and pulmonary disease; prevention [654, 655], recognition [656], and treatment of postoperative delirium [657]; adequate pain assessment and treatment, especially in cognitively impaired persons [658]; recognition of the hazards of prolonged bed rest [659] and the prevention [660] and treatment of functional impairment; use of specialised care units for older adults [661]; and discharge planning regarding rehabilitation, need for assistance, and site of discharge. All need to be actively considered and dealt with in any plan of surgical care of frail older patients. Although some single institution case series have reported excellent surgical results with well-selected octogenarians and nonagenarians undergoing surgery for incontinence and other pelvic floor disorders, these findings should be interpreted with caution because they tend to describe the results from surgery in robust, carefully selected patients undergoing procedures at specialised centres. To what extent these results are generalisable is unclear; the true risk of surgery in frail older patients is likely higher than in these reports.

Attention to cognitive and functional outcomes as well as quality of life are also important to consider in this population.

Summary of the evidence

1. gynaecological surgery in institutionalised older women appears to be characterised by poorer outcomes than in community dwelling women. (**LoE 4**)

2. Injection of bulking agents for SUI appears to give minor benefit in women, however the technique is minimally invasive, and age does not appear to correlate with outcomes. (**LoE 3**)

3. Injection of onabotulinumtoxinA might be an option in patients with idiopathic or neurogenic overactive bladder although risk of residual urine and a lower long-term success rate have been described. (**LoE 3**)

4. No studies were identified that evaluate functional or quality of life outcomes after UI surgery in frail older adults (**LoE 4**)

5. Risks of morbidity and mortality for frail patients undergoing anti-UI procedures are similar to those of other major non-cardiac surgical procedures. (**LoE 2**)

6. Surgical mortality risks are still low in older adults, and when deaths do occur, they are often due to cardiac or cancer complications. (**LoE 2-3**)

7. Operative mortality is inconsistently associated with increased age, and most studies do not uniformly control for comorbid conditions (**LoE 2-3**)

8. Patient-controlled analgesia provides adequate pain control and sedation and increased patient satisfaction compared to standard fixed and time-administered medications in cognitively intact patients. (**LoE 2**)

9. Choice of agent for patient-controlled analgesia may affect postoperative cognition. (**LoE 3**)

10. Some case series and waitlist-controlled trials suggest that minimally invasive surgical approaches may be useful in older adults, yet these trials may have little to do with whether surgical treatments are appropriate in frail older adults (**LoE 3**)

Recommendations for management

1. Age alone is not a contraindication to surgical treatment of UI (**Grade C**).

2. Urodynamic evaluation should be done before considering surgical treatment of UI in frail older adults (**Grade B**).

3. Preoperative risk should be stratified using established indices (**Grade A**).

4. Validated frailty scales may aid prognostication and planning from post-surgical care in frail older adults (**Grade C**)

5. Ensure adequate post-operative nutrition, especially in patients who cannot take oral feeding or who become delirious (**Grade C**).

6. Programmes to prevent post-operative delirium should be utilised (**Grade A**) along with proactive use of established measures to diagnose delirium (**Grade A**).

7. Pain assessment in cognitively impaired persons should use measures specially designed for this population (**Grade B**).

8. Proactive preventative approaches to hospitalisation-related functional impairment should be used (**Grade A**).

9. Specialised care units may improve selective outcomes for frail older patients (**Grade A**).

10. Discharge planning should begin before surgery takes place (**Grade C**).

11. Patient controlled analgesia can be used in cognitively intact frail older adults (**Grade B**).

12. Analgesic agents associated with delirium (e.g., meperidine) should be avoided (**Grade B**).

13. Long-term outcomes before the operation should be discussed with the patient (**Grade C**).

Recommendations for research

Further research is required to:

1. identify risk factors for surgical outcome in frail adults to identify which treatments for UI are most appropriate in real-world settings

2. Define pre- and post-surgical care to improve surgical outcome in frail older adults.

IX. NOCTURIA

1. BACKGROUND

Nocturia is defined as the number of times urine is passed during the main sleep period and is manifested by increase in both urination frequency and urine volume produced at night [662]. The definition refers to an individual's sleep cycle and commences with the intention to sleep. This allows the term to be applicable to shift workers and others who may sleep during daylight hours. Overall, nocturia is a highly prevalent symptom [663]. While a single episode of awakening to urinate would be considered nocturia, patients are more likely to experience significant bother and decreased quality of life when voiding twice or more per night and to have [664]. Overall individuals will likely consult a provider about nocturia if they have three or more episodes [665]. Given that nocturia of at least twice per night is associated with significant increased risk for comorbidities, many clinical trials include only participants with two or more episodes [666]. Of relevance in the older population is that the presence of nocturia at least twice each night increases 5-year mortality by 4% and is probably associated with a 1.3-fold increased risk of death.

The definition of nocturia does not take into account sleep patterns of older adults. Since some older adults will spend six hours sleeping while others might spend twelve hours in bed, having three episodes of nocturia would be very different for these individuals [667]. Additionally, it is hard to identify whether individuals wake to void or pass urine because of wakefulness or other specific sleep disturbances (such as seen with Parkinson's Disease or obstructive sleep apnoea) [668, 669]. Both primary and secondary insomnia that may be noted in older patients with nocturia, can be linked to depression, anxiety about life changes, disruption by a partner or pet, circadian sleep disorders and symptoms associated with comorbid disease.

The prevalence, impact, pathophysiology, diagnostic assessment, and treatment of nocturia differ meaningfully between older adults and frail older adults [669] where nocturia often results from the reduced physiological reserve of multiple systems. In older hospitalised patients nocturia has been reported in at least 76% of older inpatients [670]. Nocturia at least twice per night in older patients undergoing rehabilitation has been shown to be predicted by comorbidities (Charlson Comorbidity index OR 1.41) and lower urinary tract dysfunction (urinary frequency OR 10.9, daily urinary incontinence OR 4.9) [671]. Measures of frailty, such as the modified Frailty Index, cognitive dysfunction, decreased hand grip strength, diuretic use and cardiac parameters are significantly associated with nocturia in the older age group [672, 673]. Although the link between nocturia, morbidity and all-cause mortality is likely to be frailty, variables of poor health can increase the mismatch between bladder storage and rate of urine production. One example of this is increased diuresis rate at night inducing nocturnal polyuria, a finding in up to 77% of people with nocturia more than twice per night [674]. Accordingly, diagnostic assessment must be comprehensive enough to identify causality, directing multi-component interventions necessary for successful treatment.

2. PREVALENCE, CAUSATION & IMPACT

The prevalence of nocturia increases with age and has been reported to be as high as 90% for one episode per night in persons over age 80 [675-680]. The prevalence of two or more episodes among men between 70 and 79 is nearly 50 percent [680, 681]. This increasing prevalence is largely due to age-related conditions that underlie the pathophysiology of nocturia, such as smaller maximum voided volume and increased nocturnal polyuria [682]. With respect to sex, nocturia in young adults is more common for women than men, but this sex ratio reverses after age 60 when more men have nocturia [681]. For those over 75 years of age, the prevalence of nocturia of at least two or more times is much more common in men (70%) than in women (50%) [683]. Nocturia is a common symptom in nursing home residents and contributes to poor sleep and impaired quality of life [684].

Nocturia is a dynamic symptom related to hormonal, nephrological, urological, cardiovascular and sleep factors [685, 686]. In one study, participants recorded their urination frequency and voided volumes over a 2-year period; the incidence rate of nocturia of two or more times per night in the oldest adults participating (70-78 years) was 47.1% while the resolution rate was 26.2% [687]. This finding of resolution in one quarter of older adults is encouraging and warrants research into the identification of factors responsible for reducing nocturia. Reports of improved nocturia after successful treatment of non-dipping hypertension at night, nocturnal diuretic use, improved control of unstable diabetes mellitus in younger patients could account for some improvement in nocturnal polyuria in well managed older patients [688].

Recent data have also highlighted that the prevalence of nocturia in older adults differs by racial group. Multiple population-based epidemiological studies have shown a higher prevalence of nocturia in older men and women who are African American when compared to Caucasian cohorts [680, 689, 690]. While controlling for socioeconomic factors eliminated the differences in prevalence between non-Hispanic whites and Hispanics, differences persisted, although somewhat attenuated, between people of African versus European descent [691, 692].

Nocturia is associated with chronic medical conditions such as hypertension [693, 694] (including night time hypertension and absence of night time blood pressure dipping) advancing renal insufficiency [695-697] and cardiovascular disease [698, 699]. Nocturia has been shown to be associated with diabetes mellitus, [699], time since diagnosis, waist circumference, higher body mass index and

greater fat mass in men but not with the metabolic syndrome in older people [184, 700, 701]. Clinically, nocturia may be the herald symptom of significant underlying medical conditions, which, if overlooked, might result in significant morbidity and even mortality [666, 702] Therefore, an older patient presenting with bothersome nocturia should be evaluated for the causes of nocturia and unrecognised comorbidity. The presence of sleep apnoea, restless legs syndrome, moderate alcohol usage, poor nocturnal glycaemic control, and conditions causing night time pain should be identified [666].

Nocturia is associated with accidental falls, carrying a relative risk of 1.2 and likely to increase risk of fracture by 1.3 [275, 283, 703]. Significantly more difficulty climbing stairs and reduced skeletal muscle mass was found with older individuals who had increased frequency of nocturia episodes as compared to those who voided once or less per night. Frail older persons with nocturia, with coexisting gait and balance disorders are clearly at increased risk for falls [274, 704], injury and hip fracture [784], and consequent morbidity [705, 706]. Recent work suggests that urinary urgency further compromises posture, step length and walking speed, all factors known to predict falls. Despite these facts, no nocturia treatment trials to date have evaluated any impact on falls reduction. Nocturia also has adverse effects on quality of life [707], including an increased risk of depression and poor self-rated health, probably as the result of the impact on sleep. [708]. Adults with nocturia also complain that nocturia “makes them feel old” and they worry about falling at night [709]. Older individuals described nocturia as simultaneously debilitating, frustrating, distressing and puzzling [710].

Several recent studies have shown strong associations between nocturia and Parkinson’s disease (PD), including a negative impact on quality of life, depression, anxiety and severity of disease [711-714]. Nocturia is a frequent, early non-motor symptom in PD that is bothersome, and a common cause of sleep disruption [715, 716]. Nocturia in PD is associated with increasing age of the patient, but also with the increasing severity of PD [717]. Age of onset of PD, in addition to age, may be associated with worse nocturia [718]. Patients with PD have more nocturia episodes than their spouses, and number of nocturia episodes may be related to nighttime and total levodopa dosages [719]. While it might be difficult to clinically separate idiopathic PD from drug-induced Parkinsonism, urinary symptoms including nocturia are much more common in PD even after controlling for age and sex [720]. Additionally, nocturia and other non-motor symptoms often began prior to being diagnosed with PD, and may be a biomarker for the condition [720].

Bother attributable to nocturia increases with age. There is growing evidence to suggest that bother from nocturia relates to severity, both primary and secondary insomnia and the impact of poor sleep quality on daytime function [721-725]. Many papers have described the association between nocturia and disrupted sleep [666, 722, 726, 727]. When a group of 1,424 elderly individuals, ages 55–84 were presented with a checklist of symptoms that potentially disrupt sleep, nocturia was chosen by 53% of the sample as a self-perceived cause of sleep issues “every night or almost every night”. Nocturia was cited four times as frequently as pain, which was the next most identified cause of sleep disruption [728], and reported as a reason for insomnia in patients with congestive heart failure [721, 729]. Nocturia has been shown to be significantly associated with worse scores on sleep questionnaires, a shorter time asleep before first night void, longer awake duration and poor quality of whole-night sleep [726, 730, 731]. One of the outcomes of sleep disruption seen with nocturia is excessive daytime sleepiness [732]. Other lower urinary tract symptoms are also highly correlated with sleep disturbances with daily urinary urgency significantly predicting high nocturia-related bother [733, 734]. For older patients in hospital, waking at least twice to pass urine at night was significantly associated with daytime lower urinary symptoms: urinary frequency > half the time, urinary urgency > half the time, UI > half the time, mean AUA symptoms score, and with faecal incontinence score and the number of continence products used [671]. Nocturia is related to depression and anxiety [735, 736]. In particular, convenience voiding at night is more common in individuals with a mental health diagnosis than in those without and has been reported to be associated with a perception of urinary urgency despite equivalent urine volumes and diuresis rate [737]. All quality-of-life measures collected in a sample of older hospitalised individuals, using the EQ-5D-5L instrument, were significantly worse in patients who voided more than once at night. As nocturia episodes reduce, quality of life improves [738].

3. PATHOPHYSIOLOGY

The pathophysiology of nocturia is multifactorial, particularly in frail older persons. In age-adjusted analyses from a large survey in Finland, no single factor related to nocturia was present in greater than 50% of those with nocturia [739]. The factors with the greatest impact at the population level in men were (urinary) urgency, “benign prostatic hyperplasia” and snoring while for women being overweight or obese, urgency and snoring were risk factors [682, 739]. Colder ambient weather or internal temperatures may be associated with greater nocturia, possibly due to sleep disruption [740, 741].

A framework for clinical diagnosis and treatment is that one or a combination of primary causes underlie symptoms, all of which increase with age. Age-related changes to the bladder ± conditions that reduce bladder capacity (i.e., OAB, DO, urgency UI, or BOO in men) can cause nocturnal frequency. Nocturnal polyuria, particularly in the early hours after falling sleep, can overwhelm bladder storage. Finally, disruption of sleep for a variety of reasons, can precipitate nocturia, [742-744] although this relationship is likely bi-directional (with sleep dysfunction also likely resulting from nocturia) [745].

The proportion of a 24-hour urine volume produced at night increases with age, even among healthy older adults free of overt comorbid conditions [746, 747]. Studies of frail older adults have shown that the proportion of urine produced at night is close to 50%, as compared to 30% in young healthy adults [748-750]. In some older persons this is due to mobilisation of excess volume caused by peripheral oedema, which may be due to venous insufficiency, medications, and/or heart failure. Both hydrochlorothiazide and loop-diuretic usage in men have been associated with higher rates of nocturia, unless last dose is taken at least 6 hours before sleep. The definition selected for diuresis rate indicative of polyuria will influence prevalence and overlap of day, night and 24-hour polyuria in patients with nocturia [751, 752]. There may be an abnormality in the secretion and/or action of arginine vasopressin (AVP) or a loss of the normal diurnal rhythm (with inappropriately low values at night) in elderly patients with nocturia. [753-755]. Other research suggests that some frail older adults with nocturia have high atrial natriuretic peptide (ANP) levels at night; [756, 757] however, these investigators did not use echocardiography or evaluate brain natriuretic peptide levels to detect occult heart failure.

Sleep disordered breathing (as defined by an Apnea-Hypopnea Index >=15) is associated with circadian change in extracellular fluid, nocturia and nocturnal UI in the elderly [756, 758-761].

Community-dwelling older adult populations who have >25 breathing events per hour have nearly double the number of nocturia episodes compared with those with low rates of sleep apnoea [762]. Whether this relates to negative intra-thoracic pressure changing inducing ANP production, [756] mechanical forces on the bladder generated during apnoea event [759] or other mechanism(s) is unknown. Nocturia may be a marker or a result of endothelial dysfunction [763], vascular flow disruption, white matter hyper-intensities [764], or inflammation [765].

4. DIAGNOSTIC ASSESSMENT

The approach to the assessment of nocturia expands the routine process for UI to identify factors underlying causality. Special considerations include a frequency-volume chart of at least 24 hours duration that includes timing and volume of each void at night as well as during the day, as well as a specific indication of when the individual went to bed with the intention of going to sleep at night and awoke in the morning. Some patients may find this difficult to perform, [766] but face-to-face explanation of the procedure, a hand-held urinal or a receptacle to place in the toilet to measure volumes, and involvement of caregivers may improve compliance and accuracy. Alternatively, a collection of all urine passed during the night ± change in containment product weight and volume of first morning void will indicate nocturnal urine volume. The advent of smart technology is likely to substantially change this type of data collection [767-769].

A causality checklist for nocturia, TANGO, can be utilised to assist patients and clinicians to identify potential and co-existing causal factors [770]. This has domains related to increased urine production, sleep, urinary tract and wellbeing. Additional questions about leg movements at night, bed partner, household members and family pets may generate insightful information. Recently a symptom score for nocturnal LUTS in older people has been described that may have utility in describing the specific LUTS coexisting with nocturia. As high daily salt intake can increase frequency of voiding, history taking should include questioning about intake of sodium and other dietary osmoles in the afternoon and evening [771-773].

Older people are commonly prescribed multiple medications for comorbidities, many of which may exacerbate urine production, bladder storage or sleep quality affecting development or resolution of nocturia. Known pharmacological correlates of nocturia include calcium channel blockers (induce oedema), lithium, Sodium-glucose transport protein 2 (SGLT2) inhibitors and diuretics that increase osmotic clearance. A medication review for optimisation of polypharmacy is therefore warranted with attention to both type and timing of drugs known to influence nocturia [774-777]. Focused physical examination will evaluate volume overload (e.g., lower extremity venous insufficiency, congestive heart failure) and factors that induce nocturnal polyuria such as unstable blood sugar levels, postural hypotension and non-dipping nocturnal blood pressure can be identified with specific testing. A serum sodium check may also be considered [778]. Muscle strength, mobility impairment and any neurological disorder should be noted and considered for contribution to wakefulness, bladder storage, urgency and difficulty reaching a toilet. When poor mental health is suspected sleep parameters should be investigated (i.e., primary sleep latency, sleep efficiency, secondary insomnia, night worrying).

5. TREATMENT

While many clinical investigations are trials of single agents, experts [779] would argue that treatment of nocturia in elderly patients should be based on a holistic approach informed by identification of multiple potential underlying causes. It has been suggested that in frail older people the approach to nocturia be systematic. Firstly, optimisation of comorbidities and reduction of polypharmacy; secondly behavioural and lifestyle adjustments; thirdly addressing drug–disease interaction; and finally joint goal setting with patients and their families [777].

There is little high-quality evidence for most monotherapies or combined treatments for nocturia in older age groups. A recent review of therapies for nocturia management in the elderly cites evidence for efficacy of lower limb oedema prevention and treatment, fluid restriction up to four hours before sleep, pelvic floor muscle contraction at urge in patients with known overactive bladder, salt reduction if intake is excessive and behavioural treatment of insomnia [777]. Combination therapy is preferred over monotherapies [780]. Cure, or the complete resolution of nocturia, is infrequently achieved in either clinical practice or research.

The most common primary outcome in clinical trials is reduction in nocturia episodes, as measured by voiding diary or self-reported nocturia over a given period. Some trials have reported the percent of participants who achieve a 33% or 50% [755, 781-785] reduction in nocturia from the baseline level or the percent of individuals having a reduction equal to 1.0 fewer mean nightly episodes of nocturia [781, 783, 784]. There are few treatments that offer robust reductions of nocturia, with most ranging from 0 to 0.8 fewer episodes of nocturia. The net reduction of an intervention, subtracting the benefit seen in the control or placebo arm is often even smaller. Whether this is due to regression to the mean due to random variation in the symptom of nocturia or a result of monitoring and problematic recording night-time voids, is unclear. Patient-level outcomes related to general satisfaction questions, nocturia- related bother, and nocturia-specific quality of life are meaningful as secondary outcome measures. Recently the time initially asleep before the first nocturia episode has been reported as a measure of severity and holds potential to describe treatment response [724, 786]. The number of nocturia episodes correlates poorly with actual hours spent in bed, and may vary considerably in older persons who have no pressing need to rise at a given time [710].

There are several approaches to drug therapy for older patients with nocturia; most of the published guidelines suggest targeting “primary” or “principal” causes of nocturia (e.g., nocturnal polyuria). Because older adults with nocturia have multiple potential causes, treatment will require combination therapies of behavioural strategies, and intervention for medical, lower urinary tract and sleep disorders. In an uncontrolled study, lifestyle modification of 1) restriction of fluid intake, 2) refraining from excess hours in bed, 3) moderate daily exercise and 4) keeping warm in bed resulted in a positive reduction of nocturia from 3.6 episodes per night to 2.7 for 56 participants aged 59-85 (mean age 74.5, 84% male) [787]. While some trials may report statistical significance for reduction in nocturia, the clinical meaningfulness of these changes if a participant still voids multiple times per night is questionable [784].

6. BEHAVIOURAL APPROACHES AND TREATMENT OF COMORBIDITY

The use of specific behavioural strategies (e.g. altering fluid intake, reducing sodium intake, leg elevation for oedema) on nocturia in older patients have largely been made based on consensus and in light of their favourable safety profile [777]. Using bedside commodes or urinals, minimising the distance necessary to reach a toilet, providing a safe, adequately lit path may reduce the risk of night-time falls related to nocturia, especially in those with underlying gait instability and other risk factors for falls.

Trials of behavioural intervention for nocturia overwhelmingly fail to differentiate between patients with known OAB and those with confirmed nocturnal polyuria. Recent work suggests that nocturnal polyuria and reduced bladder capacity may co-exist, particularly when nocturia is severe [788, 789]. The interventions differ markedly between the patient groups, meaning generic treatment does not specifically target underlying causes. The first secondary data analysis of a RCT which demonstrated that behavioural therapy, with an emphasis on pelvic floor muscle exercises and urgency suppression strategies, showed that nocturia was reduced in women (mean age 68) with urgency- predominant UI [790]. The median reduction of 0.5 episodes per night was significantly more effective than drug treatment or placebo (no reduction). A second secondary data analysis of an RCT, that did not show benefit with respect to the primary endpoint of urgency incontinence in women (mean age 55), did not show benefit of behavioural therapy plus anticholinergic medication for nocturia [791]. An additional RCT in men (mean age 64) examined the impact of the addition of either titrated bladder relaxant therapy (oxybutynin XL 5-30mg) versus behavioural therapy for pelvic floor muscle exercise after failure of alpha-blocker therapy. Nocturia was a secondary outcome; the behavioural group showed greater reductions in nocturia (mean= -0.70 vs. -0.32 episodes/night; P = .05) [785]. Trials where individuals are sub-classified by nocturnal polyuria, OAB or both pathologies and where reduction in nocturia episodes is the primary outcome are warranted.

Individuals shown to have nocturia and obstructive sleep apnoea (OSA) should be treated for OSA initially, which may reduce nocturia and associated hypertension [792]. Similarly, initial management of non-dipping hypertension or postural hypotension should precede behavioural intervention.

7. PHARMACOTHERAPY

7.1. Antimuscarinic therapy

Members of a recent nocturia consensus conference agreed on the following statements with regards to overactive bladder and antimuscarinics:

1. Most patients with nocturia do not have OAB
2. Most patients with OAB do have nocturia
3. antimuscarinics are not usually efficacious for nocturia
4. Antimuscarinics may be effective for nocturnal voids due to urgency [793, 794].

In general, if the history, bladder diary, and physical examination suggest that nocturia is related primarily or in part to OAB/DO/urgency UI, then treatment with an antimuscarinic agent should be considered. While there are several trials examining the effect of antimuscarinics for nocturia reduction, there is poor evidence for efficacy in frail older adults, with the net benefit of reduction in nocturia being 0.0 to 0.3 episodes. Use of anticholinergic medications in older people has potential for serious detrimental side effects including constipation, dry eyes and mouth and urinary retention [777].

7.2. Beta-3- adrenoreceptor agonists

Whilst there are data demonstrating the efficacy of mirabegron for the treatment of nocturia on OAB, the effects are small, but superior to placebo treatment & tolterodine in a systematic review & meta-analysis [795]. In an exploratory pilot study investigating the effectiveness of mirabegron for improving sleep disturbance and nocturia, 34 men and women with disordered sleep and lower urinary tract symptoms received mirabegron 25 mg daily for 4 weeks, then 50 mg. Patients completed the Patient-Reported Outcome Measurement Information System Sleep Disturbance Short Form (PROMIS-SDSF), Jenkins Sleep Scale (JSS), International Prostate Symptom Score (IPSS), voiding diaries, and QoL questionnaires. The PROMIS-SDSF scores decreased from 26.5 points to 19.3, representing a categorical improvement from clinically 'mild' to 'none to slight' sleep disturbance ($p < 0.001$). JSS scores also decreased from 14.1 to 8.3 ($p < 0.001$). Voiding diaries revealed 0.8 fewer night-time voids ($p < 0.05$). There are no data which report efficacy in older or frail older adults [796].

7.3. Agents directed towards benign prostatic obstruction

Alpha-adrenergic agents used in patients with symptoms suggestive of BPO have a modest impact on nocturia, with a mean reduction of slightly less than one episode per night [754, 797]. 5-alpha reductase inhibitors [754] and saw palmetto (*Serenoa repens*, saw palmetto berry extract) [798] have not shown statistical benefit for nocturia except in one study within one subset of participants age >70 years [781]. This statistical advantage did not persist beyond one year, and the net benefit compared to placebo was a difference of < 0.2 fewer nocturia episodes. A recent systematic review concluded that potentially small benefits of α-blockers alone for the treatment of nocturia in men should be weighed against the risks of orthostatic hypotension and the risk of subsequent falls and that there was no evidence to support use of alpha-blockers in women [777].

7.4. Other medication approaches

Among postmenopausal women, one uncontrolled trial of oestradiol in combination with a progestogen showed a dramatic reduction in nocturia over 6 months [799]. There are few studies that have focused on treatment of nocturia with the use of medications for sleep. One RCT evaluated melatonin for treatment of nocturia associated with BOO in older men [800, 801]. Melatonin showed only a trend towards reduction in nocturia compared to placebo but did significantly reduce reported bother from nocturia. Reducing volume overload associated with lower extremity venous insufficiency or congestive heart failure with a late afternoon dose of a rapid acting diuretic may be helpful in reducing nocturnal polyuria and nocturia in selected patients [802, 803]. Treating sleep apnoea with continuous positive airway pressure can reduce nocturia severity, but these trials exclude the frail older adults [804].

7.5. Antidiuretic treatment: desmopressin

There is a potential role of exogenous AVP (desmopressin or DDAVP) for the treatment of nocturia in older patients [805-818] with meaningful reductions in nocturia and nocturnal urine volume and increases in first undisturbed sleep period. A major concern related to DDAVP treatment in older patients is fluid retention (which can exacerbate underlying cardiovascular disease) and hyponatraemia [819]. Many older adults may have pre-existent hyponatraemia due to a variety of medical conditions and drugs and will develop re-

nal insufficiency or congestive heart failure [820, 821]. Because so few frail older adults are included in anti-diuresis trials, the actual incidence of clinically significant hyponatraemia from DDAVP that might occur is unknown. Use of DDAVP is currently limited by risk in frail older adults and has been identified as a potentially inappropriate medication in the Beers [553]. Low dose sex-specific DDAVP has been shown to be effective in adults with nocturia and nocturia due to nocturnal polyuria, but not in frail older adults, without significant hyponatraemia [822, 823] [824]. A randomized controlled trial of desmopressin nasal spray (10 µg/spray once daily or placebo) in community dwelling older adults with nocturnal polyuria, showed that desmopressin was not superior to placebo with respect to micturition frequency or sleeping hours. Those with decreased ADH levels seemed to benefit from treatment with desmopressin. The unexpected results in the placebo group were thought due to the intensive outpatient care and information on NP given to all patients [825].

Summary of the evidence

Late afternoon administration of a diuretic may reduce nocturia in persons with lower extremity venous insufficiency or congestive heart failure unresponsive to other interventions. **(LoE 2)**

If OAB, DO, and/or urgency UI is felt to be a major contributor to nocturia, antimuscarinic agents should be considered. **(LoE 3)**

If nocturia is due to insomnia alone, then a very-short acting sedative hypnotic may be considered. **(LoE 3)**

DDAVP (0.1microgrammes) should not be used in frail older adults because of the risk of hyponatraemia. **(LoE1)**

Recommendations for management

Nocturia investigations should be carried out utilising both frequency-volume charts and validated questionnaires capturing QoL, and bother related specific to nocturia (e.g., NQoL). **(GoR C)**

Recommendations for research

- Validation and clarification of the definition of both nocturia (in regard to any night awakening owing to the desire to pass urine, the ICS definition vs. the more clinically bothersome nocturia, of 2 or more episodes)
- Ways in which to understand, and potentially diminish, the robust effect of placebo/control arms
- Epidemiological research regarding studies of nocturia involving the following aspects: incidence/ natural history, bother, effect on quality of life
- Further clinical trials examining the impact of sleep focused treatments
- Trials examining the effects of multiple incremental and multicomponent therapies for nocturia

X. FAECAL INCONTINENCE IN FRAIL OLDER ADULTS

1. INTRODUCTION

Faecal Incontinence (FI) in older people is a distressing and social isolating symptom and is associated with a possible increased risk of morbidity [826, 827] and dependency [827-830]. Frailty is an independent risk factor for FI in community-based and institutionalised populations of older adults [347, 831-834] Many older individuals with FI will not volunteer the problem to their general practitioner or nurse, and, health care providers do not routinely enquire about the symptom or follow guidelines regarding evaluation and treatment [835-837]. The condition can especially take its toll on caregivers of home-dwelling patients, [838] with FI being a reason for requesting nursing home placement and leading to early mortality, especially in those with complex disease [827, 828, 839-841]. FI is associated with a significant decline in physical function in older adults [842] and any FI is associated with an increased risk of falls in older adults [342].

Even when older people are noted by health care professionals to have FI, the condition is often managed with the use of absorptive or containment products, especially in the long-term care setting where it is most prevalent. The importance of identifying treatable causes of FI in frail older people rather than just managing passively (e.g. pads provision without assessment) is strongly emphasized in national and international guidance, [826, 843] but audits show that adherence to such guidance is generally poor, with non-integrated services, and sub-optimal delivery by professionals of even basic assessment and care [837, 844].

For the 7th ICI, the literature review covered the period 2016 to 2021. Readers interested in seeking older data are referred to the relevant Chapter in the 6th ICI

FI is strongly associated with ageing in many studies and studies only involving older adults have higher prevalence estimates. The National Health and Nutrition Examination Survey (NHANES) in the United States (US) provides one of the best estimates of FI prevalence to date because it surveyed both sexes, all major races represented in the US, and a range of older adults by age decade (55-69 and 70 years of age and older) [845, 846]. NHANES also provided separate estimates for different types of FIS (e.g., solid, liquid, mucus, and flatus) and frequencies of stool loss. The age-adjusted prevalence of FI (defined as accidental loss of solid, liquid, or mucus incontinence in the month preceding the interview) in the non-institutionalised population of the United States is 8.9% of women and 7.7% of men, with higher rates in older adults (16.6% in adults aged 70 years of age and older, equally prevalent in older men and women) [845, 846]. Liquid stool incontinence was the most common type of FI reported in the NHANES data. Rates of FI in older, frail adults are not sex-specific, with recent studies suggesting equal rates of FI among older men and women [830, 831, 847-851].

2. PREVALENCE AND INCIDENCE ESTIMATES OF FI

In a study of 2517 older adult residents from 883 long term care facilities in Japan, 44 (1.7%) and had FI only and 1034 (41.1%) had

double incontinence [202]. In a multisite cross-sectional survey of 10 rural villages in China (1250 residents), the prevalence of faecal and double incontinence was 12.3% and 9.3%, respectively. Factors associated with faecal incontinence included urinary incontinence, lack of social interaction, traumatic brain injury, cerebrovascular disease, and poverty. Physical activities of daily living dependence, traumatic brain injury, lack of social interaction, and poor sleep quality were associated with higher odds of having double incontinence [852]. In a study in urban China, prevalence of FI in 28 196 adult females was 0.43% (95% confidence interval: 0.35%-0.51%). Among women with FI, 42.96%, 82.96%, and 42.22% reported having leakage of solid, liquid stool, and gas, respectively. The overall FI prevalence and the incidence rate of solid stool/liquid stool/gas leakage increased with age [853]. In a systematic review (up to 2017) of 23 studies of FI in older care home residents, there were 12 high-quality studies, 5 medium-quality studies, and 6 low-quality studies. The medians for prevalence (as reported by the studies) of isolated feacal incontinence, double incontinence, and all feacal incontinence were 3.5% [interquartile range (IQR) = 2.8%], 47.1% (IQR = 32.1%), and 42.8% (IQR = 21.1%), respectively. The most frequently reported correlates of faecal incontinence were cognitive impairment, limited functional capacity, urinary incontinence, reduced mobility, advanced age, and diarrhoea [854].

In an international cross-sectional study comparing the prevalence of incontinence among cognitively impaired older residents in long-term care facilities in East Asia, including Japan, Korea, China, Taiwan and Thailand between 2015 and 2016 of 662 participants (age 82.6 ± 9.9 years, 57.6% women, the prevalence of urinary incontinence ranged from 10.1% in Taiwan to 71.0% in Korea. The prevalence of faecal incontinence (FI) varied from 4.0% in Taiwan to 57.0% in Korea. A higher Clinical Dementia Rating score was a significant predictor of urinary and FI and toilet use dependence (P < 0.0001) For adults receiving home hospice care, in a retrospective cohort study the prevalence of FI was (64.5%; n = 4314) of 15 432 patients Increasing age represented a risk factor for FI (hazard ratio [HR] = 1.01 [confidence interval, CI = 1.01-1.01]) FI was detected on average 18 days after home hospice admission [855].

A nationally representative sample completing an internet survey on GI health in Mexico reported that among 71,812 individuals 14.4% reported FI in the past; of these, 33.3% had FI within the past 7 days. Older age, male sex, and Hispanic ethnicity increased the likelihood of having FI within the past week. Individuals with Crohn's disease, ulcerative colitis, coeliac disease, irritable bowel syndrome, or diabetes were more likely to report FI. Non-Hispanic black and Hispanic individuals and individuals with Crohn's disease, coeliac disease, diabetes, human immunodeficiency virus/acquired immunodeficiency syndrome, or chronic idiopathic constipation had more severe symptoms of FI than individuals without these features [856].

In a Brazilian prospective study in women aged 65 years or older evaluated in 2006 and re-evaluated in 2010, including 864 older women, the prevalence rate of double incontinence (DI) was 4.9%. The incidence rate of DI in the period between 2006 and 2010 was 13.8/1,000 person-years. Associated factors were the presence of chronic obstructive pulmonary disease, hypertension, difficulty with basic activities of daily living (BADL) and instrumental activities of daily living (IADL), polypharmacy and falls in the last year. Poisson's regression analysis showed that falls in the last year and difficulty with at least three IADL were risk factors for DI [857] .

Data on the prevalence of faecal incontinence in elderly patients admitted to outpatient clinics in Turkey were addressed in older outpatients in a cross-sectional survey. Three hundred and sixty-four patients (64.8% female, n = 236) with a mean age of 73.2 ± 8.1 years were enrolled. The prevalence of FI was 9.9% (10.2% female, 9.4% male). UI was 42.6%. Co-occurrence of FI and UI was 7.4%. The most frequent type of defaecation was liquid stool (61.1%). While the predictive factors for FI were polypharmacy (standardized coefficient, [r] = 0.203, 95% confidence interval [CI] = 0.009-0.040, p = 0.002), UI (r = 0.134, 95% CI = 0.006-0.156, p = 0.035), and being married (r = 0.200, 95% CI = -0.088 to -0.020, p = 0.002) in females, In males they were UI (r = 0.306, 95% CI = 0.093-0.309, p < 0.001) and polypharmacy (r = 0.251, 95% CI = 0.009-0.043, p = 0.003) [858].

3. FAECAL INCONTINENCE IN OLDER ADULTS – THE "HIDDEN" PROBLEM.

Evidence reaffirms that about 30% of adults with FI seek care and that health care practitioners are not likely to inquire or document discussions regarding FI [836, 837, 839, 859-861]. Increasing awareness is important aspect of the identification, prevention, and treatment of FI in older adults [826]. Using appropriate terminology for FI for individuals that is consistent with health literacy levels may be an important factor. Terminology such as "bowel" or "accidental bowel leakage" may be more appropriate than the term "faecal" or "faecal incontinence" [862]. Barriers that prevent adequate identification and treatment include social and cultural issues about discussing symptoms, duration of symptoms, perception that treatments may not exist, access to trained health care providers in the community, access to providers in long-term care settings, and access to training and treatment protocols. Given the high prevalence rates of FI in the hospital, home care, and long-term care settings, health care practitioners should directly inquire or directly observe bowel control issues and document any findings. Other high-risk groups of older adults that should be questioned about bowel control include older adults that have mobility problems, cognitive impairment/dementia, frailty, prior pelvic/lower abdominal radiation exposure, prior anal or rectal surgery, urinary incontinence, chronic constipation, chronic diarrhoea, and older adults with multi-morbidity.

4. PHYSIOLOGICAL FACTORS SPECIFIC TO FRAIL OLDER ADULTS.

Physiological studies of the lower bowel in older adults tend to be variable due to a) a variety of different techniques used in measuring anorectal function, b) unclear definition of the normative range of manometric measures for older people, c) poor matching between cases and controls of clinical factors which may affect gut function (e.g. level of mobility or functional status), or inadequate clinical information, d) usually small subject numbers, e) few studies deal with subjects over 80 years, and f) improvements in imaging quality with anorectal manometry with new 3-dimenisional equipment, endoanal ultrasound, and MRI with and without defecography [863-866]. Studies reviewed are cohort case-control to evaluate age-effect, [867-874] young-old healthy subject comparisons,[875-878] and age- and sex-matched case-control studies of continent versus incontinent patients [879, 880] .

5. ANORECTAL FUNCTION IN HEALTHY OLDER ADULTS

Studies of age effect in healthy volunteers have shown a linear reduction with ageing in squeeze pressures (external anal sphincter tone) in women after the age of 70, and in men from the 9th decade onwards [874]. Studies of normal men and women demonstrated a significant but similar linear decrease in anal resting pressure and maximum squeeze pressures in both men and women with increasing age [878, 881]. Studies of asymptomatic females showed a significant decrease in both anal resting and squeeze pressures with age [881, 882]. Two studies comparing young and old continent women found a decrease in anal resting pressure but no decrease in squeeze pressures between the two groups [869, 876]. Age beyond 70 years was associated with reduction in anal resting pressures (internal anal sphincter tone) in both sexes, but to a greater degree in women than men,[872, 874] but not reaching statistical significance [883].

Rectal sensory thresholds may also decrease with ageing in healthy older adults despite normal compliance and tone [877]. There was a significant increase in pudendal nerve latencies with age in women; [873] however, clinical practice guidelines do not recommend testing pudendal nerve latencies [884]. In patients older than 65 years there is >30% loss of enteric neurones when compared to people aged 20 to 35 years. This loss is associated with an increase in fatty tissue deposition [885]. Increase in thickness of internal sphincter may be related to an increase in collagen deposition, with increased thickness seen in older versus younger women and in older nulliparous women [871, 876]. In addition, the increase in internal sphincter thickness was associated with a significant decrease in the external anal sphincter thickness in women [863, 886, 887]. A study of men and women using endoanal MR imaging showed a significant decrease in the external anal sphincter thickness in men but not women with age [888].

Other studies in humans have found increases in elastin and collagen deposition in the myenteric plexus in the colon. It is unclear if rectal motility is affected by healthy ageing, [889] but there is an age-related increase in anorectal sensitivity thresholds [873, 877, 878]. Rectal compliance was not affected in one study but reduced rectal sensation was associated with reduced rectal compliance in another [877, 881]. Other studies have evaluated the impact of the relationship of glycaemic control on gastric emptying and found that fasting blood glucose levels were associated with faster gastric emptying [890].

Gut microbiome and metabolome studies in older adults show that diet and antibiotic usage have an impact on gut microbiome and metabolome findings [891, 892]. Older adults residing in long-term care have less variation in the gut microbiome compared to older adults in the community [893]. Changes in the gut microbiome from older adults in long-term care settings may also be influenced by diet and inflammatory biomarkers [893].

5.1. Anorectal function in older adults with faecal incontinence.

Studies have reported an age-related increase in pudendal neuropathy in incontinent women, which may be unrelated to squeeze pressures [894, 895]. A study comparing anorectal function in young (mean age 42) and old (mean age 72) women with FI (patients with constipation and/or pelvic floor dysfunction excluded) showed that older women were more likely to have bilateral pudendal neuropathy, but less likely to have a sphincter deficiency of >90 degree and less likely to have had a previous sphincteroplasty [875]. Anorectal function in older incontinent patients and continent age- and sex-matched controls showed that individuals with FI had reduced anal resting pressures [876, 896]. In one study comparing 8 older incontinent women (mean age 71.6 SD 7.5) with 9 older continent women (mean age 71.6 SD 7.5) and 9 younger continent women (mean age 28.7 SD (7.3) found women with FI were more likely to have decreased maximum squeeze pressures and levator ani (LA) defects [897]. Older FI females tolerated lower balloon anorectal manometry volumes before urge to defaecate indicative of rectal hypersensitivity [876].

6. CAUSES OF FAECAL INCONTINENCE IN OLDER ADULTS

Stool consistency is important aspect of determining the cause and the associated factors for the evaluation of FI in an older adult [898-900]. Loose, as well as hard, stool can be related to FI in frail, older adults [901 - 903]. Evidence shows that loose stool consistency and chronic diarrhoea are important contributing factors for FI [898-900, 904] [9179734]. Loose stool and chronic diarrhoea can result from multiple causes, such as malabsorption syndromes (e.g., lactose intolerance, gluten sensitivity, and fat-malabsorption), acute diarrhoeal illnesses, microcytic colitis, irritable bowel syndrome (diarrhoea dominant), and other chronic diarrhoea. Any change in stool consistency along with other warning symptoms (weight loss, bloody stools, change in stool calibre, and painful defaecation) should prompt further evaluation for colorectal cancer. Potential reversible causes of loose stools may include excessive laxative use, lactose intolerance, drugrelated sideeffects, bacterial overgrowth, and possible bowel obstruction with “overflow” FI. “Overflow” FI secondary to constipation and stool impaction is also important to consider in older adults, potentially more common in men than women [905, 906] those with mobility problems, [902, 903, 907] and those that reside in nursing home settings [902, 907]

Overflow incontinence or FI resulting from stool impaction can be difficult to diagnose, may be more common in certain frail, older populations, and should be evaluated and treated when suspected. Evidence suggests that constipation and symptoms of constipation are common among nursing home residents with FI [902, 907, 908]. However, the true prevalence of impaction and FI in nursing home residents remains unclear. Constipation and associated symptoms (straining and incomplete evacuation) were common among nursing home residents in a 4-site randomised controlled trial to improve FI and urinary incontinence among nursing home residents [902]. At baseline, 81% of the 111 nursing home study participants had less than 3 bowel movements in 5 days. Another study that identified factors associated with FI in different health care settings found that 70% of nursing home residents experienced “faecal loading” compared to 63% in rehabilitation wards, 57% in acute care wards, and 20% in the home care setting [907]. Constipation is also associated with FI in non-nursing home dwelling older adults [909].

Urgency associated with bowel movements should be assessed in older adults. Many studies do not evaluate urgency as an independent risk factor. However, among the studies that evaluated a sense of urgency associated with bowel movements, urgency consistently is strongly related to FI and having a negative impact on quality of life even after controlling for other known confounding factors [899, 909-911].

Other bowel-related disorders or complications of prior anorectal surgery and radiation can contribute to FI in older adults who otherwise would be continent, especially when functional status, mobility and cognition become impaired. Other bowel related disorders that have been associated with FI in adults (but not limited to frail older adults) include: haemorrhoids, [875, 905], posterior compartment prolapse (rectocele), [900], inflammatory bowel disease, [856, 912] and irritable bowel disease [856, 900, 913]. Types of prior anorectal surgery that contribute to FI include: haemorrhoid surgery, [905], prior fistula repair, [914, 915] sphincterotomy for anal fissures, [916], partial or total colectomy, [917] low anorectal resection and re-anastomosis for colorectal cancer, [918, 919], prostatectomy, [850] and prior pelvic/perineal radiation [850, 920]. All of these bowel-related disorders, surgeries, and radiation should be part of the focused history in older adults with FI. More studies are needed to identify causal pathways for FI in the older adult.

Functional FI, defined by mobility problems or restricted accessibility to the toilet despite normal bowel sensation and capacity, is also cited as a common reason for FI in epidemiological studies among community-dwelling older adults and those in residing in nursing homes [204, 832,833,901,921-928].

Other causes of FI in older adults can be related to **co-morbid chronic disorders, increased body mass index, and multimorbidity, especially diabetes and neurological disease**, which increases the risk having FI. Number of comorbidities and number of drugs have been associated with FI in a Spanish population-based study of people older than 65 years [909]. Poor self-rated health and depression are associated with bowel symptoms in adults 50 years and older [929]. Even after adjusting for age and sex, diabetes mellitus is associated with gastrointestinal symptoms including FI in population based studies, [909, 930-932], nursing home residents, [928] and has been associated with impaired rectal sensitivity and sphincter weakness [933]. Neurological diseases that contribute to FI in older adults include cognitive impairment, stroke, traumatic brain injury, and sacral cord dysfunction. Older adults are living longer with significant neurological conditions. Cognitive impairment and dementia have been found to be independent risk factors with FI in older adult populations from epidemiological studies and among those in nursing homes [850, 901, 922, 924]. Having a stroke is an important risk factor for FI with three and half times the rate of FI compared to adults who did not have a stroke in one population-based study [934]. FI affects 30-56% of stroke survivors in acute period after having a stroke (1-30 days), with a lower prevalence (11%) of FI after 3-months, and 11-22% at 12-months following the initial stroke event [935, 936]. Recent evidence demonstrates toileting disability can be present after stroke potentially linked to behavioural, cognitive and physical function impairments [388].Traumatic brain injury has also been linked with urinary incontinence and FI, but limited data exist on older adults from registry studies and single site studies [937, 938]. Spinal cord injury (depending on the level of injury) may result in impaired muscular strength of the external anal sphincter, delayed transit time, abnormal defaecation reflexes, and impaired sensation [939].

Summary of evidence for prevalence and risk factors for FI in frail older adults

Summarised below are key points that are specific to the frail elderly population. The level of evidence is given in brackets.

- FI affects 1 in 5 older people (aged 65+) living in the community and in residential care facilities, and half of those residing in long-term care homes [**LoE1**]
- The prevalence of FI increases with age alone, particularly in the 8th decade and beyond **[LoE1]**
- The prevalence of FI is higher in the acute hospital, and nursing home setting than in the community **[LoE 1]**, thus the group most affected is frail older people.
- The prevalence of FI in frail older men is equal to or greater than in women in the community and in long-term care residents **[LoE 2].**
- The prevalence of FI varies dramatically between institutions in nursing home studies due to measurement differences **[LoE 2].**
- FI usually coexists with urinary incontinence in frail older people **[LoE 1]**
- Aside from age, the following are primary risk factors for FI in older people **[LoE 2]:**
  - Stool consistency -- Loose stool
  - Bowel-related disorders, such as prior rectal surgery
  - Impaired mobility
  - Functional impairment
  - Dementia
  - Neurological disease
  - Diabetes mellitus
  - Chronic medical conditions
  - Depression
- Loose stool or diarrhoea may be a cause of transient FI in older people, if the diarrhoea is evaluated and treated **[LoE 2]**
- Faecal loading and constipation are clinically linked to FI, but there is little epidemiological work assessing this association **[LoE 3]**
- Physicians and nurses in primary care, acute hospital, and long-term health care settings do not have a high awareness of FI in older people **[LoE 2]**
- Within nursing homes, there is a low rate of referral by nursing staff of residents to primary care physicians or continence nurse specialists for further assessment of FI **[LoE 2**], and there is a tendency toward passive management (e.g., use of pads only without further evaluation) [**LoE 2].** Faecal loading is often present in older care home residents with FI **[LoE 2]**
- Older people may be reluctant to volunteer the symptoms of FI to their health care provider for social or cultural reasons, or due to a popular misperception that the condition is part of the ageing process and therefore 'nothing can be done about it' **[LoE 2]**
- FI is associated with reduced quality of life, and poor health perception **[LoE 2]**

Recommendations – identifying faecal incontinence in frail older people

Bowel continence status should be established by *direct questioning and/or direct observation* in:

- all nursing/long-term care and residential home residents
- hospital inpatients aged 65 and over
- people aged 80 and beyond living at home
- older adults with impaired mobility
- older adults with impaired cognition
- older adults with neurological disease
- older adults with chronic disease, especially diabetes
- older adults with constipation
- Primary care staff, hospital ward staff, home health staff, and long-term care staff should routinely enquire about FI in frail older patients
- Enquiry about FI should be systematic and include stool consistency, severity of FI and impact on activities of daily living and quality of life
- Health care providers should be sensitive to cultural and social barriers discouraging patients from talking about the condition
- Frail older patients with restricted ability to access primary care such as nursing home residents, and those with mobility, chronic illness, or cognitive impairment, should be screened for FI through systematic case-finding methods
- Systematic outreach programmes which make it easier for frail older people and those who care for them to volunteer the problem to their primary care provider should be implemented
- There are significant geographical variations in provision of specialist expertise in bowel care (both medical and nursing) nationally and globally, which may affect case-finding in older people
- Further examination of underlying reasons for the variations in prevalence of FI between nursing homes (standards of care, patient case-mix, reporting) is needed
- Urinary and FI often coexist; continence care workers (e.g., nurse specialists) should be trained in identification and management of fecal as well as urinary incontinence in older people
- Key requirements to improving detection in the practice setting should be implemented:
  - education of health care workers to embed both a sense of value in identifying FI, plus confidence that the condition can be treated
  - protocols should be in place clarifying all details of screening enquiry (who will ask, how to ask, when to ask, and who to ask)
  - patients and caregivers should have access to educational materials at the point of enquiry

7. EVALUATION OF FI IN FRAIL OLDER ADULTS

The algorithm contained in this chapter delineates a systematic approach to the clinical evaluation of frail older people with FI.

An initial assessment can be undertaken by any suitably trained health care practitioner, often this will be by either a physician or nurse practitioner. In the majority of cases, a clinical history of bowel symptoms, dietary assessment, [884, 940] and symptom evaluation will provide sufficient diagnostic information upon which to base further management. As many older patients will not offer the information, it is important for primary care providers to ask about feacal incontinence as well as urinary incontinence [941] Using questionnaires for assessment of symptoms is recommended, although psychometric validation of specific instruments to asses FI severity and impact on quality of life in frail older adults compared to healthy adults are not available. In spite of this, symptom assessment instruments can provide insight into concerns such as feacal urgency in nursing home residents [942], although high rates of dementia among residents may limit usability in some settings. Bowel diaries, including assessments of stool consistency, may also be useful to diagnose the type and frequency of FI [943, 944].

Physical examination should include skin inspection, pelvic exam (females) and a digital rectal exam. Faecal incontinence is also associated incontinence associated dermatitis, development of pressure injury and higher body mass index in older nursing home residents [945]. Thus, an assessment of skin integrity and provision of appropriate pressure relief is important. A pelvic examination to rule out rectal prolapse and posterior compartment vaginal prolapse is also important given the association between prolapse FI and other pelvic floor disorders in older community dwelling women [946]. A digital rectal examination should be undertaken to assess anal sphincter tone [944]. Digital rectal examination can assess resting anal sphincter tone, muscle isolation, and squeeze pressure and appears to be as good as sphincter manometry in discriminating continent from incontinent people. Constipated patients should also have an abdominal exam; those with an empty rectum on digital examination may have high impaction. Abdominal radiographs to assess the extent of faecal loading and to rule out an obstruction or sigmoid volvulus could be considered. For adults with FI, it is important that current guidelines for colon cancer screening be followed, along with careful consideration of screening in older adults with limited life expectancy [947]. While a change in bowel habits with weight loss, anaemia, rectal pain and rectal bleeding should raise the suspicion of an underlying malignancy, prior review of colonoscopy findings and discussion with gastroenterologists for further testing may be warranted. The symptom of FI and chronic constipation does not usually warrant colonoscopic investigation, however, little data exist to guide evaluation in frail older adults. The use of formal testing is hampered by both lack of relevant data from frail older people and the poor correlation between symptoms and abnormalities [869, 875, 948, 949, 863, 864, 869, 950-952]. Given the increased difficulty of adequately preparing frail older people for either endoscopy or barium studies and potential increased risks of hyponatraemia with hospitalisation [949, 953]; CT colonography, although not studied in frail older adults, may be considered as an alternative investigation where available as no sedation is required

[947]. Toileting disability may be present in frail older persons in residential care [333] and the evaluation of the capacity to successfully toilet should include an assessment of mobility, visual acuity, manual dexterity and cognition. If acceptable to the older person, observing the process of transferring to the toilet, manage their clothing, redress and leave the lavatory is a good measure of ability. Caregivers should additionally be aware of the surroundings in which the frail older person lives in terms of access, lighting, distance and clutter. The design of commodes should also be considered in the light of the individual's capabilities.

Evidence that the assessment of faecal incontinence in older people is poorly done, despite the existence of guidelines, has been a persistent finding throughout the history of this chapter and in other guidelines [837, 954]. What actions need to be taken to ensure that older people receive assessments which are consistent with current guidelines remain to be defined.

8. TREATMENT OF FI IN FRAIL OLDER ADULTS

In the previous review, it was noted many FI intervention studies have small sample sizes, inadequate power to detect clinically meaningful difference in outcomes, and biased methodology along with low strength of evidence ratings [955, 956]. Interventions for FI are reviewed in detail in Chapter 15

As in the previous edition, this section addresses FI treatments applicable or potentially applicable to older adults including multi-component behavioural treatments for FI, pharmacological treatments for FI, treatments aimed at specific populations of older adults (e.g. nursing home populations and neurological conditions), anal bulking injections, transcutaneous and percutaneous tibial nerve stimulation, bowel-control devices, and less-invasive surgical options. The section on combination biofeedback, behavioural treatments for FI was modified to include studies that included pharmacological treatments for FI combination with biofeedback and behavioural treatments. Issues related to more invasive surgery (including sacral nerve stimulation and antegrade continence enemata), containment with absorptive products or devices, and skin care are discussed in other chapters

8.1. Prevention of FI in older persons

Using data from the US Nurses Study, the association of risk of FI and long-term dietary fibre intake was studied in 58330 older women with a mean age of 73 years. Women in the highest quintile of fibre intake (25 gm/day) had an 18% decreased risk of FI [957]. Although this study focused on older women, no data on frailty were provided.

8.2. Multi-component biofeedback and behavioural treatments +/- pharmacological treatment for FI.

In the previous edition it was noted that few studies exist in the literature involving multi-component interventions for FI in older adults. In some studies, old persons are included, but those with risk factors for frailty such as stroke, cognitive impairment and neurological diseases such as Parkinson's are excluded e.g., Ussing, 2019 [958]. Given the multifactorial causes for FI in frail older adults and the wide range of ages in many trials, a definitive assessment of the role of pelvic floor muscle training and/or biofeedback, pharmacologi-cal therapy in the treatment of FI, or the treatment of FI and constipation in adults with central neurological diseases remains unclear as previously reported [959-962]. A small descriptive pilot study of a patient-controlled biofeedback device (n= 10 women, mean age 64.1 years, range 50-73 years) reported improvement on manometric, FI symptom scores and quality of life but details about the participants are minimal [963]. Given the demands of using the device it is not clear if frail older women would be able to benefit.

Studies that incorporated pharmacological treatment in the combination have included broad age range of participants with limited or no subgroup analysis of data from older participants. The last version included an RCT of 57 women attending an anorectal clinic (mean 58 years range age), treated with biofeedback on pelvic floor contraction, stool bulking agents (stericulia or isphagula husk) and loperamide showed a decrease in FI, urgency and loose stool [964]. However, those with neurological conditions and insulin dependent diabetes were excluded. In a recent four arm US trial in which 300 women (mean age 63.7 ±11.1) were randomized to placebo plus education, placebo with anal exercise plus biofeedback, loperamide plus education or loperamide plus anal exercises plus biofeedback, no treatment or treatment combination was found to be superior,[965] leading the authors to recommend combining loperamide, anal manometry-assisted biofeedback and a standard educational pamphlet with counselling on possible constipation. Those with neurological disorders, including Parkinson's and inability to provide written consent were excluded. Although both studies included older women, exclusion criteria potentially limit application to the frail population.

8.3. Pharmacological treatments for FI.

No studies focused solely on frail older adults were identified. Low-strength evidence exists that psyllium may be beneficial compared to placebo for improving FI episodes (n=206, mean age 55-60 years per randomisation group) [966]. Psyllium was better tolerated while having no differences in efficacy compared to loperamide for improving FI episodes (n=80, mean age 61 ±10 years) [967]. A non-randomised case series of methylcellulose also reported improvement in FI (N= 83, mean age 65 years SD +/- 12 [968]. No new trials of laxatives in frail older persons to treat constipation and faecal impaction leading to FI were identified.

According to the 2016 AHRQ review [955] included in the last edition, evidence was treatment benefit was insufficient for loperamide, topical phenylephrine, zinc-aluminium ointment, oestrogen cream, and valproate sodium. Clonidine given orally was not effective for improving FI severity compared to placebo. No new studies in frail older persons were identified.

Small studies were previously reported on the evaluation of the safety of a new adrenergic alpha-1 receptor agonist suppository to improve anal sphincter tone, NRL001, for FI treatment in adults, with safety data in older participants [969, 970]. Results from a 4 group parallel designed placebo-controlled RCT (n=446, mean age 62.1 years) did show difference in FI severity scores after 8 weeks of treatment with 3 different dosages of the alpha-1 receptor agonist suppository compared to placebo [971]. No new studies in older adults were identified. Evidence for pharmacological treatments for improving FI in community-dwelling frail older adults with cognitive or functional impairment was again not found.

8.4. Treatment of FI in long-term care/nursing home settings.

Treatments for FI in long-term care settings have involved the treatment of constipation and faecal loading or faecal impaction. Two studies were previously reported. In a French RCT (n=206 nursing home residents in 4 homes) lactulose alone was compared to lactulose plus daily suppositories along with weekly enemata. Although there was no difference in FI episodes between the groups,

residents in the intervention group that achieved complete rectal emptying had 35% reduced number of FI episodes by 35% with staff workload reduction of 42% compared to the rest of the group. [908]. Schnelle *et al* (2010) completed a multi-centre, multi-component RCT for improving FI and constipation in 112 cognitively impaired nursing home residents (mean age 86 ± 10 years) [972] . The intervention group received toileting assistance, exercise, and choice of food/fluid snacks every 2 hours for 8 hours/day for 3 months, with improved bowel movement frequency and percentage of bowel movements in the toilet ($p<0.01$), but not the frequency of FI episodes Urinary incontinence episodes also improved with this intervention ($p<0.05$). 29 nursing home residents had ano-rectal manometry, with a dyssynergic defaecation pattern identified in 89%. The authors concluded further work to improve stool consistency and treatments for dyssynergia may be warranted. No new studies of laxatives for constipation or faecal loading in the nursing home setting were identified.

Additional work is ongoing to improve nursing education, evaluation, and treatment of FI in long-term care settings [973, 974] . By improving knowledge of nursing staff, outcomes related to FI management and treatment may also improve [973]. A recent realist synthesis of what works to improve FI in care home residents [975] highlights the importance addressing dementia and FI in this setting. Potential areas for improvement include clinician led support, ongoing feedback to staff, interventions suitable for the cognitive and physical capacity of residents, common understanding of potential reduction and recovery and integrating the care of persons living with both dementia and FI into the everyday patterns of work for staff.

8.5. Treatment of FI in Adults with Neurological Conditions

In the previous edition, it was noted that a 2014 Cochrane report on the treatment of FI and constipation in adults (not yet updated) reviewed evidence from 20 clinical trials involving 902 adults [961]. and concluded that “remarkably little research” and “low methodological quality” evidence exists on bowel management in specific neurologic conditions. Most of trials are single site, measuring outcomes against control and without comparative effectiveness data. Individuals’ trials did report symptom improvement using bulk-forming laxative (psyllium) in Parkinson’s disease, an isosmotic macrogol laxative to manage bowel symptoms, abdominal massage, electrical stimulation and an anticholinesterase-anticholinergic drug combination (neostigmine-glycopyrrolate) in spinal cord injury compared to no treatment or controls. There was also evidence in favour of transanal irrigation (compared to conservative management) in spinal cord injury, oral carbonated (rather than tap) water, and abdominal massage with lifestyle advice (compared to lifestyle advice alone) in stroke survivors [961]. A previously reported 2015 RCT among 200 bedbound acute care patients over 60 years with acute neurological impairments were randomised to a suspension positioning system or usual care. Rates of perianal faecal contamination, skin break-down, incontinence associated dermatitis, pres-sure ulcer development, and urinary tract infection (UTI) were significantly lower in intervention vs usual care group ($p<0.05$) at 6-months after treatment [976]. Two new studies of transanal irrigation adherence that included older persons were identified. In a descriptive study of 507 patients using transanal irrigation (mean age 56, range 19-86 years) attending an anal physiology clinic with either FI or constipation reported 216 had continued use at 1 year with symptom improvement [977]. In the second retrospective study of (n= 108, predominantly women (mean age 55 years, range 18-83, only 43% continued to use the procedure after one year, with discontinuance attributed to technical problems or constraints [978]. Neither study provided detail on older participants health history nor was subgroup analysis of older persons was reported, limiting understanding of use of this technique among frail older persons.

8.5.1. Perianal injectable bulking agents for the treatment of FI

Perianal injectable bulking agents for the treatment of FI identified in the previous review have limited data related to older, frail adults [955, 979]. Use of dextranomer tissue-bulking injections were more effective than sham injections for improving FI-free days, 50% reductions in FI episodes and quality of life (n=206, mean age 61 years, age range for recruitment 18-75 years), but not more effective than pelvic floor muscle exercises and biofeedback (n=126) [955, 980, 981] One new small non randomised study (n= 17, mean age 54, range 40-87, 16 female) of patients who had failed conservative treatment received injection with hyaluronate [982]. Fourteen patients met the criteria for successful treatment (greater than 50% improvement on FI events) after first injection. No detail on the older persons included in this study were provided, thus the utility of this treatment in frail older people is not clear.

8.6. Percutaneous tibial nerve stimulation (PTNS) for FI

Two trials were included in the previous edition. In one trial, PTNS was compared to sham stimulation in an RCT (n=227 mean age 58 years) [983]. After 12 weeks of treatment, both groups had improvements with at least a 50% reduction in FI episodes, participants in the PTNS did reporting improvements in the total number of FI episodes ($p=0.02$) and the urge FI episodes ($p=0.02$) compared to sham stimulation group. Those with neurological diseases (Parkinson’s, diabetic neuropathy) were excluded; no subgroup analysis of older participants is reported. The other was pilot study in older adults (mean age 84.2 ± 10 years), transcutaneous posterior tibial nerve stimulation (TPTNS) or sham stimulation was given weekly for 12-weeks to older adults (n=30) in residential care homes. Lower urinary tract symptoms improved during the pilot study, but the rates of improvement in bowel leakage did not meet thresholds for statistical improvement (47% in the TPTNS group, 27% in the sham group, $p=0.11$) [984]. One new observational study of low quality was identified which included older adults (n=22 participants who failed conservative treatment, mean age 64.1 years, range 26-81, various causes for FI) [985]. The authors reported that 77.2% of participants improved in terms of episodes of FI with bilateral PTNS, but no detail on the older participants was provided. A larger, well controlled RCT of PTNS (mean age 64 years) versus sham (65.5 years) was undertaken in 59 participant who previously failed conservative treatment [986]. Results showed a decrease in medium number of FI episodes per week in the intervention group, but no details on older participants or subgroup analysis of these participants is reported.

8.7. Other Nonsurgical Management Options

Anal plugs (n=76) [987] and a new vaginal bowel control device (n=110) [988] have prospective trial data showing improvements in 50% reduction of FI episodes, overall FI episodes, and quality of life. A secondary analysis of the data from the second study reported that shorter vaginal length and previous surgery for prolapse were associated with risk of fitting failure for the device [989]. Subgroup analyses of older adults were not described in any of these trials.

In summary, most treatment studies of FI either exclude older persons at risk of frailty and/or do not provide subgroup analysis of data for older persons. Studies of treatments for FI in both community dwelling and nursing home frail older persons are needed.

Summary of evidence treatment of FI in frail older people

- Evidence shows that stimulant laxatives, osmotic laxatives (PEG and lactulose), suppositories and enemata can be effective in treating faecal impaction in older people at risk of overflow **[LoE2]**. ***Included in 5th ICI chapter***
- Complete rectal clearance is required to reduce overflow FI **[LoE2]** but may be hard to achieve in frail older patients **[LoE 2]**.
- Structured multi-component approaches to bowel care did not reduce the frequency of FI in the nursing home setting, but did improve bowel frequency and number of bowel movements in the toilet **[LoE 2]**
- Older people with FI may benefit from biofeedback and sphincter strengthening exercises, if they are able to comply **[LoE 3]**
- Loperamide can reduce frequency of FI, particularly when associated with loose stool (once infection and other causes have been excluded) but should be used with caution **[LoE 2]**
- Addition of fibre supplementation to loperamide may not improve FI outcomes **[LoE 2]**
- Multi-component structured nurse-led assessment and intervention can improve bowel symptoms and alter bowel-related habits in older stroke patients **[LoE 2].**

Recommendations: treatment of FI in frail older people

All following recommendations are Grade C

- Patients identified as having constipation with overflow should have effective bowel clearance (using a combination of laxatives and enemata), and then maintenance therapy with stimulant or osmotic laxatives ***Included from 5th ICI chapter***
- Suppositories are useful in treating rectal outlet delay and preventing recurrent rectal impaction with regular use
- Loperamide is a useful treatment in FI, in the absence of constipation, but should be used with caution in older adults
- Causes of loose stool must be identified and treated.
- All frail older adults with FI should have structured multidisciplinary assessment and treatment of their bowel problem.
- Patient and caregiver education (using verbal and written materials) should be undertaken to promote self-efficacy and other coping mechanisms, and where appropriate self-management (e.g., reducing risk of constipation and impaction through dietary and lifestyle measures, advice on how to take loperamide). Advice on skin care, odour control, and continence aids is also important.
- Privacy and dignity of care during defaecation should be afforded to all older people in insitutionalised settings. Particular attention should be paid to this in patients with FI, as privacy may be relatively overlooked in their care.
- Greater emphasis needs to be placed on systematic and effective management of FI in older people backed up by sound communications between all health care providers, especially in the nursing home and acute hospital setting.
- Education of health care providers with regards to heightening awareness of the problem plus methods of identification, assessment and management of FI in older people should be broad-ranging and include geriatricians, general practitioners, hospital physicians, hospital, community, general practice and long-term care nurses, and related disciplines (physiotherapists, occupational therapists, dieticians, pharmacists).
- Cyclical national audit with provider accountability, of current practice in managing FI in older people is needed to lay the groundwork for standardised care and provide a culture of continuous quality improvement. Such audit tools should be developed using standardised consensus methods. Incentives to providers could be benchmarking their practice against national averages, opportunities to share successful practice change strategies, and professional validation linked to good practice.

Recommendations for research

- Trials of laxative and nonpharmacological treatment and prevention of faecal impaction and overflow are needed to optimise standards of prescribing and care.
- Future studies focused on frail older adults, both community dwelling and in nursing homes, are needed to identify treatments that are efficacious and reasonable in this population

XI. CONTINENCE AT THE END OF LIFE

1. BACKGROUND

Palliative care is an approach that aims to improve the quality of life of people and their families who are facing problems associated with life-threatening illness that cannot be cured. It prevents and relieves suffering through the early identification, assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual. As they approach death, people identify loss of dignity as a major concern. In up to 83% of patients This concern is often related to lack of control of their bodily functions [990] and loss of privacy, particularly during intimate care such as washing, toileting and potential bowel interventions.

In a study looking at the preferences for continence care at the end of life in patients receiving palliative care, [390] patients prioritised pain, responsive behaviour and urinary incontinence as the most important symptoms. This is closely aligned with a study of nursing home residents at end of life [991]. if necessary, Patients were willing to give up dignity to address the symptoms causing them more distress.

End of life care is defined as support for people who are in the last year or months of their life. This group often comprises people who have an advanced incurable illness or who are generally frail and have co-existing conditions such that death is expected within 12 months. The 2 terms are often used synonymously but differ in their meaning. Here we have provided evidence from studies in both areas

The most frequent primary diagnoses in studies examining faecal and urinary incontinence and other bladder and bowel related symptoms in palliative or end of life care are:
- cancer
- dementia
- heart failure
- stroke
- pulmonary disease

and patients cared for in a variety of settings:
- home
- care home
- hospice
- hospital

Cognitive decline and functional decline increase risk of developing UI or FI or both [834] and these are often affected when people are progressing towards end of life with any underlying condition leading to increased need for help and intervention.

2. PREVALENCE & IMPACT

There are few studies describing the prevalence of UI and FI in palliative/EOL care settings. However, what evidence does exist suggests that approximately 14% of patients in receipt of palliative care have urinary symptoms of some description [992]. For older patients with cancer receiving palliative care, the proportion experiencing UI, constipation or FI is much higher, occurring in up to 77% of patients [993].

In the home hospice setting, approximately 30% of patients are diagnosed with UI, with women and those with stroke or dementia at higher risk [199]. Nurses providing care viewed UI as an important issue facing patients and their families and stated that failing to manage it properly resulted in adverse events such as wounds, sores, rashes, skin breakdown, pain, discomfort, loss of dignity and emotional distress [994].

In patients with genitourinary cancer, late or long term effects of treatment included alterations in skin integrity, pain, altered urinary function and organ dysfunction specific to the type of cancer [995].

There is a high prevalence of FI in the home hospice setting with >40% presenting with some FI and > 64% of those having FI when referred [996]. In patients with heart failure, FI occurred in 16 % of patients and it was the symptom most frequently reported as being very distressing (64%). UI occurred in 29% and persisted for greater than 6 months in 55% of the cohort. Constipation was reported in 37% of patients, 42% of these found it very distressing; over 50% of patients In this study died in hospital [997].

Constipation is one of the most common problems experienced patients in receipt of palliative care. Fifty percent of patients admitted to the hospice cited constipation as a concern [998]. Chronically ill patients and palliative care patients share risk factors for constipation. These include decreased physical activity, fibre-deficient diets, illnesses that are progressive and often severely incapacitating and the use of constipating medications. Constipation has been identified as the most troublesome side effect of pain management in patients with cancer [999].

3. QUALITY OF THE DATA

There is a paucity of data to guide continence practice in palliative and end of life care. Comprehensive validated end of life assessment tools are lacking. The majority of clinical care guidelines are aimed at curative treatment as opposed to providing management that promotes comfort although there is clearly some overlap. Clinical guidelines do not tailor for those people who have terminal illnesses with urinary and /or faecal incontinence but available end of life guidance suggests that management of symptoms should be focused on maintenance of quality of life in accordance with the patient's values and preferences.

The principles applied to managing all incontinence should be carried through to palliative and end of life care. There should be structures that support dignity-protective continence care for care dependent older adults: time to deliver care and flexible working practices; staff knowledge and beliefs about incontinence; an adequate number of staff as well as staff who are trained; managerial support and leadership; a predictable work environment; regulation that does not constrain caring practices and a health system that ensures an equitable access to adequate and appropriate care and treatment, across the population.

4. MANAGEMENT OPTIONS

Managing incontinence at the end of life is complex and requires a comprehensive assessment of symptoms a drive to understand the underlying causes and realistic goals for treatment. It is also important to include patients and their relatives or care partners in medical decision making. Alongside the ethical imperative to deliver patient-centred care and respect patient autonomy, shared decision making is also associated with positive patient outcomes such as higher satisfaction with the decision and trust in the physician [1000].

5. ASSESSMENT

Assessment at the end of life should be focused on thorough investigation of the patient's experience of their symptoms, changing needs and preferences and planning ahead, including a holistic assessment of the impact of symptoms [1001, 1002]. No validated assessment or outcome measurement tools focusing on end-of-life incontinence were found. Despite the high prevalence of incontinence at the end of life, generic assessment tools assessing a broad range of symptoms at the end of life often exclude reference to incontinence (for example Edmonton Symptom Assessment Scale or Memorial Symptom Assessment Scale). Although many elements of generic incontinence questionnaires discussed in Chapter 4 such as the Kings Health Questionnaire are unlikely to be relevant at the end of life, they may offer prompts for assessing the impact of incontinence on patients' quality of life.

As patients' ability to communicate deteriorates in the last days and hours of life and many care settings implement a 'dying phase' care pathway to manage symptoms [1003]. A recent Cochrane review of these pathways concluded that there is currently limited evidence to support their use [1004]. In the UK, there has been considerable activity to provide individualised care, including the Royal College of Physicians "End-of-Life Care in the Acute Care Setting [1005] and NICE Guideline "Care of dying adults in the last days of life" [1002]. Neither of these resources refer to incontinence.

6. URINARY INCONTINENCE

There is evidence that nursing staff rely on 'practical wisdom' rather than evidence-based guidance to care for patients with urinary problems approaching end of life. [1006].

6.1. Containment products:
Pads are often used at end of life. A wide variety of product options should be available to meet individual patient needs and preferences. [1007].

6.2. Female urinals:
In a multicentre evaluation testing 13 female urinals with community-based women, they were described as easy to use without spillage when standing or crouching, or when sitting on the edge of a bed or chair. Few were used successfully when lying and women who had a higher level of dependency found fewer suitable products [1008].

In a further study looking at using a female urinal as an acceptable, safe and effective product to meet the toileting needs of women receiving palliative care on oncology wards in hospitals, the Vernafem disposable female urinal was found to be a suitable option for consideration of use in palliative patients. Its use was particularly appropriate for hospital as it can be pulped [1009].

6.3. Catheterisation:
There has been very little published on the management of urinary incontinence and the use of urinary catheters in terminally ill patients. An audit of case notes of patients who died on two oncology wards and a hospice at a large teaching hospital showed that 63% of patients had an indwelling catheter during their admission confirming that indwelling catheters are frequently used as a tool to manage urinary difficulties at the end of life [1010].. Potentially, there are several indications for catheterisation including, existing wound damage or pressure ulcers exacerbated by incontinence, pain or difficulty caused by getting in and out of bed or frequent changes of pads or bedlinen and urinary retention. In a prospective study [1011], 61 patients were admitted to the hospice and either had catheters already (23) or they were inserted in the hospice (22) for patient comfort, the conclusion for the 45 of 61 patients who were catheterised, was that it did not contribute to mortality and morbidity was mostly due to bacteriuria and any complications were relatively easily treated.

In a study of 145 deaths in an Intensive care Unit, 52 patients had UI in their final week, and 13 of these patients had extreme problems with UI. It was found that extremely poor Quality of death (QoD) measured with a validated score was associated with extreme UI problems. Indwelling catheter use was associated with a significantly better QoD [1012].

A further study to elicit preferences for different urinary incontinence (UI) treatments of cognitively intact, over age 80, geriatric patients in a geriatric hospital (not palliative or necessarily end of life but potentially nearing this phase, found that in discussion surrounding potential UI most respondents preferred diapers (79%), medications (78%), and scheduled toileting (79%) to urinary catheters. In addition, the study looked to contrast these answers with those from potential health proxies and providers and found that the preferences of cognitively competent geriatric patients for treatment of UI differed from those of their potential proxies e.g. health care providers or family members (other than spouses) illustrating the importance of early conversations regarding patient's wishes. [472].

6.4. Faecal incontinence, constipation & bowel care
Palliative care and end of life patients can experience many difficulties with bowel habit including diarrhoea, faecal incontinence and constipation. Assessment of bowel dysfunction should be part of an overall holistic palliative care assessment but currently there is no standardised assessment.

Some patients, for example those with end stage neurological diseases such as Parkinson's disease and MS, may have experienced FI or constipation since their initial diagnosis and therefore usual regimens should be maintained if they are successful.

There are guidelines for managing complex neurogenic bowel in patients with spinal cord injury [1013]. Spinal Cord Compression included studies related to bowel management in patients with MSCC specifically [1014]. Even specialists at a regional cancer centre lack the necessary skills to give effective bowel care for these patients. Given the lack of guidance, there can be many dilemmas presented to the clinicians looking after patients.

Diarrhoea: The Scottish Palliative care guidelines define diarrhoea as the passage of frequent loose stools with urgency or the passage of more than 3 unformed stools within a 24-hour period. These guidelines suggest considering the following potential causes as part of an assessment:

Drugs such as laxatives, antacids, antibiotics, NSAIDS, chemotherapy agents, disaccharide-containing (sugar free) elixirs and iron.

Radiotherapy, particularly when involving the abdomen or pelvis

Faecal impaction resulting in diarrhoea as overflow.

Obstruction – malignant faecal impaction, narcotic bowel syndrome (severe constipation caused by opioid analgesia) as well as malabsorption.

Concurrent disease such as diabetes mellitus, hyperthyroidism, pancreatic insufficiency, inflammatory bowel disease Pancreatic carcinoma, pancreatic islet cell tumour, carcinoid tumour, GI infection

Diet – ingestion of bran, fruit, hot spices or alcohol.

Specific measures can be undertaken to reduce the adverse consequences of the diarrhoea even if it is part of the patient's palliative or end of life condition. In trying to ascertain the cause of the diarrhoea, there could be potential improvements, for example treating proven infections or changing medications, disimpaction, if required, or considering bacterial overgrowth in certain groups such as ileo-colic resection. In carcinoid syndrome – octreotide can be considered.

The consequences of diarrhoea, such as depletion of vitamins and minerals may require replacement. If absorption of medicines is affected – alternative routes of administration can be sought. if the skin becomes excoriated as a consequence of diarrhoea or faecal incontinence, the area should be cleaned with a soft disposable cloth, patted dry and barrier cream should be applied to protect the skin.

6.5. Faecal incontinence
Management strategies for patients with faecal incontinence in frail older men and women at the end of life should be focused on promoting comfort rather than on cure. Data on the effectiveness of

these methods in palliative care or EOL patients in the home, care home, hospital or hospice are lacking.

Causes of faecal incontinence at the end of life are similar to those leading to diarrhoea.

The National Institute of Clinical and Healthcare Effectiveness (England & Wales) guidelines suggest that patients at the end of life may benefit from a faecal collection device if they experience persistent faecal incontinence as this would be best to maintain their dignity in the dying process. These devices are only suitable for very loose stool, and they might be used when a patient is confined to bed and needs assistance with bowel management. These devices also aid in maintaining skin integrity by preventing faecal leakage to delicate skin areas or reduce disruption when frequent linen changes are difficult.

6.6. Constipation

Constipation is one of the most common problems experienced by palliative care patients. Patients' perception of constipation is more influenced by ease of defaecation than bowel frequency and factors that healthcare professionals use to assess constipation such as absolute frequency of defaecation, frequency compared to normal habits and difficulty defaecating do not always align with those of patients [1015].

The Scottish Palliative care guidelines suggest possible causes of constipation including:

- Medication (opioids, antacids, diuretics, iron, 5HT3 antagonists)
- Secondary effects of illness (dehydration, immobility, poor diet, anorexia)
- Tumour in or compressing bowel wall
- Damage to lumbosacral spinal cord, cauda equina or pelvic nerves
- Hypercalcaemia
- Concurrent diseases such as diabetes, hypothyroidism, diverticular disease, anal fissure, haemorrhoids, Parkinson's disease, hypokalaemia.

Non-pharmacological management strategies include, considerations of diet and fluids, ensuring privacy, mobility and optimised toileting.

The Cochrane Collaboration review on laxative use for the management of constipation at the end-of-life notes uncertainty about the 'best' management of constipation [1016]. in this review all considered laxatives were of similar effectiveness but the evidence was limited by data from only a few small RCTs. None of the studies evaluated polyethylene glycol or any intervention given rectally. There is a need for more trials to evaluate the effectiveness of laxatives in palliative care populations. Extrapolating findings on the effectiveness of laxatives evaluated in other populations may be invalid.

In the UK, senna, lactulose and docusate are the three oral laxatives with the lowest cost base and these options were used as primary laxatives for 46% of patients, in keeping with previous hospice based research in the UK [998] and USA [1017]. No studies examining the effectiveness of docusate for constipation specifically in palliative care patients have been published. Treatment of constipation with docusate in chronically ill patients and terminally ill patients is based on inadequate experimental evidence [1018].

For opioid induced constipation, peripheral opioid antagonists can relieve constipation but allow preservation of centrally mediated analgesia. Methylnaltrexone and naloxegel should only be used under specialist advice, and use is often restricted to those with expertise in palliative care.

Comprehensive assessment, including a full history and performing a physical examination is variably recorded in practice. Education on prevention is poorly recorded and evidence of non-pharmacological intervention is less likely to be recorded than if pharmacological intervention is prescribed [1019].

Recommendations for practice

1. Physical and cognitive function will often vary from day-to-day. Regular assessment and individual management plans are required, taking in to account patient preferences and the context of care.

2. Timely environmental or behavioural interventions might be of benefit for individual patients for a limited period dependent on the illness trajectory.

3. Caregivers (professional and informal) should be educated in supporting the changing incontinence needs of dying patients.

Recommendations for research

Further research is required to:

1. Explore the patients' preferences for the management of UI and FI at the end of life.

2. Explore how carers (professional and informal) can be supported to care for the incontinence needs of people dying in different settings.

3. Identify the risks and benefits of using IDCs to provide comfort at the end of life.

Evaluate the impact of environmental and behavioural interventions to improve comfort and quality of life.

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COMMITTEE 15

ASSESSMENT AND CONSERVATIVE MANAGEMENT OF FAECAL INCONTINENCE AND QUALITY OF LIFE

Chair
Bliss, Donna. Chair (United States)

Co-Chair
Mimura, Toshiki. Co-Chair (Japan)

Members
Berghmans, Bary (Netherlands)
Bharucha, Adil (United States)
Carrington, Emma (United Kingdom)
Hunter, Kathleen (Canada)
Kumaran, Thiruppathy (United Kingdom)
Sakakibara, Ryuji (Japan)
Santoro, Giulio (Italy)

Consultants
Emmanuel, Anton. Consultant (United Kingdom)
Panicker, Jalesh. Consultant (United Kingdom)

COMMITTEE 15

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ABBREVIATIONS

ABL accidental bowel leakage
Ach acetylcholine
AFT anorectal function tests
AI anal incontinence
ANS Autonomic nervous system
ARA anorectal angle
ARM anorectal manometry
BET balloon expulsion test
BF biofeedback
BMI body mass index
CAPABLe trial Controlling Anal Incontinence by Performing Anal exercises with Biofeedback or Loperamide trial
CI confidence interval
CN-EMG Concentric needle electromyography
CNS central nervous system
CRADI-8 Colorectal-Anal Distress Inventory short form
DRESS Digital rectal examination scoring system
DKT Dai-Kenchu-To
EAS external anal sphincter
EAUS endoanal ultrasound
ENS enteric nervous system
ES electrical stimulation
ESGAR European Society of Gastrointestinal and Abdominal Radiology
ESUR European Society of Urogenital Radiology
FD fluoroscopic defaecography
FI faecal incontinence
FICA Fecal Incontinence and Constipation Assessment
FIE faecal incontinence episode
FISI Fecal Incontinence Severity Index
FISS Fecal Incontinence Symptom Severity Score
FIQL Fecal Incontinence Quality of Life scale
FODMAP fermentable oligo- di- and mono-saccharides and polyols
GI gastrointestinal
HBT home biofeedback therapy
HDAM high definition anorectal manometry
HRAM high resolution anorectal manometry
HT 5-hydrozytryptamine
IAS internal anal sphincter
IASD.D.2 Incontinence-Associated Skin Damage and Severity Instrument, version D.2
IBS irritable bowel syndrome
IBS-D irritable bowel syndrome with diarrhea
ICI International Consultation on Incontinence
ICIQ-B International Consultation on Incontinence modular questionnaire - the Bowel version
ICIQ-IBD International Consultation on Incontinence modular questionnaire - the Irritable Bowel Disease version
ICS International Continence Society
IQR interquartile range
JAMA Journal of the American Medical Association
LA levator ani
LBD Lewy body diseases
LUTS lower urinary tract symptoms
LVR laparoscopic ventral rectopexy
MCID minimum clinically important difference
Meps motor evoked potentials
Mes mucosal electrosensitivity
MIBG metaiodo-benzylguanidine
MRD magnetic resonance defaecography
MRI magnetic resonance imaging
MS multiple sclerosis
MSA multiple system atrophy
MUPs motor unit potentials
NO nitric oxide
NS not statistically significant
OASIS obstetric anal sphincter injury
OBT office-based biofeedback
PCL pubo-coccygeal line
PD Parkinson's disease
PFDI-20 Pelvic Floor Distress Inventory Short Form 20
PFIQ-7 Pelvic Floor Impact Questionnaire Short Form 7
PFMT pelvic floor muscle training
PTNS percutaneous tibial nerve electrical stimulation
QOL quality of life
OASIS Obstetric anal sphincter injury
RAFIS Rapid Assessment Faecal Incontinence Score
RAIR rectoanal inhibitory reflex
RBD REM sleep behavior disorder
RCTs randomized controlled clinical trials
REM rapid-eye movement
RKT Rikkunshi-To
RST rectal sensory test
SCFAs short chain fatty acids
SCI spinal cord injury
Sd standard deviation
Seps somatosensory evoked potentials
SF-EMG single fibre electromyography
SLT sacral latency test
SMD standardized mean difference
SNR signal-to-noise ratio
TNS tibial nerve electrical stimulation
TPUS transperineal ultrasound
Tsp teaspoon
UI urinary incontinence
VAS visual analog scale
VIP vasoactive intestinal peptide
XSLJZT Xiang-Sha-Liu-Jun-Zi tang

I. BACKGROUND

This chapter reviews evidence of a wide-ranging set of topics integral to the conservative management of faecal incontinence. A summary of the findings of the 6th Consultation on Incontinence (ICI6) (1) is provided as background to the current review. Topics without new evidence since ICI6 are not included. The chapter provides an updated review of evidence from studies about the initial clinical assessment of faecal incontinence, initial and secondary conservative management interventions, and specialized diagnostic testing for secondary and tertiary interventions. The focus is primarily on adults living in the community independently or with minimal, informal care assistance. Conservative management of faecal incontinence in individuals with neurological diseases or conditions is now included here as interventions used are similar. Recognizing the cyclic nature of faecal incontinence and constipation there is appropriate attention given to managing constipation for preventing incontinence. Because quantitative instruments or scales assessing the severity of faecal incontinence symptoms are sometimes used as part of clinical assessment, an evaluation of the common scales is included in this chapter. The impact of faecal incontinence on associated quality of life assessed from qualitative studies is reviewed using an evaluation system designed for those types of studies.

Levels of evidence are evaluated and recommendations for clinical practice that consider the body of available evidence have been developed. Recommendations for future research are offered. An

algorithm organized according to the three levels of intervention for conservative management is provided. Strategies for searching the literature for studies to review in this consultation are summarized at the end of this chapter.

1. SUMMARY OF ICI6 FINDINGS

1.1. Initial Clinical Assessment and Secondary and Tertiary Diagnostic Testing - ICI6

ICI6 (1) showed the reliability of a digital rectal examination to assess anal sphincter strength as part of the initial clinical assessment of faecal incontinence by experienced clinicians. The digital rectal examination scoring system (DRESS) was identified as a useful tool to describe anal sphincter tone. There is a valid and reliable scoring tool for the presence and severity of incontinence associated dermatitis/skin damage named the Incontinence Associated Skin Damage tool (version IASD.D.2) that has been tested using dark and light-toned skin colors. There have been numerous instruments developed for scoring the severity of anal incontinence. Six of the most commonly used scales were evaluated in ICI6. The tools contained differing items involved in scoring of faecal incontinence severity such as frequency of faecal leakage, flatus, urgency, use of pads, and impact on quality of life; none of the tool enabled scoring of faecal incontinence severity only. The tools had varying degrees of psychometric testing.

Regarding secondary and tertiary diagnostic testing, endoanal ultrasound (EAUS) is considered an important test in evaluating faecal incontinence. Use of 3D-EAUS improves outcomes after OASIS repair and some anorectal surgeries. High resolution (vs. usual) anorectal manometry (ARM) provides more detailed information about anal sphincter function. Defaecography is useful in the assessment of rectal intussusception and rectocele. Endocoil magnetic resonance imaging (MRI) is an accurate alternative to EAUS for detecting anal sphincter injuries. MRI can be used for anorectal malformations and external anal sphincter atrophy.

1.2. Lifestyle Modifications - ICI6

There is low health literacy about faecal incontinence and its management in patients with the condition and in family/informal caregivers. Observational studies described the need to educate patients and their caregivers about faecal incontinence but the most effective methods of educating different groups are undetermined. Supporting patient self-management of faecal incontinence in an essential part of its conservative management.

There were additional findings associating being overweight or obese with increased risk for faecal incontinence, primarily in studies of women and those with dual incontinence. Results of the effectiveness of weight loss from diet programs and after bariatric surgery in reducing faecal incontinence continue to be mixed; therefore recommendations for weight loss as a management strategy for faecal incontinence could not be made.

Evidence from two randomized clinical trials showed the effectiveness of supplementation with the dietary fibre psyllium in decreasing faecal incontinence. Low and higher amounts of supplemented fibre can be effective and intolerance symptoms are low suggesting options for incrementally increasing the fibre dose to an optimal amount. Formation of a gel in feces may be a mechanism of the effect of psyllium.

The use of trans-anal irrigation (mainly on a daily basis) by individuals with various causes of faecal incontinence has shown to reduce anal incontinence and defecation frequency and improve quality of life. Different types/brands of irrigation systems were used. Patients require education about how to perform trans-anal irrigation and use the supplies.

1.3. Medication Treatment - ICI6

There was new evidence that taking the anti-motility medication loperamide or a supplement of psyllium fibre decreased faecal incontinence. Other findings showed a reduction in faecal incontinence after a combination therapy of biofeedback, loperamide and dietary fibre supplementation. Medications for treating diarrhoea in inflammatory bowel syndrome with diarrhoea or increasing anal sphincter pressure have shown effects that have potential to reduce faecal incontinence but have not yet been studied for that problem.

1.4. Behavioural Therapies - ICI6

Behavioural therapies continued to be recommended as a secondary intervention for faecal incontinence. Pelvic floor muscle therapy has potential for reducing faecal incontinence but findings of studies remain mixed. A standardized optimal procedure is lacking. Home-based biofeedback using battery operated portable devices can be an effective adjunct to clinic-based therapy in reducing faecal incontinence. Young patients seem to be more responsive to this approach. There is initial evidence that higher frequency electrical stimulation (ES) combined with biofeedback may be more effective in reducing faecal incontinence than low-frequency ES alone or biofeedback alone.

1.5. Quality of Life from Qualitative Research - ICI6

Findings from several qualitative studies were consistent with those of earlier studies showing a negative effect on quality of life. Quality of life domains that are affected include bodily symptoms, self-esteem and body image, time and planning, dietary issues, social relationships, and sexuality. Negative feelings associated with living with faecal incontinence included anger, frustration, injustice, guilt, shame, disappointment, hopelessness, despair and sadness.

New information identified that other chronic illnesses and aging worsened bowel control. The unpredictability of faecal incontinence and urgency are some of the most troubling bodily symptoms. Attempting to have a sense of control over symptoms was a main theme of living with faecal incontinence in women, while some men became resigned to it. Men and women often adapted to faecal incontinence and tried to make the “best of it.” Receiving an explanation for symptoms made them easier to accept. After years of dealing with the symptoms of faecal incontinence, some individuals developed a sense of mastery and self-confidence. The low level of public knowledge of faecal incontinence created feelings of stigma.

II. INTRODUCTION

Faecal incontinence affects adults across age groups and sexes. It is a distressing and embarrassing condition that impairs quality of life and well-being, and interferes with work, social interactions, and intimacy (2-7). Faecal incontinence increases risk of skin damage in the extended perineum (including buttocks and inner thigh areas) from inflammation of epidermal skin layers (8, 9), to pressure injury (10). Conservative management of faecal incontinence is recommended in the absence of acute traumatic anal sphincter rupture or a major defect in the external anal sphincter confirmed by endosonograph in the presence of gross faecal leakage (See algorithm). Patients with these problems should be referred for surgical evaluation.

Conservative management refers to a variety of non-surgical and generally non-invasive interventions that are aimed to improve faecal incontinence or prevent worsening of its severity. In community-living adults, success of conservative management of faecal incontinence relies on patient self-management and self-management support by their clinician. Self-management can be defined as the ability of a person along with family and care from a clinician to manage symptoms, treatments, lifestyle changes, and psycho-social, and cultural consequences of chronic diseases (11). Self-management support is defined as the systematic provision of education and support by health care staff/systems to increase patients' skills and confidence in managing health problems, including goal setting, monitoring progress, and problem-solving (12). Conservative management with support of a patient's ongoing self-management is recommended as the initial approach of treatment in the vast majority of patients before considering surgical treatments. These conservative approaches are comparatively inexpensive, have low risk for morbidity or mortality, and outcomes may be satisfactory and sufficient to achieve the treatment goals of many patients.

Initial conservative management begins with a clinical assessment a clinician with knowledge of the condition's presentation and experience with its management. Self-management support is guided by an evidence-based management plan developed by the clinician and patient that considers a patient's goals for treatment (13). Depending on the patient's response, various conservative interventions and lifestyle modifications may be introduced, tried, evaluated, and changed at different times. Clinical experience shows that patients may need to use more than one self-management intervention at a time and that adjustments to their plan may be needed over time. Environmental factors such as toilet availability can promote self-management and continence, activity and socialization in public spaces and improve quality of life whereas environmental barriers are created when these are lacking. If initial conservative management interventions are unsuccessful or unsatisfactory, there are numerous secondary interventions that may be used or added to a patient's management plan. Inclusion of a clinician with expertise in these secondary, specialized interventions in the patient's care team is recommended. For faecal incontinence that is refractory to conservative management, additional specialized diagnostic testing and tertiary level management including possible surgery are indicated. Faecal incontinence can significantly decrease quality of life and assessing the areas it impacts can guide development of goals for therapy and supports a holistic management plan.

1. DEFINITIONS

1.1. Definitions of Types of Bowel Incontinence

This committee uses and recommends the following definitions for types of bowel incontinence (1):

- Anal incontinence (AI) is the involuntary loss of flatus and faeces and/or mucus.
- Faecal incontinence (FI) is the involuntary loss of faeces.
- Flatus (or Flatal) incontinence is the involuntary loss of rectal gas or flatus.
- Mucus incontinence is the involuntary loss of mucus only (without faeces).

The terms and definition of FI and AI are not synonymous. The committee recommends that whichever definition is used in studies and publications, the conceptual and operational definition be made explicit and used in a consistent manner. In particular, scores of symptom severity should allow for quantification of FI severity separately from that of AI to facilitate comparison with findings of studies of FI , describe the contribution of faecal and flatus leakage to guide management, and expand the body of knowledge in this area. Similarly, quantifying the severity of flatus or mucus incontinence separately is optimal. The choice of which definition to use depends on the outcome of interest and scientific and clinical judgement. The prevalence of the different types of bowel incontinence and the percentage of anal incontinence that the different types constitute are not fully known. Use of these definitions in research studies will enable collection of these data. This committee acknowledges that the degree of bothersomeness, embarrassment, or distress associated FI or AI is subjective and may influence a patient's treatment seeking.

1.2. Definitions of Subtypes

Subtypes of FI and AI are leakage that is passive, associated with excessive urgency to defaecate, and due to functional or multimodal limitations. Passive FI is the involuntary leakage of faeces without forewarning. Seepage between the buttocks or on a small pad without the patient's awareness is an example of passive FI.

- Passive FI thought to be related to internal anal sphincter dysfunction; (14-16); it may also occur after normal defaecation, which is can be related to internal anal sphincter dysfunction or poor "snapping shut" (i.e., closure) of the external anal sphincter after defaecation (16, 17). FI associated with defaecation urgency is the inability to defer defaecation once the urge is perceived for long enough to reach a toilet. However, as distances to a toilet, waiting time for a public toilet to become available, and mobility level will vary, urgency is an inconsistent and uncontrolled condition that is difficult to measure and hence assess accurately.
- FI associated with excessive urgency is often associated with external anal sphincter dysfunction (14, 15). Faecal incontinence associated with urgency has also been associated with reduced rectal capacity and with increased rectal sensitivity (18, 19). Preliminary findings from 3D endoanal ultrasound show that patients with urgency had a higher rectal compression ratio during Valsalva compared to those with passive FI suggesting there may be a dynamic anatomic component to urgency (20).
- Functional (disability associated) FI occurs in the context of limitations in such activities as mobility, ability to manipulate clothing, cognitive impairment or delayed assistance with toileting. Functional (disability associated) incontinence when referring to UI is also termed dependent incontinence (21). Fonda and Abrams (21), proposed "contained incontinence" as a term to describe where urine leakage is contained in an absorbent pad or appliance. This definition has some relevance to FI that is managed solely with absorbent products or an appliance such as a peri-anal pouch.
- Multimodal incontinence refers to incontinence due to multiple health and functional comorbidities that reduce toileting ability. Being obese and having shortness of breath due to chronic obstructive pulmonary disease that reduce walking speed to the toilet is one example.

III. INITIAL CLINICAL ASSESSMENT AND DIFFERENTIAL DIAGNOSIS FAECAL INCONTINENCE

1. INTRODUCTION

The initial clinical assessment of FI is critical for successful management. The initial clinical assessment includes a focused history (including symptom assessment), focused physical examination, medication and diet review, and an assessment of impact on quality of life. As FI is maintained by complex mechanisms and relies on several different factors, including stool consistency, anal sphincter function, anorectal sensation, intra-rectal pressure, rectal capacity and compliance, colonic function, and cognitive processes (22, 23), and the aetiology of FI is often multifactorial. Therefore, a detailed history and physical examination, including an anorectal exam, is essential to evaluate these factors for its initial management.

Patient completed bowel diaries can be a useful part of the assessment process (24). A 7-14 day bowel diary can identify the relationship of bowel patterns, rectal urgency and daily routine to FI in women (25). Bowel diaries often include items such as stool frequency, shape, consistency and colour, along with episodes of faecal urgency, incontinence or the need to strain to pass stool. Additional items might be food and fluid intake and medications, particularly laxatives. At present there are no standardized items to include in a bowel diary, but an ICS working group is working towards identifying and making recommendations as to the most useful and clinically relevant items to incorporate.

Initial management may also include referral for proctosigmoidoscopy and/or colonoscopy as needed to assess for specific conditions including haemorrhoids, inflammatory bowel disease or suspected cancer, if history and physical examination suggest these conditions are included in the differential diagnosis.

2. HISTORY

History gathering requires sensitivity, but patients prefer clinicians (physicians, nurse practitioners, continence nurse specialists, physiotherapists, etc.) to ask them directly about FI (26, 27). More than two thirds of women with FI do not seek care voluntarily (28), while men take longer than women before asking for treatment (29). The aims of history taking and examination are to identify conditions that are amenable to management and to characterize symptoms so that they might be reduced.

In taking a history, assessing the impact of FI on quality of life (See Section XII-Qualitative Research on the Experience of Faecal Incontinence and Quality of Life), the patient's goals of treatment (30), and symptom severity (31), are important in planning care and to engage the patient in the plan. Questionnaires to assess symptom severity of AI such as the Fecal Incontinence Severity Index (FISI) (32), Fecal Incontinence Symptom Severity Score (FISS) (18, 33), or St. Mark's/Vaizey Score (34), should be used in the symptom assessment (See below). Use of valid and reliable measures is recommended for clinical practice and essential in research. In clinical practice, short, simple, and easy to use questionnaires are preferable for all patients.

A history should include:

- Daily bowel habits, the nature of the incontinence, past surgical & obstetric history, co-morbidities and current medication, including laxatives. Daily bowel habits include bowel frequency and stool consistency. Stool consistency can be quantified with Bristol stool form scale (35), **(Level of Evidence 3)** or a simpler and shorter stool consistency classification developed by Bliss and colleagues (18, 34) **(Level of Evidence 2)**.
- Ask about symptom onset and duration, and the nature of the incontinence by subtype (e.g., passive), frequency, amount, consistency of the leakage and the presence of urgency (23, 36) **(Level of Evidence 4)**. Timing of faecal incontinence (e.g. post-defaecation, during the night, any time) is important as faecal incontinence is not always associated with a bowel movement. Leakage can occur immediately before or in between bowel movements (37) **(Level of Evidence 3)**. Nocturnal faecal incontinence is uncommon, most frequently encountered in patients with neurogenic disorders, faecal impaction, low anterior resection syndrome, post-restorative proctocolectomy, diabetes mellitus and scleroderma (23) **(Level of Evidence 4)**.
- Differentiate the type (anal, faecal or mucus) as well as subtype of FI (passive, urge, and functional faecal incontinence) may help identify aetiology (31) (See Section I in this chapter about subtypes of FI).

2.1. Assessing Risk factors

The clinician must identify risk factors potentially associated with aetiology of FI. This is a part of constructing a comprehensive list of potential items in a differential diagnosis that need to be evaluated through the process of clinical reasoning to identify the most likely diagnosis and contributing factors to the FI. (See Chapter 1 for more detailed information regarding FI risk factors). Assessment of risk factors includes inquiring about:

- Diet – including intake of caffeine **(Level of Evidence 4)** and poorly absorbed carbohydrates (e.g. fructose, high fructose corn syrups and sorbitol) sorbitol (Level of Evidence = 3) as they may stimulate GI transit or diarrhoea (38-41). Medication - overdose or abuse of laxatives could cause chronic diarrhoea leading to faecal incontinence, particularly in older persons (42) **(Level of Evidence 4)**.
- Anti-anginal and antihypertensive medications (e.g., calcium channel blockers and adrenergic alpha-1 receptor antagonists) may reduce internal anal sphincter tone (43), magnesium containing antacids (40, 44) and metformin (45). Menopausal hormone therapy may increase risk for FI in postmenopausal women (46), as can obesity **(Level of Evidence 3).**
- Co-morbidities – risk factors for FI include older age, diabetes mellitus, irritable bowel syndrome, inflammatory bowel disease, constipation (faecal impaction with overflow), benign anal disease (haemorrhoids, fistula, anal warts), and scleroderma. Low activity level in older women is also a risk factor (46) **(Level of Evidence 4).**
- Neurological disease and disorders - brain (e.g., Parkinson's disease, stroke and dementia), spinal cord (e.g., spinal cord injury, tumour, multiple sclerosis) and peripheral nerve (e.g., diabetes mellitus) disorders increase the risk for developing FI (22, 23, 47-49) **(Level of Evidence 4).**
- Obstetric history - Obstetric anal sphincter injury (OASIS) (sphincter disruption, tear or pudendal neuropathy) risk factors following vaginal delivery include: primiparous delivery, forceps or ventouse (vacuum) use, birth weight > 4 kg, occipital-poste-

rior position at delivery, and prolonged second stage of labour (50-53) **(Level of Evidence 3).**
- Anal intercourse has been identified as a risk factor for FI in both women and men **(Level of Evidence = 3)** (54).
- Surgeries - including anal fissure surgery (sphincterotomy or anal stretch), haemorrhoidectomy, fistula surgery and low anterior resection (55-57) (Level of Evidence = 3). Cholecystectomy could cause post-cholecystectomy diarrhoea, leading to FI (57) **(Level of Evidence = 3)**.
- Pelvic radiation - risk of radiation prostatitis causing decreased rectal compliance and internal anal sphincter damage (58). Radiation dose may increase risk of late FI (59) **(Level of Evidence = 4)**.
- Symptoms of other pelvic floor problems (urinary incontinence and pelvic organ prolapse), which have similar risk factors (57, 60, 61) **(Level of Evidence = 3)**.

3. INSPECTION AND PHYSICAL EXAMINATION

3.1. General and Perianal Examination

Although there is a lack of well conducted studies in clinical examination comparing subtypes of FI (62), it remains a key component of evaluation. Examination is focused on the detection of evidence of FI and identifying its causes, if possible. True FI must be differentiated from conditions that cause discharge or seepage of mucus such as prolapsing external haemorrhoids, fistulae, and low rectal or anal tumours as well as from poor perineal hygiene. Physical examination should include inspection of underclothing for soiling and staining by stool, pus, or mucus. Perianal skin should be examined for signs of irritation such as erythema, rash, and excoriation (63). The Incontinence-Associated Skin Damage and Severity Instrument, version D.2 for use with light to dark toned skin (IASD.D.2), is a validated and useful tool to assess inflammatory damage of the upper skin layers resulting from FI (64, 65).

Perianal inspection should also include attempts to identify a patulous anus or one which gapes on gentle traction of the anal verge and/or a “keyhole” deformity of the anal canal which suggests a persisting sphincter defect. Inspection may reveal scars from previous episiotomies, or obstetric tears. Abnormalities at the anal verge from previous surgery or a gaping anus suggestive of marked loss of function may be present. Perianal inspection should identify the following (22, 23) **(Level of Evidence = 4)**:
- Scars from previous surgery or obstetric injury
- Perianal disease - prolapsing haemorrhoids, fistula, anal warts
- Presence of sensory deficits – numbness on the perianal skin
- Absence of perineal body - suggestive of obstetric trauma; at its worst this may manifest as a cloacal deformity

3.2. Vaginal Examination

For women, a vaginal exam using a Simms speculum may show a rectocele, cystocele and/or uterine prolapse, all of which may contribute to developing FI (66, 67) (Level of Evidence = 4). Physiological and complementary radiological tests are used to confirm clinical suspicion and provide objective data on the function of the anorectum. Pelvic floor dysfunction is a complex problem and multiple tests may be needed based on initial findings and complexity of the planned intervention.

3.3. Digital Rectal Examination

A digital rectal examination should be undertaken to assess the following (22, 23, 68, 69) **(Level of Evidence = 4)**. Assess for:
- Rectal contents - if faecal impaction is present, this could explain incontinence
- Rectal tumour or mass – if palpable, colonoscopy is required.
- Resting tone - indicative of internal anal sphincter function.
- Voluntary and reflex squeeze pressure – indicative of external anal sphincter function and potential function, respectively. The latter is elicited most commonly by asking the patient to cough while assessing sphincter tone - a cough causes a reflex near-maximal external sphincter contraction.
- Function of the puborectalis muscle (palpable at the anorectal junction) - assessed by asking the patient to squeeze the sphincter at which time the puborectalis should push the examiner’s finger anteriorly.
- Regional sphincter defects - detected as asymmetry.
- Paradoxical puborectalis contraction - this may be valuable in assessing constipated patients to identify paradoxical contraction as a cause of retained stool, and hence overflow incontinence (70).

The evaluation by the digital rectal examinations is reasonably correlated with anal canal manometry for resting pressure (68, 71-73), squeeze pressure (68, 71, 73, 74) **(Level of Evidence = 3)**, although there are some conflicting data (75), and more experience examiners have better correlation with manometry than beginners. The digital rectal examination scoring system (DRESS) describes anal sphincter tone on digital rectal examination (68), using a scale of 0 to 5 for both resting and squeeze pressures, ranging from 0 = no discernible pressure to 5 = extremely tight and 3 = normal. The DRESS correlates very well with anal manometry pressures for both resting and squeeze pressure **(Level of Evidence = 3)**. Experienced clinicians can reliably use the digital rectal examination to assess the anal sphincter strength, although anal inspection and digital rectal examination is not accurate enough to identify small to moderate external anal sphincter defects, which require further diagnostic work-up such as endoanal ultrasonography in select patients (73, 76) **(Level of Evidence = 3)**. For persons with known or suspected neurological disease, perineal sensations over the sacral dermatomes examined by using the pinprick method (69), and assessing the bulbocavernosus reflex may be relevant **(Level of Evidence = 4)**.

If rectal prolapse is suspected by history of mass prolapse per anus or perianal discomfort on straining or walking, but cannot be confirmed by Valsalva manoeuvre on a couch, the patient should be asked to sit on a commode and attempt defaecation and the perineum should then be inspected for evidence of a rectal mucosal or full thickness prolapse on straining.

3.4. Laboratory (Blood) Tests

There is no set panel of laboratory tests for FI. The clinician should be directed by the history and physical exam findings, and refer to practice guidelines for suspected conditions for guidance on laboratory testing.

3.5. Assessments for Condition-Specific Management

Referral for proctosigmoidoscopy and/or colonoscopy may be made at the time of initial assessment to assess for evaluation of specific conditions. Anoscopy and proctoscopy with a rigid instrument or flexible sigmoidoscopy are examinations of value in excluding potentially treatable causes of FI: anorectal tumours or polyps, inflammatory bowel diseases and haemorrhoids (22, 77), and solitary rectal ulcer syndrome, a functional disorder of evacuation

in which repeated straining at stool and or rectal self-digitalisation may result in an ulcerated area of the anterior rectal wall (77) **(Level of Evidence = 4)**.

3.6. Referral for Other Condition-Specific Problems

Based on the history and physical examination findings, referrals to appropriate providers should be made. For example, if a rectal mass is identified during the digital rectal examination, referral should be made for further assessment and investigation (e.g. rigid proctoscopy, biopsy) by a colorectal surgeon (78).

3.7. Referrals for Secondary Interventions

Based on the initial assessment, referrals to incontinence specialists including a specialist continence nurse or physical therapist, with assessment for potential surgery to a urogynecologist or gynaecologist, for secondary interventions may be made. Pelvic organ prolapse of the posterior compartment of the vagina could be improved with conservative management such as lifestyle interventions and physical therapies or reconstructive surgery (79). Referrals might also be for pelvic floor muscle therapy or incontinence products. The clinician conducting the assessment for FI should be knowledgeable about referral resources and clinical in their local area.

New Evidence about Clinical Assessment

There is further evidence that clinicians experienced with digital rectal examination can reliably use the procedure to assess the anal sphincter strength for both resting and squeeze pressure, and that more experienced examiners have better correlation with manometry than beginners (80).

An electronic diary (e-diary) designed to be used on a mobile phone was developed and data collection about FI, urgency, and continent bowel movements from the e-diary was compared to that on a paper diary in a randomized, crossover trial (81). Sixty of 67 women (87%) with refractory FI completed up to three consecutive 14-day diaries in two sequences. Study participants were required to report about each FI episode or bowel movement on both a paper diary and the e-diary. Paper and e-diaries were moderately or highly correlated for number of FI episodes per week (r = .66) and number of FI associated with urgency per week (r = .72). Test-retest reliability of the e-diary was good (ICC =.74 for number of FI episodes per week, and .62 for number of urgency FI episodes per week). Similar findings were reported for bowel movements. Usability of the e-diary, measured by the System Usability Score, was high (score = 82.3 ± 17.5). Approximately three-quarters of the users (75.9%) preferred the e-diary over a paper one.

Recommendations for Practice Related to Clinical Assessment

- Perform a baseline assessment including a focused medical history, a general physical examination, and an anorectal examination with inspection of perineal skin (Grade of Recommendation = C).
- The history should include risk factors and comorbid conditions, neurological and non-neurological, that could contribute to FI (Grade of Recommendation = C).
- Use of a validated questionnaire can assist in assessing symptoms in clinical practice (Grade of Recommendation = C).
- Try to differentiate the type of FI (passive and/or urge, or functional), which can help identify its aetiology (Grade of Recommendation = C).
- Several conditions should be specifically assessed for in the history and physical examination, as they may be amenable to definitive treatment, including anorectal tumour, rectal prolapse, haemorrhoids, faecal loading, potentially treatable causes of diarrhoea (e.g., inflammatory bowel disease, infection and irritable bowel syndrome), acute anal sphincter injury, and neurological disease (e.g., spinal cord injury and cauda equina syndrome) as they may be amenable to definitive treatment, including (Grade of Recommendation = C).
- Conduct a digital rectal examination to assess the strength of the internal and external anal sphincter as well as puborectal muscle (Grade of Recommendation = B).
- Clinicians trained in anoscopy and proctoscopy with access to equipment can undertake these examinations as part of initial assessment to exclude potentially treatable causes of FI (e.g., anorectal tumours, haemorrhoids, inflammatory bowel disease) (Grade of Recommendation = C).
- Further diagnostic work-up such as anorectal manometry, endoanal ultrasonography and defaecography are required, when the initial management fails to improve symptoms sufficiently (Grade of Recommendation = C).
- Assess and manage skin damage associated with FI (Grade of Recommendation = C).

Recommendations for Research on Clinical Assessment

- Establish Identify optimal approaches the best way for clinicians to ask patients directly about FI.
- Characterise the FI in men, who are remain less studied. This is inspite of although according to the epidemiological studies reporting both sexes are equally affected.

4. SYMPTOM SEVERITY SCALES FOR FAECAL (AND ANAL) INCONTINENCE

4.1. Description Of Scales

There are over 20 scales for rating the severity of FI or AI. Many scales were developed prior to 1992, are rarely used and have been reviewed elsewhere (82); these are not included in this review. Subsequently, six other scales; the instrument developed by Pescatori and Wexner (44, 82), which is also known as the Cleveland Clinic incontinence score, the Vaizey or St. Marks incontinence score (34), the Fecal Incontinence Severity Index Modified Manchester Health Questionnaire (83, 84), and the Fecal Incontinence and Constipation Assessment (FICA) symptom severity instrument (18, 33, 84, 85), now referred to as the Fecal Incontinence Symptom Severity Scale (FISS) have been developed and used in clinical studies to rate the severity of FI or AI. More recent instruments, the Bowel version of the International Consultation on Incontinence modular questionnaire (ICIQ-B), (86, 87), the ICIQ-IBD, which is tailored for patients with inflammatory bowel disease (88), and the Revised Fecal Incontinence Scale (89), have been developed and validated but not been widely used in clinical studies. The scales are summarised in Table 16-1.

In addition to the severity of FI, these scales also score the severity of flatus leakage and/or the impact of FI or AI on quality of life/lifestyle. However, none of the currently available scales provide a score for the severity of faecal leakage only, separately from anal/flatus incontinence, urgency, or quality of life. Use of these instruments typically relies on patient recall as they are not part of a daily diary.

All of these instruments contain an assessment of frequency of different types of rectal leakage suggesting that frequency is considered one of the most important dimensions of incontinence severity. Some scales assess additional issues related to incontinence, such as rectal urgency, amount or volume of leakage, or use of perineal protective products (e.g., pads). Five scales, Vaizey, FICA (FISS), ICIQ-B, ICIQ-IBD, Rapid Assessment FI Score (90), and the Accidental Bowel Leakage Evaluation instrument (91) include a measure of rectal/ defaecation urgency (18, 33, 34, 87, 88). The Vaizey scale (34), evaluates urgency with a question that asks about the "lack of ability to defer defaecation for 15 minutes" for which two response options are provided; weekly or daily. However, clinical observations suggest that this question may not accurately discriminate between people who have and do not have urgency because most people with severe urgency have a few, perhaps 5 minutes, at most to reach the toilet.

Population-based studies from the Rochester Epidemiology Project defined urgency as the need to "rush to the toilet" often (>25% of time) or usually (>75% of time) because of an "urgent need to empty the bowels" (18). Through an initial survey followed by a case-control study that included a two-week daily bowel diary, this study observed that bowel disturbances are the most important factors associated with FI and for incontinent bowel movements in women with FI (18, 25, 33, 57, 92). Rectal/defaecation urgency was an independent and the strongest factor associated with FI even after adjusting for other bowel disturbances.

Urgency is a distressing symptom (93). Patients with more severe urge FI report greater use of pads (94). Urgency is associated with loose stools, increased rectal sensitivity (18, 94), and reduced rectal capacity (i.e., a smaller reservoir) (18). Nonetheless, the time required for measuring the inability to reach a toilet before leakage occurs is not standardised and patients' estimates and sense of being rushed may vary greatly.

A state of the science summary emanating from a workshop organized by the U.S. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (31), emphasised the importance of considering the amount/volume of leakage when characterizing the severity of FI. When the amount of leakage was greater, the impact on quality of life was worse (92). Only one scale, the FISS, incorporates the amount of leakage into the assessment of AI severity, with a question that categorises the "usual leakage" as staining, a moderate amount (i.e., requiring change of underwear), and a large bowel movement (i.e., requiring change of all clothes) (18, 25, 33, 57, 92). Conceivably, a matrix defined by amount*frequency, which assesses the amount of leakage for each consistency of faeces leaked (e.g., solid or liquid) may more comprehensively characterise the severity of FI. This type of matrix scoring of FI severity was used by Bliss et al. (37), in summarizing data from a stool diary in a clinical trial of fibre supplementation for the treatment of FI. Using this assessment for AI would comprise four options for type of leakage (i.e., solid and liquid faeces, flatus, and mucus) and three for amount/volume (e.g., small, moderate, and large) requiring 12 items. The challenge is to develop measures that are comprehensive and useful for clinical practice and research but are not overly burdensome. One FI severity instrument also inquires about the bother related to leakage, predictability of leakage, lack of control over leakage, and bowel symptoms (91).

The current AI severity scoring systems assume that leakage of solid and liquid stools is equivalent. However, the FISI study observed that patients and physicians have different perspectives of severity; loss of liquid and solid stool was the worst for patients and physicians respectively (32). Patients with FI are able to reliably distinguish solid from loose/liquid stools (36, 37). Some measures (e.g., Wexner (44) and Vaizey (34) scales) consider the use of pads when characterising severity. However, use of these measures may conceivably reflect not only the severity of AI but also fastidiousness regarding one's sense of hygiene. Finally, the relationship between symptom severity and anorectal functions (e.g., anal resting and squeeze pressures) has not been established.

4.2. Assessing Clinically Important Differences in Symptom Severity

Most contemporary clinical trials have considered a 50% or greater reduction in the number of days or episodes of FI recorded with bowel diaries as the primary endpoint (95, 96). However, in an internet based survey, some patients, especially women aged 65 years and older, reported that they would not consider a 50% reduction in the frequency of FI to be sufficient; on average they considered a 77% reduction as sufficient (97). In accepting this assumption, it is necessary to ascertain whether a statistically significant change in the frequency of FI is also clinically significant (98). One way to accomplish this is to assess the minimum clinically important difference (MCID), which is the smallest change detected by an instrument that is associated with a clinically meaningful change (99). The MCID can be identified with distribution-based (½ of standard deviation of the population mean at baseline (100), and the effect size (mean change /standard deviation at baseline or an anchor based approach (98). These anchor-and distribution-based approaches (99), have been used to estimate the MCID for the FISI, FISS, Modified Manchester Health Questionnaire, and the Accidental Bowel Leakage Evaluation instrument (91, 101, 102). For example, based on the 0.5 SD threshold, the improvement in FISS exceeded the MCID in 75% and 83% of patients in whom the FI frequency declined by 50– 74% and ≥75% respectively (102).

A few practical issues pertaining to assessment of the MCID deserve emphasis. First, the distribution-based MCID (e.g., 0.5*SD, effect size) can be readily calculated. The SD is not a universal value but is unique for each study. The anchor-based methods require additional data to be collected at all follow-up assessments. This may be as simple as adding one additional item to the "post" measurement (for e.g., a global rating of better/worse for the time period between baseline and post measurement.) While MCID represents a step in the right direction and current methods have demonstrated a utility relative to identify meaningful 'day-to-day' life changes for a person with FI, we have to be more cautious if considering them "Clinically Important." None of the methods rely on a clinical gold standard to determine the amount of change that is clinically significant as defined by a gold standard. These methods rely on either distributional properties (1/2 standard deviation, MCID) or other self-reported assessments (anchor based) to identify meaningful change, not clinical indicators. These two questions may be considered as the anchor for assessing the MCID:

Over the past <period of time> please rate whether or not the frequency of bowel accidents has become: Much Less Frequent, Moderately Less Frequent, Somewhat Less Frequent, Somewhat More Frequent, Moderately More Frequent, Much More Frequent. Thinking about the bowel accidents you have had over the past <period of time> do you think that you are getting: Much Better, Moderately Better, Somewhat Better, Somewhat Worse, Moderately Worse, Much Worse.

4.3. Blending Symptom Severity and Quality of Life Scales

FI and AI can have a devastating impact on quality of life (QOL), which can be evaluated by generic or disease-specific instruments

(103). Some symptom severity scales also include typically one (34, 44, 89), sometimes more (87), questions related to impact of FI on lifestyle and QOL. The alternative approach is to use dedicated instruments with more questions that provide a more refined assessment of the impact of FI or AI on QOL (e.g., Fecal Incontinence Quality of Life Scale and modified Manchester Health Questionnaire, and FICA QOL scale) (33, 83, 104). There is a significant correlation between symptom severity and QOL in FI and AI (33, 104, 105).(See Qualitative Research section below). The Pelvic Organ Prolapse/Incontinence Sexual Questionnaire - IUGA Revised is validated in women with FI, allowing for measurement of sexual function with a condition-specific measure (106).

Bowel diaries are widely used to record bowel habits and track the severity of FI or AI. Bowel diaries are less prone to recall bias than questionnaires. They not only quantify FI or AI but also the relationship of episodes of incontinence to bowel habits, e.g., whether episodes of FI or AI are related to liquid or formed stools or preceded by urgency (25). These features are useful for guiding therapy. However, maintaining daily bowel diaries entails more work for patients and more analysis. With advancements in digital technology, mobile “apps”, internet, and telephone-based daily reporting of symptoms will likely be increasingly used in future.

New Evidence about Symptom Severity Scales

As detailed above and in the Table 15-1, there are two new scales for characterizing the severity of FI (90, 91). Of these instruments, the Accidental Bowel Leakage Evaluation instrument characterizes the frequency (and bother related to) leakage of solid faeces, liquid feces and flatus; urgency; awareness of leakage; sense of complete evacuation; predictability of leakage; control over leakage; and ancillary bowel symptoms. While treatment success is generally defined as a 50% reduction in the frequency of FI, a new study suggests that some, especially older, women consider this threshold to be higher (i.e., 77% reduction) (97).

Summary of Symptom Severity Scales

- The severity of FI or AI is based on symptoms evaluated by a self-report questionnaires. Questionnaires should be standardised and possess validity and reliability, but existing questionnaires vary in these quality properties.
- A scale that scores the severity of FI separately from AI that includes flatus incontinence is lacking and development is needed.
- The assessment of AI severity is currently comprised of the following domains: frequency, consistency, amount, subtype of leakage (e.g., urgency, passive leakage). Not all AI questionnaires incorporate all domains.
- At present, a 50% or greater reduction in the number of days or episodes of FI is a primary outcome measure in therapeutic trials. In one study, this outcome measure reflects a clinically important difference as measured by the minimal clinically important difference in 75% of patients.

Recommendations for Practice Related to Symptom Severity Scales

- The severity of FI should be assessed using standardized, quality instruments that incorporate score/grade its symptoms (Grade of Recommendation C).
- The severity of FI is correlated with its impact of the quality of life (Grade of Recommendation B).

Recommendations for Research on Symptom Severity Scales

- Develop and test an instrument offering a severity score for FI only, separate from that of AI and from quality of life measures.
- Evaluate the addition of weighting the scoring of the consistency of leaked faeces (e.g., liquid vs. solid) in FI or AI severity scales.
- Further studies are necessary to ascertain whether use, size, or number of pads is an indication of FI or AI severity, hygiene preference, affordability, or a coping mechanism that mediates the relationship between severity and QoL.
- Evaluate the role of behavioural and coping factors (e.g., staying near a toilet, ability to respond to urgency) in FI or AI severity. Develop measures for including the effects of these factors in FI severity scales if they have a significant impact.
- If rectal/defaecation urgency is to be used as an item in FI or AI severity scales, a way to standardize and measure urgency is necessary.

Table 15-1. Instruments for Rating Severity of Faecal or Anal Incontinence and Their Quality

Scale Name Reference	Content included in score and Type of Score (AI, FI or Blended with Impact on QOL)	Inclusion of Urgency or Amount/Volume of Faecal Leakage*	Construct Validity	Criterion Validity	Internal Consistency†	Test-Retest Reliability	Responsiveness
Pescatori (82)	Frequency of leakage of solid and liquid faeces, flatus, and flatus AI score	Urgency - Amount/Volume -	A (19)	B	B	A (19)	B
Wexner (44)	Frequency of leakage of solid and liquid faeces, flatus, pad use and lifestyle restriction AI QOL impact score	Urgency - Amount/Volume -	A (19,(107)	A (216)	A (107)	A (19)	A (217)
St Mark's Incontinence Score (34)	Frequency of leakage of solid and liquid faeces, flatus, and altered lifestyle Presence of urgency (inability to delay defaecation), needing to wear a pad or anal plug, or use of constipating medication AI score	Amount/Volume -	A (107)	A (218)	A (107)	A**	A (218)
FISI (32)	Frequency of leakage of solid faeces, liquid faeces, flatus, and mucus AI score	Urgency - Amount/Volume -	B	A	B	A (21)	A (206)
FICA (FISS) (18, 33, 84, 85, 102)	Frequency of incontinence, type/amount of leakage (flatus only, small or large amount of faeces), number of pads changed, presence of urgency AI score		A	A	A	A	A (219)
Modified Manchester Health Questionnaire (83, 84)	Frequency of: urgency, leaking faeces in various conditions (e.g., coughing and sneezing, walking), leaking solid or liquid faeces, flatus, not wiping clean, and effects on various activities (physical activity, sexual relations, etc) AI QOL impact score	Urgency + Amount/Volume -	A (21)	A (21)	A (21)	A (21)	A (21
ICIQ-B (86, 87)	In the Bowel Control section: Frequency of: ability to control solid faeces, liquid faeces, mucus, and flatus, frequency of needing to wear a pad, frequency of leakage in between bowel movements, frequency of unpredictability of incontinence In other sections: frequency of urgency, and using medication to stop leakage along with usual bowel pattern and impact on lifestyle AI QOL impact score	Amount/Volume -	A	A	A	A	B

Scale Name Reference	Content included in score and Type of Score (AI, FI or Blended with Impact on QOL)	Inclusion of Urgency or Amount/Volume of Faecal Leakage*	Construct Validity	Criterion Validity	Internal Consistency†	Test-Retest Reliability	Responsiveness
Revised FI Scale (89)	Frequency of leakage of solid faeces, liquid feces, urgency, needing to change underwear and needing to alter lifestyle FI QOL impact score	Urgency - Amount/Volume -	A	B	A	B	A
ICIQ-IBD (88)	ICIQ instrument adapted for patients with inflammatory bowel disease (IBD).		A	B	B	A	B
Rapid Assessment FI Score (90)	Frequency of stool leakage – does not discriminate between solid or liquid FI. Flatus leakage (yes-no response, not frequency). Few questions on perception related to FI. No questions on QOL.	Urgency + Amount/volume –	A	A	A	A	B
Accidental Bowel Leakage Evaluation instrument (91)	Frequency (and bother related to) leakage of solid faeces, liquid feces and flatus; urgency; awareness of leakage; sense of complete evacuation; predictability of leakage; control over leakage; ancillary bowel symptoms	Amount/volume +	A	A	A	A	A

QOL refers to Quality of Life.
"A" refers to attributes that have been partly or adequately validated. "B" refers to attributes that have not been validated.
**** Items which are not incorporated in the instrument are indicated by a - sign; those items included have a + sign***
†Internal consistency has been evaluated with Cronbach's α coefficient, which may not provide the most appropriate assessment of this characteristic
*****For cells with an "A" rating that do not include a citation, the citation is provided in the row heading.***

IV. INITIAL CONSERVATIVE MANAGEMENT OF FI

The initial management of FI involves patient and/or caregiver education, setting of patient goals for treatment outcomes, and conservative therapies including support of patients' self-management efforts by clinicians.

1. PATIENT AND CAREGIVER EDUCATION AND SELF-MANAGEMENT SUPPORT

Knowledge and awareness about FI in the general population is low (4). Moreover, many patients with FI and their informal caregivers who assist them with self-management lack knowledge and understanding about how the bowel functions normally, how it may be altered in some disease processes, the influence of lifestyle practices that might influence defaecation and FI, and available therapies (4, 108-110). Therefore, educating patients and caregivers about these topics is an important part of the initial management of FI (13). Managing FI is also influenced by stigma, taboo attitudes, negative emotional reactions, and change in family roles (4, 109, 111-114). Numerous qualitative studies reviewed later in this chapter reveal the tremendous negative impact of FI. The impact on emotional distress and personal relationships is greater for younger versus older (>65 years) women (115, 116). Providing counselling and emotional support is integral in supporting self-management.

Past and recent studies show that individuals with FI living in the community have insufficient knowledge about the name of their health problem, its risk factors, therapies, and self-management strategies (4, 27, 110, 117). In a recent survey about self-management of FI (termed accidental bowel leakage, ABL), nearly half of 161 female respondents (47%) "did not know anything" before visiting a clinician, and only 4% "knew a lot" (117). The vast majority (89%), of respondents thought that it was important to have ongoing guidance and support for self-managing ABL regardless of the level of knowledge about ABL self- management and effectiveness of one's own self-management efforts. For example, 91%, of participants who had "no knowledge" about ABL self-management and 67% of those who had "a lot" of knowledge thought that receiving support or guidance was "very important". Nurse-led education and advice about conservative FI management alone was as effective in reducing FI as a combined intervention that added exercises and/or biofeedback to nurse-led education and advice (118). Nurse-led education and advice addressed diet modification, medication titration, and bowel retraining. Education about FI is integral to support of patient's self-management. Qualitative research, summarized later in this chapter, shows that women and men differ in their experiences managing FI and gender-specific educational strategies may be beneficial. (5, 6, 119).

Informal caregivers assisting family members living at home in managing incontinence also have numerous incontinence literacy needs. Bliss *et al.* (27), was one of the first to describe the health literacy needs of informal caregivers assisting in managing incontinence and associated skin problems in their care recipients with cognitive problems (Alzheimer's disease or dementia) who were living in the community. Results can guide the selection of educational topics for patients with FI and their caregivers. From focus groups and interviews of 48 family and friend caregivers with culturally diverse backgrounds, three main areas of incontinence literacy needs were identified: knowledge, skills, and attitudes. For example, caregivers wanted information about the risk of and reasons for incontinence in dementia, therapies other than using absorbent products, selecting absorbent products and over-the-counter skin care products, and trustworthy resources. Caregivers were interested in improving their skills for managing incontinence, cleansing soiling and preventing skin problems, and lessening resistance of care recipients. Most caregivers expressed a desire for incontinence to be framed as a health versus behavioural problem and saw a need for greater public awareness and empathy so the stigma associated with incontinence would be less (27). These results were supported and had further insights added by recent preliminary findings of Murphy *et al.* and Talley *et al.*

Caregiving for a person with dementia and incontinence presented unique concerns and challenges depending on the type of informal caregiver (spouse versus children versus extended family member or friend) (109). For example, husbands often had limited physical caregiving experience and skills, children needed to manage reversal of caregiving roles, while showing respect for parents, and extended family members often felt excluded from visits and consultations with clinicians.

1.1. Resources

A series of educational and supportive materials for clinicians to provide to patients and informal caregivers is available free via the webpage of the Nursing Committee of the International Continence Society (ICS) (120), or the first author of the study (27). A continence product advisor website (121), to assist in selecting absorbent products has also been developed from a collaboration of ICS, International Consultation on Incontinence, University College of London and University of Southampton.

The most effective approaches for educating patients about FI and its management have yet to be identified. Teaching approaches may be in-person, online or internet-based, or use telehealth, or video/remote or mobile applications. In teaching women about FI management (122), patients were randomized to a standard counselling group or counselling and use of a mnemonic to assist them to recall the types of lifestyle therapies that they were to perform. The mnemonic was RELIEF: routine lifestyle and routine bowel habits, exercise, live, Imodium, effort, and fibre and food diary. At two months following counselling, there was no difference in recall of FI treatments between groups. The group using the mnemonic had higher (better) scores on the Manchester Health Questionnaire however.

Mobile health applications for managing urinary incontinence (UI) show positive outcomes. (123, 124). Women seen in a urogynaecology clinic for FI were surveyed about interest in a mobile application to support their self-management plan (117). Half (50%) of the 161 participants had "a lot of" interest in and 30% had "some" interest. A mobile health app for supporting self-management of FI is currently under development (1R21NR019676-01, NINR, NIH).

1.2. Goal Setting

Cure of FI and amelioration of all symptoms is the ultimate goal of treatment but may not always be possible. Reduction of symptom severity, resumption of self-restricted activities, and improvement of quality of life are goals of therapy for many individuals when complete cure is not attainable (125). Manthey *et al.* (125), surveyed 176 men and women with FI revealing five themes of patient-identified goal statements related to improving their FI severity, lessening the impact on lifestyle and desire for a more normal life, emotional responses such as wanting more confidence and better control of

their symptoms, and reducing adverse effects of FIand need for self-care practices such as wearing pads. The top investigator identified goals were having fewer and less liquid consistency of leakage and feelings of greater control.

1.3. Environment Resources: Information about Public Toilet Availability

The lack of availability or information of public toilets are factors that can contribute to episodes of FI in public and lower quality of life of those with the condition due to deterring activity and socialization in public areas. Qualitative studies have shown that a common and effective self-management strategy of individuals with FI is to make note of the locations of toilets in public areas (6). Australia offers a free online interactive map of toilet locations throughout the country that serves as an outstanding example of such a resource for supporting self-management (126). The map can be portable with mobile applications on Google Play and Apple Store. The United Kingdom (UK) has also created an interactive map of its public toilets that has a "find a toilet" function and a filter to search on features of a toilet such as accessibility and having a baby changing station (127).

New Evidence about Patient and Caregiver Education, Goal Setting, and Environmental Resources

There were new studies identified for this review:One study investigated the effectiveness of patient education for reducing FI as an arm of a randomized trial (107), two studies examined use of social media for obtaining information about FI management (128, 129), one study reassessed patient goals for FI treatment (130), one study identified outcomes of therapy in research studies of interest to patients (97), and two studies identified locations of public toilet in the environment (131, 132).

Regarding patient education, the CAPABLe trial used a 2x2 factorial design and randomly assigned 300 women with FI in a 0.5:1:1:1 allocation to one of four treatment groups: (1) oral placebo and an educational pamphlet about FI management, (2) placebo and biofeedback exercises assisted by anorectal manometry (ARM), (3) loperamide and an educational pamphlet, and (4) loperamide and ARM-assisted biofeedback exercises (107) Women with hard or liquid stools, previous abdominal or pelvic floor radiation, or positive colon cancer screening were excluded. The primary outcome was the change from baseline to 24 weeks in the St Mark's (Vaizey) FI severity scale, calculated from reports on a 7-day bowel diary. At 24 weeks, there was no significant difference among the treatment groups and all groups had some improvement in the St. Mark's score. Limitations of the study are inclusion of only women and those with normal stool consistency, no reporting of results for FI only separately from AI, and lack of monitoring adherence to exercise in subjects not randomized to the ARM-assisted biofeedback group. These results support those reported earlier by Norton *et al.*(118), that patient education about conservative management of FI is an important component of supporting self-management and in reducing symptom severity.

Internet and social media (Facebook and Twitter) sites have been evaluated for information about FI. Using the DISCERN quality analysis tool and JAMA benchmark criteria, Kadam-Halani *et al*. (128), concluded that the quality of information varied by the search term used, with FI (versus ABL , for example) having the highest quality. Leo *et al.* (129), identified that Twitter was used more than Facebook to exchange information about FI between health care providers and patients, possibly due to its anonymity. Sources of tweets were mainly a few dominant hospitals and physicians rather more broad perspectives. Website search engines also yielded product advertisements, and scientific journal information. The abundance of information posed difficulties to sort through and identify appropriate, quality information. The COVID-19 pandemic resulted in emergent changes to the use of telehealth, video conferencing, and online resources for continence care and education. These approaches extend access to care and some may remain after the crisis is resolved but will need evaluation.

In reassessing patient goals for FI treatment, Halder *et al*. (130), conducted a retrospective chart review of 100 women with FI who were asked to identify up to three goals for treatment prior to their initial visit with a health care provider. Identified themeswere, compete elimination or control of faecal leakage, improvement of symptoms, and prevention of worsening of their condition. Women emphasized the importance of working toward feasible/realistic outcomes. Findings supported previously identified goals of wanting greater control and confidence in managing symptoms and decreases in frequency of leakage (30). Goals that were added were reducing the need for self-care such as performing incontinence-associated hygiene and having pelvic health in general. In seeking to identify outcomes for research studies, Heymen *et al.* (97) quantified patients' acceptance of FI improvement when cure was not possible using an online focus group (n=28 individuals) and an online survey (n=186 individuals). Satisfaction with treatment outcomes ranged from 50% to 80% reduction in symptoms.

There were two studies that identified and mapped the location of public toilet facilities in parks/recreation area and open spaces in major international cities and in the United States using geographic information systems (131, 132). Also, toilet density by population and residential area (mi^2 or km^2) was calculated, and toilet distribution was visualized using Choropleth maps. Results showed differences among the cities in availability (i.e., distribution and density) of these public toilets in their park and recreation areas. For example, considering city population and area, availability of public toilets in parklands or open spaces is generally high in Paris, Seoul, Minneapolis, Philadelphia, and Sydney and low in Berlin and Brussels. Sydney has the highest toilet density in open spaces per km^2 even though they have the lowest population density. There is a relatively even distribution of public toilets in parkland areas per km^2 in Minneapolis and Toronto. Limitations of these early investigations is the unavailability of a single score for toilet availability, use of freely available public databases whose information may not keep up with recent changes, and lack of these databases in some cities.

Summary of Patient and Caregiver Education, Self-Management Support, and Environment

- Patients with FI and their informal caregivers have low incontinence literacy (Level of Evidence 3).
- The internet contains a variety of information related to FI that can pose difficulties to patients to identify accurate, quality information. Women across age groups have interest in a mobile application to support self-management of FI (Level of Evidence 3).
- Patients have goals for outcomes of conservative therapies when cure is not possible including feelings of greater control, reduced symptom severity and hygiene needs/products, participation in social and public activities, and improved quality of life (Level of Evidence 2).
- Publicly available maps of the location, distribution and density (per population and area) of public toilets in urban and park/recreation areas are helpful resources to support self-management of FI and for community planning (Level of Evidence 2).

Recommendations for Practice Related to Patient and Caregiver Education, Self-Management Support, and Environment

- Educate patients (and their informal caregivers if appropriate) about bowel function, FI, and conservative therapies and self-management practices (Grade of Recommendation B).
- Advocate for developing and communicating freely accessible information about the location and availability of public toilets (Grade of Recommendation C).
- Support patients' self-management of FI by providing a variety of educational resources including those on the internet (Grade of Recommendation C).

Recommendations for Research on Patient/Caregiver Education, Self-Management Support, and Environment

- Identify effective teaching strategies that are gender-specific and culturally appropriate
- Develop mobile applications to support self-management with conservative therapies for FI

2. LIFESTYLE CHANGES

Lifestyle modifications are part of the initial conservative management of many chronic health conditions including FI. For some lifestyle modifications for managing FI where there is insufficient research-based evidence and low/few risks of harm to patients, expert opinion or experience can be encouraged and their effectiveness evaluated on an individual basis.

3. DIET, FLUIDS, AND DIETARY FIBRE

3.1. Diet and Fluid Modification

Individuals with FI modify their dietary intake as a self-management strategy to reduce severity of symptoms and improve quality of life. Evidence comes mainly from observational and qualitative studies (reviewed later in this chapter) initially reported in studies by the team of Peden-McAlpine and Bliss (6, 133), and more recently supported by Andy *et al.* (134). Dietary modifications include avoiding certain foods or fluids worsening FI severity periodically or permanently and restricting the amount of those foods consumed. Foods identified as worsening FI from several studies and samples include certain vegetables especially those increasing flatus (such as cabbage, broccoli, onions, and garlic), fruits (such as strawberries and apricots), fatty or greasy foods, spicy foods (spare ribs, ethnic foods), foods and fluids containing caffeine (such as coffee and chocolate), and dairy products (ice cream, cream, cheese) (135, 136). Younger adults are more likely to report that fatty foods worsened their FI than older adults (135). There are differences in use of diet modification by age and sex. More women than men avoid foods as a self-management strategy for FI (133, 135). Some women with FI modify their diet based on suggestions for managing other gastrointestinal problems (e.g., lactose intolerance and IBS) that they find in the professional or lay literature (6, 136).

Some foods and fluids reported as aggravating FI by some patients have physiological effects on gastrointestinal function but there are few studies about this association. Caffeine, of which coffee is a popular source, can increase rectosigmoid motility and induce a desire to defecate in normal individuals (137-139). Caffeine has also been observed to stimulate defaecation urgency in some patients with FI (140). However, regular consumption of coffee was not associated with prevalent or incident FI in elderly men and women (140). There remains no study on caffeine restriction to improve FI.

Chronic consumption of alcohol has been associated with accelerated gastric emptying and small bowel transit in animal studies whereas a single large dose has an inhibitory effect (125, 141, 142). Excessive alcohol consumption leads to damage to the duodenal and upper jejunal mucosa and inhibition of sodium and water absorption. There is an increased prevalence of bacterial overgrowth in the small intestine of alcoholics, which may contribute to loose stools, diarrhoea, incontinence, and other GI symptoms (125). More younger versus older adults reported that alcohol worsened their FI but the amount of alcohol consumed associated with this effect was not known (135). No studies were found in which alcohol restriction was reported to reduce FI.

In addition to modifying dietary intake, individuals with FI change their eating patterns, eating schedules, and food preparation/recipes to reduce their symptoms (134, 136). They skip meals before going out into public, eat small amounts or avoid eating while at a social event, and eat at home rather than at restaurants. They may eat at the same times of day in an attempt to achieve regular bowel movement pattern or avoid going into public after they have eaten a desired food that worsens FI symptoms. Recipes are adjusted to reduce spiciness or omit some spices altogether, and baked rather than fried foods are preferred.

Concerns about dietary manipulation and skipping meals are nutritional deficiencies and subsequent poor health, especially in those at higher risk for malnutrition. Bliss *et al.* (38), found few significant differences in the nutritional composition of a usual western diet of those with FI compared to the usual diets of age and sex matched controls with normal bowel function. Those with FI had a greater intake of carbohydrates, manganese, and vitamin B1.

3.2. Prebiotics, Probiotics, Synbiotics, and FODMAP Diets

Prebiotics, probiotics, or synbiotics are used as complementary or alternative therapies for gastrointestinal problems. A prebiotic is a general term describing a food ingredient that is not digested in the human small intestine and thus stimulates the growth and/or activity of one or more types of bacteria in the colon that have the potential to improve the health of the host. Fructo-oligosaccharides and galacto-oligosaccharides are popular prebiotics. Dietary fibre can also be considered a prebiotic. A probiotic is a food supplement containing live non-pathogenic and non-toxic microbes that have the potential to affect the balance of colonic microbes and thereby improve the host's health. Bifidobacteria and lactobaccilli are the most commonly used probiotics, and yogurt which has active microbial cultures can be considered a probiotic. A synbiotic refers to a product that combines a prebiotic and probiotic. FODMAPs are foods that include different types of short-chain carbohydrates including fructans (fructo-oligosaccharides) and galacto- oligosaccharides, polyols (sugar alcohols) of which a common one in the diet is sorbitol, fructose and lactose (143). FODMAPs can be can be poorly digested or absorbed by certain people & can increase volume of liquid and gas in the intestines.

3.3. Dietary Fibre

Dietary fibre is the non-starch, polysaccharide component of plant cell walls and lignin that resists digestion by human intestinal enzymes (144). Dietary fibres have various physiological effects depending on their structure and properties, amount ingested, extent of their degradation and fermentation in the colon, and health of

colonic cells. Dietary fibre that is not completely degraded and fermented by colonic bacteria increases bulk, water-holding, and gel-formation in faeces while those that are metabolized to short chain fatty acids (SCFAs) promote water absorption and serve as an energy substrate for colon cells (37, 145). Thus supplementation with dietary fibre might lessen FI by increasing rectal distension and sensory awareness of the need to defecate, promoting more complete elimination of faeces and leaving less in the rectum to leak, or normalizing the consistency and reducing the liquidity of faeces making it easier to control (37, 146).

Low dietary fibre intake from food has been associated with FI in women. In a study about weight loss for reducing urinary incontinence, women with urinary and FI were 2.5 times as likely to have a low dietary fibre intake (≤ 10 g/d) than those without FI (147). Randomized controlled clinical trials (RCTs) (37, 146, 148), provide **Level 1 evidence** that a supplement of moderately fermentable, soluble dietary fibre (i.e., psyllium) significantly reduced the frequency and severity of FI in community-living men and women (Table 15-2). Significant reductions in FI resulted from lower (3.4 g/d) (148), and higher doses (16 g total fibre/d) (37), of psyllium. Stool analyses showing the formation of a gel in subjects' stools during psyllium supplementation are consistent with other observations of psyllium's effects (149), suggesting this as a mechanism in FI (37).

Dietary fibre has also been used in combination with other therapies and as part of staged management. Results of these studies are mixed. In one non-experimental study, faecal soiling resolved in 24% of patients after psyllium supplementation alone, in 48% who added transanal irrigation to psyllium supplementation, and in 2% in those who added cholestyramine to psyllium supplementation and transanal irrigation (150). An RCT investigated two combination treatments for AI; one treatment included loperamide, a diet advice sheet describing a high vs. low fibre diet, and a low-dose psyllium fibre supplement, and the other treatment used loperamide and a placebo supplement of a food thickener and some locust bean gum fibre (151). There was no difference found between the groups, suggesting no additional reduction of AI from a dietary fibre supplement and diet advice sheet over antimotility medication. In a staged intervention with a non-experimental design, 46% of women taking a supplement of methylcellulose alone (n=19) or with the antimotility medication loperamide (n=40) resolved their FI compared to no one in the control group who declined study treatment (n=10) (152).

Adverse gastrointestinal (GI) symptoms are a potential problem mediating tolerance of dietary fibre. In community living adults with FI, supplementation with 16 g/d of psyllium, gum arabic, or carboxy-methyl-cellulose fibre was associated with minimal adverse symptoms (153). A greater feeling of fullness in the psyllium group was the only symptom that differed compared to the placebo group. However, subjects with greater symptom severity were more likely to request a reduction in fibre amount or discontinue supplementation (153). Lesser amounts of psyllium supplementation have few symptoms (146).

New Evidence about Diet, Fluids, and Dietary Fibre

There were five new studies about diet modifications, dietary fibre, and fluid intake and FI. One study compared the types of foods ingested by women with FI and a national sample of women in Japan (154). A cohort study examined the association of long-term dietary fibre intake and fecal incontinence in female nurses (155). There was a retrospective chart review reporting effects of eating a diet low in fermentable oligo- di- and mono-saccharides and polyols (FODMAP) on FI (156). One study tested an intervention that was comprised of methylcellulose fiber and dietary advice (157). A retrospective study examined the relationship between fluid intake and bowel symptoms in women with and without FI (158).

In an observational study, data about the dietary intake of 100 women with FI symptoms were compared to that of 3,332 women from Tokyo who had completed a national health and nutrition survey (154). The dietary intake of the samples was calculated differently. Women with FI completed a one-week food diary from which a one-day mean of foods consumed was calculated. For woman completing the national survey, a one-day mean of foods consumed during one month was calculated. The age of both samples ranged from 20 to 70^{+} years but the percentages in the age groups differed between the samples; therefore, a weighted mean of diet intake per day was calculated for every year over 20 years based on the national survey data.

Differences in food intake were observed. There were significantly higher intakes of wheat products, fruits, and snacks containing dietary fibre and a significantly lower intake of rice by women with FI compared to those from Tokyo completing the national survey. Study limitations include the limited types of food in the analysis, lack of adjustment of diet intake for body weight, and differences in calculating dietary intake between the groups. Generalizations to other populations are limited by potential national/cultural and regional differences in diets and exclusion of men.

In a longitudinal cohort study, FI incidence and dietary fibre intake of 58,330 older female nurses (average age = 73 years) was obtained using a mailed survey and a food frequency questionnaire, respectively (155). Dietary fibre intake was reported at 7 time points at two to four year intervals from 1984-2006. Development of FI was surveyed three times at two-year intervals from 2008-2012. There were 7,056 incident cases of FI (12%) overall. A multivariate analysis adjusting for several FI risk factors such as BMI, parity, smoking, etc. showed that women with dietary fibre intake in the highest quintile (25 g/d) had a significant decrease in risk of FI of 18% compared that in the lowest quintile (13.5 g/d) (HR=0.82, 95% CI (0.76-0.89)). The decrease in risk (31%) was greatest for liquid FI (HR=0.69, 95% CI (0.62-0.75). Risk was not associated with fibre source (e.g., fresh fruit, vegetables, cereal, whole grains, etc.).

The effectiveness of a low a low fermentable oligo- di- and mono-saccharides and polyols (FODMAP) diet in reducing FI was examined in a retrospective review of health records of 65 patients (87% female, mean (sd) age = 62 (14) years) who had some loose/liquid stools (156). Occurrence of FI was self-reported. The low FODAP diet was associated with a reduction in FI symptoms in 64.6% (42/65) of patients; 88% of patients reported a reduction of 50% in FI episodes and 35.7% had no FI episodes while on the diet. Limitations of the study are the absence of a randomized control group and statistical testing of differences, use of non-validated tools for evaluating FI, and lack of control of concurrent therapies such as anti-diarrhoeal medications, antibiotics, and physiotherapy.

Ribas & Munoz-Duyos (157), studied the effects of a supplement of methylcellulose fibre (500 mg every 8 hrs for 6 weeks) and dietary advice (foods recommended to eat and foods to avoid) on several AI outcomes in a one-group study using a non-experimental design. Of the 83 patients enrolled, 61 (73%) completed the study. Subjects completed the Fecal Incontinence Quality of Life scale (FIQL), a three-week bowel diary from which St. Mark's AI score was calculated, stool form using the Bristol Stool Form scale, and defaecation deferment time (using a four-point scale) before and at the end of six weeks of fibre supplementation. Of those who completed the study, 11 (18%) did not report any AI during the baseline period,

explaining they did not leave their house. After the methlycellulose and dietary advice period, St. Mark's score significantly decreased (mean 8.6 (6) (sd)) compared to baseline (14 (4.4)). There was no significant difference among the categories of defaecation deferment time. Although 33% subjects reported improvement of overall deferment time, no statistical testing was done. The Bristol Stool Form score improved in 38/61 (62%) of subjects. Approximately half (n=37) of the subjects completed the FIQL and there were significant improvements in lifestyle and coping/behaviour subscales. As secondary outcomes, the number of urge AI episodes/week but not passive AI episodes/week significantly decreased after treatment compared to baseline. Study limitations are absence of a randomized control group, inclusion of subjects without AI during the baseline period, and a lack of monitoring if subjects consumed the fibre supplement as they were required to buy the methylcellulose on their own.

In a retrospective study, records of fluid intake and bowel symptoms of 924 women presenting to a urogynaecology clinic for evaluation of pelvic floor disorders were analyzed. Forty-one percent (379), of the women -reported that they had FI. Data on bowel symptoms were collected using the Colorectal-Anal Distress Inventory short form (CRADI-8). Data about fluid intake was collected using the Questionnaire- based Voiding Diary, which is based on food frequency questionnaires. A greater percentage of women with FI consumed lesser amounts of water (p=.009) and greater amounts of carbonated beverage than those without FI (p=.009). Median water intake of women with FI = 1065 mL (IQR, 518–1774 mL) and without FI = 1420 mL (IQR, 710–2129 mL). Median carbonate beverage intake of women with FI = 0 mL (IQR, 0–710 mL) and without FI = 0 mL (IQR, 0–311 mL). There were no significant differences in caffeine, alcohol, juice, or milk intake between those with and without FI. Limitations of the study are the inability to assess a causal relationship between FI and fluid intake.

Summary of Diet, Fluids, and Dietary Fibre

- Patients consider diet a factor affecting the severity of their FI symptoms (Level of Evidence 3).
- Many patients can identify foods and fluids that worsen the severity of their faecal incontinence and they modify dietary intake, cooking practices, and eating patterns as a self-management strategy (Level of Evidence 3).
- Consumption of higher amounts of dietary fibre, i.e., near the recommended daily amount, is associated with lesser severity of FI (Level of Evidence 2).
- Supplementation with psyllium dietary fibre appears to be a safe and tolerable intervention that can reduce the frequency and severity FI (Level of Evidence = 1).
- The severity of adverse symptoms of supplementation with some dietary fibres up to 16 g total fibre/day are small on average but tolerance may be more individual (Level of Evidence 1).
- Gel formation in faeces may be a mechanism by which psyllium dietary fibre exerts its effect in FI (Level of Evidence 1).
- A supplement of a low amount of psyllium fibre (3.4 g/day) was as effective as a low dose of loperamide (2 mg/day) in reducing FI (Level of Evidence 1), but may not lower FI more when taken in addition to loperamide (Level of Evidence 2).
- Studies of effectiveness of supplementation with other dietary fibres such as methylcellulose have differing results, possibly due to differences in the composition and properties of the fibres, amounts given, and methods and quality of studies (Level of Evidence 2/3).
- Use of diets low in fermentable oligo- di- and monosaccharides and polyols may reduce AI or urgency in some patients with liquid stools (Level of Evidence 3).
- Dietary fibre as an adjuvant to trans-anal irrigation can reduce FI (Level of Evidence 3).
- Regular consumption of coffee is not associated with FI in older men and women (238) (Level of Evidence 3).
- Alcohol intake may worsen faecal incontinence symptoms in some individuals, more so in younger patients (Level of Evidence 3).

Recommendations for Practice Related to Diet, Fluids, and Dietary Fibre

- Patients should identify and reduce/eliminate intake of foods and fluids associated with worse FI symptoms as a self-management strategy for reducing symptom severity (Grade of Recommendation C).
- Modifications of eating patterns and food preparation have been reported as a useful, temporary self-management strategies. Dietarymodifications should be evaluated by clinicians for their nutritional impact and effectiveness (Grade of Recommendation C).
- Consuming the recommended daily amount of dietary fibre from dietary supplements and/or foods should be encouraged to reduce FI (Grade of Recommendation C).
- Psyllium dietary fibre supplementation is recommended for the management of FI. Starting with a lower fibre amount (3.4 g/d) then increasing to a higher amount as needed is suggested (Grade of Recommendation A).
- Psyllium dietary fibre should be recommended as part of a combination therapy involving rectal irrigation (Grade of Recommendation B).
- Supplementation with stool bulking dietary fibre such as methycellulose at small amounts or using a low FODAP diet for patients with liquid stools may be tried in managing FI (Grade of Recommendation C).

Recommendations for Research on Diet, Fluids, and Dietary Fibre

- Further studies on the effect of dietary fibre and other diet modifications on FI are required to build a greater body of evidence.
- Determine the optimal type and amount of dietary fibres to reduce FI since dietary fibres differ in their chemical composition and properties.
- Evaluate the effect of modifying usual diet and eating patterns as a management strategy for FI.
- Determine the extent to which dietary/fibre interventions can augment other behavioural and pharmacological interventions and the optimal sequence of initiating and changing interventions.
- Controlled studies on the effectiveness of low FODMAP diets.

Table 15-2. Intervention Studies Using Dietary Fibre for Managing FI

Study and Country	Design and Sample	Intervention and Outcome Measures	Findings	Strengths	Limitations
Ribas & Munoz-Duyos 2018 (157) Spain	One-group pilot study 61 of 83 patients with FI and/or faecal urgency associated with loose stools or diarrhoea completed the study	The intervention was dietary advice and intake of methylcellulose 500 mg every 8 h for 6 weeks. All assessments were carried out at baseline and 6 weeks after the intervention. Data collection tools were the Bristol Stool Scale, a 3-week bowel diary, the St. Mark's score, the FI Quality of Life scale (FIQL) and defaecation deferment time (using a four-point scale).	Bowel diaries showed a statistically significant reduction in the number of bowel movements, urge episodes, urge FI episodes and soiling per week. The St Mark's score improved after methylcellulose (mean 8.6 (6) (sd) compared to baseline (14 (4.4)). Bristol Stool Form score improved in 38/61 (62%) of subjects FIQL significantly improved in the 2 subscales of lifestyle, coping/behaviour but only half of subjects provided these data.	Independent pharmacists dispensed the treatment	Absence of a randomized control group, Inclusion of subjects without FI during the baseline period and lack of monitoring if subjects actually consumed the fibre supplement. Inability to distinguish faecal from AI as an outcome. Use of data collection tools without validity and reliability, and some data were not reported by all subjects.
Markland et al. 2015 (148) USA	Double-blind, randomised, cross-over design 80 veterans with FI or liquid or solid stool at least weekly for 3 months	Random assignment to loperamide (2 mg/day) first then a supplement of psyllium fibre (3.4 g/day) or psyllium first then loperamide for 4 weeks each with a 2 week washout and a 2 week non-equivalent baseline period FI frequency was reported daily on a diary for 7 days during each period	No significant difference in FI between treatment groups. Within each treatment group, FI frequency significantly decreased from baseline during the first treatment period for both treatments, but did not significantly change after the crossover to the other treatment.	Double-blind, and used a longitudinal analysis	Use of a stool diary untested for validity and reliability, potential error due to subjects needing to prepare part of the supplement, possible unmeasured cross-over effects, non-equivalent baseline period, and attrition during the washout.
Bliss et al. 2014 (37) USA	Single-blind, randomised, placebo controlled, parallel groups 206 community-living adults with at least 2 episodes of FI of loose/liquid stools in 2 weeks	One of 3 dietary fibre supplements, carboxy-methylcellulose, psyllium, or gum arabic, (16 g total fibre/day) or placebo for 32 days each FI frequency was reported daily on a diary for 14 days at the end of each period	Both the intent-to-treat and per protocol analyses showed that FI frequency significantly decreased after supplementation with psyllium fibre compared to placebo. The percent change of FI in the psyllium group was 51%	Blinding of subjects, pre-prepared supplements with a known amount of fibre, monitoring dietary intake with a food diary and adherence with appearance of a dye in faeces, and a longitudinal analysis that adjusted for baseline values	Use of a diary and FI severity index whose parts had not all been tested for validity and reliability; not double blinded; lab measures only on a subsample

Study and Country	Design and Sample	Intervention and Outcome Measures	Findings	Strengths	Limitations
van der Hagen et al. 2011 (150) Netherlands	One non-experimental study 50 consecutive patients (41 men) who had faecal soiling and normal sphincter function were recruited	For two months, patients consumed 3.25 g psyllium fibre per day and a fibre rich diet. Patients with persistent faecal soiling added rectal irrigation using 500 ml of tap water daily for two months. Patients whose faecal soiling continued added 4 g of cholestyramine daily.	Faecal soiling resolved completely in most patients. In some, soiling resolved after psyllium supplementation alone.	Abnormalities were excluded prior to the study (such as rectal tumours, prolapses, etc.) A conservative treatment algorithm	Absence of a randomized control group, lack of monitoring if subjects actually consumed the fibre rich diet
Sze & Hobbs 2009 (152) USA	Staged intervention with a non-experimental design 69 women with FI	If the incontinence persisted after taking the maximum dose of methylcellulose for two weeks, loperamide, one capsule twice a day was added, which was increased to two capsules three times a day as needed. If both fecal urgency and incontinence resolved, the therapy was continued for a three□month treatment period.	59 subjects were treated with methylcellulose, (1-2 tsp/day) 40 also required loperamide (1-2 capsules/day). 10 women who declined study treatment served as controls. 46% Women treated with methylcellulose and/or loperamide resolved FI vs 0% in the control group.	The use of a control group Regulation of fluid intake	Nonrandomized study, possible changes in diet
Lauti et al. 2008 (151) Australia	Double-blind, randomised, cross-over design using blocks of 10 63 adults with incontinence of mucus, or liquid or formed stools. started study, and 47 subjects (91% female) completed the study Treatment A n= 31 and treatment B n= 32 49 crossed-over Treatment A = 27 and B = 22	Treatment A: self-titrated dose of loperamide (starting at 2 mg twice/day), 1 tsp of a food thickener containing starch, maltodextrin, and locust bean gum twice/day, and a diet advice sheet about a low-fibre residue diet. Treatment B: same self-titrated dose of loperamide, 1 tsp of psyllium fibre in water twice/day, and a diet advice sheet about a high and low fiber residue diet. Treatments were for 6 weeks each Primary measure was self-reported AI for the last 4 weeks of each treatment using the FISI. Secondary clinical measures were FIQL and SF-36, a measure of general health.	67% of treatment A fibre and 73% of treatment B fibre were taken. The mean difference in the FISI score between treatments was not statistically significant.	A power analysis was used for sample size calculation. Independent pharmacists dispensed the treatments. The interval for data collection during both treatments was the same. 75% of subjects completed the study protocol and reasons for attrition were reported.	Possible carry-over effects between treatments; Period and treatment effects were not assessed; Attrition resulted in low statistical power; Possible confounding from fibre in the placebo; Subjects mixed their own fibre supplements and intake was not controlled; Doses of the anti-motility medication and suppositories for constipation were uncontrolled.

Study and Country	Design and Sample	Intervention and Outcome Measures	Findings	Strengths	Limitations
Bliss et al. 2001 (159) USA	Randomised, parallel-group, placebo-controlled, single blind trial Subjects, statistician, lab technician, and subjects' clinicians were blinded. 39 adults (79% female) with FI of loose or liquid stool at least weekly. A block scheme resulted in equal numbers (n=13) in each group. Groups' characteristics were comparable at baseline.	Intervention: soluble dietary fibre supplements mixed into fruit juices: 7.1 g of psyllium/day, 21.5 g of gum arabic/day, or placebo (0.2 g pectin/day). Supplements taken for 31 days in addition to usual diet FI reported daily on a stool diary for 8 days in baseline and supplement periods Primary measure was the proportion of incontinent stools. Secondary clinical measures were stool consistency and frequency, and flatulence reported daily al Secondary lab measures were stool wet and dry weights, % of water, pH, total fibre content, water-holding capacity of stool solids, and faecal short chain fatty acids.	Proportion of incontinent stools in psyllium or gum arabic groups was significantly lower than placebo. Percent of loose or liquid stools in psyllium and gum arabic groups was significantly lower than placebo. The water-holding capacity of stool solids was highest for the psyllium group. No significant differences among the groups in other measures.	Sample size was based on a power analysis. Data collection period was equal during baseline and supplement periods. Control of concomitant treatments. Supplements were premixed and ready-to-take. 95% of subjects completed the study and reasons for attrition were reported.	Details of the procedures for random assignment and allocation concealment were not provided. Although adequately powered, small group sizes reduce generalizability of findings.

4. COMPLEMENTARY AND ALTERNATIVE THERAPIES

Complementary and alternative therapies are those that are not part of standard, conventional medical therapies. Complementary therapies are performed alongside conventional medicine to help patients feel better, improve quality of life, and cope with symptoms while alternative therapies are used instead of conventional medicine (160). There are a numerous complementary and alternative therapies including acupuncture, aromatherapy, herbal medicine, imagery, relaxation, and yoga. These therapies are sometimes administered along with prebiotics or probiotics for managing FI.

A survey of patients using a biofeedback service revealed that a variety of complementary or alternative therapies were used for bowel problems (161).The most common therapies for bowel problems were the use of herbal medicines or acidophilus/ probiotics. Other therapies included acupuncture, massage, homeopathy, kinesiology, relaxation therapy, reflexology, and traditional Chinese medicine. Of the 93 survey respondents, 31% were being treated for FI, but use of complementary therapies for FI was not specified. Users considered complementary or alternative therapies safe, natural, and providing them with some control over their health feeling that conventional treatment had failed them or was unavailable.

Case reports of complementary or alternative therapies reveal mixed results. For example, use of a herbal preparation considered antimicrobial and a probiotic followed by different herbal mixture and a bioceutical product was reported to cure FI in a woman with multiple sclerosis (162). In another case report of a woman with multiple sclerosis, trigger-point acupuncture for pain triggered the development of FI (163).

New Evidence about Complementary and Alternative Therapies

Acupuncture is a form of traditional Chinese medicine that aims to strengthen the relationship and regain a balance of power between energies in the body through the application of needles, seeds, beads, suckers etc. (164). In one study, 18 adults with FI (2 men, 16 women; age range = 28-76 years) underwent acupuncture using 22 traditional acupuncture needles in 10 weekly sessions. Patients reported the severity of FI using a visual analogue scale (VAS) and completed the FIQL scale for assessing FI related quality of before and after acupuncture treatment. After acupuncture, FI severity improved in all patients and all domains of the FIQL scores ($p<.05$) improved. Seven of 18 patients reported they no longer had FI after acupuncture. Study limitations were the absence of a control group and random assignment, lack of a valid and reliable measure of FI severity, and reporting data about FI by individual patients without any summary values or analyses.

Summary of Complementary or Alternative Therapies

- Patients may use complementary or alternative therapies to manage FI (Level of Evidence 3), Studies of their effectiveness are few and lacking in quality

Recommendations for Practice Related to Complementary or Alternative Therapies

- Clinicians should inquire about use of complementary or alternative therapies and evaluate their safety and effects (Grade of Recommendation 3).
- Complementary or alternative therapies are not recommended for the management of FI (Grade of Recommendation 4)

Recommendations for Research on Complementary/ Alternative Therapies

- Randomized clinical trials, or at minimum pragmatic clinical trials, of effects of complementary or alternative therapies for reducing FI are required

5. WEIGHT LOSS AND PHYSICAL ACTIVITY

Of the lifestyle modifications for FI, weight loss for obesity has been a frequent topic of investigation.Many of these studies are in women only (Table 15-3). Weight loss has been proposed as a lifestyle modification to reduce FI based on improvements in urinary incontinence after weight loss (165), but associations between obesity and FI are mixed (166-170). For example, in one study, overweight or obesity was associated with an increased risk of anal and FI in women with a BMI over 30 compared to women with a normal BMI (i.e. <25) (56). The odds ratio for obese women was 2.5 for loose stool incontinence, 1.3 for solid stool incontinence and 1.8 for flatus incontinence. Conflicting results were reported in two studies of U.S. women. (171, 172). Being overweight (BMI 25-29) or obese (BMI >29 or 30) was not predictive of FI in a study of identical twin sisters (171) or in a large population-based survey of women (172). When examining the severity of FI in both men and women, being overweight was marginally associated with leaking a greater amount of faeces (OR 1.4) (95% CI 1.002-2) (173). Risk factors for FI from anorectal manometry testing in women who were obese were higher baseline anal resting tone and squeeze pressures compared to normal or overweight women, suggesting a lower threshold to leakage with pressure increases in one study (174).

Results from past studies examining decreases in FI after weight loss resulting from diet programmes or bariatric surgery have been inconclusive. In two secondary subgroup analyses of obese women with dual (faecal and urinary) incontinence on a non-surgical dietary weight loss programme, AI was not significantly different from that of the control group receiving education (147, 165). In one subgroup analysis of 80 women (147), there was no significant difference in the FI Severity Index (FISI) or FI consistency between the weight loss programme and control groups. The 6-month intervention focusing on dietary intake was not correlated with a decrease in AI. On the other hand, women who showed improvement in AI had a lower weight at baseline (89 kg) than those with no improvement in AI or no AI (97 kg).

A subgroup analysis of of 338 obese women with dual incontinence showed an overall decrease in AI in 13% of women when combining data from 6, 12, and 18 months of the study, but the change was not significantly different from that of the control group (165). In comparing women with and without improvement of AI (using the FISI), those who showed a decrease in AI had a lower weight and BMI at baseline. A decrease in lower urinary tract symptoms (LUTS) was associated with lesser AI severity in all women. Limitations of this study included use of an untested modification of the FISI score and the lack of adjustment for baseline AI severity in the analysis.

Studies of decreases in FI after weight loss following bariatric surgery for morbid obesity have had conflicting results with some studies showing increases in FI ; study comparisons are confounded by different outcome measures (i.e., AI versus FI) (168, 175, 176).

There are few studies about the relationship of exercise or physical activity and anal/ FI or if increasing activity lessens the risk or severity of these problems. Available studies of the association of exercise and anal or FI show mixed results. In a cross-sectional study of more than 60,000 middle to older aged female nurses, the odds of developing FI increased with decreasing physical activity (56). An internet survey of 311 female triathletes showed that 28% reported having AI (177). A quasi-experimental pilot study published in abstract form reported that a general exercise program improved symptoms of AI measured by the ICIQ-B questionnaire in 30 women after treatment for gynaecological cancer (178). Vitton *et al.* (179), reported that the prevalence of AI was higher (14.8%) in younger female athletes (18-40 years) who engaged in intensive sports than those who performed non-intensive sports (4.9%). For the majority, the reported incontinence was categorized as flatus incontinence. In a recent review of studies about effect of general exercise on the pelvic floor (180), no studies were found on AI in weight/power lifters and none reporting that women exercising have less AI.

New Evidence about Weight Loss and Physical Activity

There are 10 studies about obesity or weight loss and FI or AI included in this review. There was one observational study about the risk of obesity for FI in women (49), and one study examining anorectal manometry values and clinical characteristics in obese versus non-obese patients with FI . (181). A secondary analysis of data from a randomized trial of nonsurgical therapies in women with FI described baseline characteristics associated with significant treatment responses (182). There were three observational studies (183, 184), about the association of obesity and FI/AI in patients awaiting bariatric surgery. There were two observational studies (185, 186), and two systematic reviews (187, 188), about the effects of bariatric surgery and accompanying weight loss on FI/AI. Regarding physical activity and FI, there were two observational studies. One prospective cohort study analysed the association of different levels of physical activity and risk of FI in women (49). Using a retrospective cohort design, Vitton *et al.* (189), examined the associations of wearing high-heeled shoes with severity of FI and with anorectal manometry values.

In a large cohort study, the development of FI and association of body mass index (BMI) and FI at two time points two years apart was examined in 51,708 middle to older aged female nurses who were free of FI at the starting time of the analysis (49). Data were collected using a mailed questionnaire. FI was defined as ≥ 1 FI episode of liquid or solid stool in the past year in each follow-up years. Being overweight was defined as BMI = 25-29 kg/m^2 and obesity as BMI = 30$^+$ kg/m^2. There were 5,954 incident cases of FI (11.5%) and no significant association between BMI and FI. Limitations of the study were its observational design, the age of the data (2008-2012), and limiting the definition of FI to liquid and solid faeces only.

In a 1:2 case-matched study, a total of 201 obese (n=67) and non-obese (n=134) patients with AI (87% women 13% men; mean (sd) age = 61.9 (12.1) years) were evaluated using anorectal manometry and endosonography (181). Obese patients with AI had significantly better anorectal function than non-obese patients with I with regard to a longer anal canal length and higher resting pressures at the lower and upper part of the anal canal. The obese patients had higher abdominal pressures and higher anal resting pressures than the non-obese patients, which was thought to reflect a decreased threshold to leakage. With regard to the clinical characteristics, obese patients had a comparable severity of FI to that of non- obese patients. Obese patients were more likely to have liquid stools and diarrhoea-predominant inflammatory bowel syndrome (21/67 (31.3%) than non-obese patients (20/134 (14.9%); p=.0065).

A secondary analysis of baseline clinical and demographic characteristics of 296 women participating in an intervention trial for FI identified that being overweight, defined by body mass index (BMI), was associated with response to treatment (182). The parent study (107), used a 2x2 factorial design in which women with FI were randomly assigned in a 0.5:1:1:1 allocation to one of 4 groups: (1) oral placebo and an educational pamphlet, (2) placebo and biofeedback exercises assisted by anorectal manometry (ARM), (3) loperamide and an educational pamphlet, and (4) loperamide and ARM-assisted biofeedback exercises, respectively. Women with hard or liquid stools were excluded. Results showed no significant difference in FI severity, measured by changes in St. Mark's scores from baseline to 24 weeks. In the secondary analysis, treatment response was defined in 3 ways from baseline to 24 weeks: minimal clinically important difference (MID) of -5 points in St. Mark's score, ≥50% reduction in FI episodes, and combined St. Mark's MID and ≥50% reduction of FI episodes. Being overweight versus normal/underweight was a significant as a factor associated with a positive treatment response using the one outcome of St. Mark's MID (adjusted odds ratio=2.15, 95% CI 1.07–4.34). Results were unable to explain why being overweight was associated with treatment success, and authors suggested that other factors such a lower dietary fibre intake, which was 2.5 times more likely to in overweight and obese women with FI symptoms, may be influential in outcomes (84). Limitations of the study are discussed in the section of this chapter about Patient and Caregiver Education and Self-Management Support.

Two studies with case-matched designs showed that more obese patients before bariatric surgery had FI/AI than non-obese patients (183, 184). Seventy-five obese women awaiting bariatric surgery (BMI=41.7 (8.6) kg/m^2 mean (sd)) were age and parity-matched with 91 non-obese (BMI=24.9 (2.9) kg/m^2) controls (183). FI was reported in 21% of obese vs 7.7% of non-obese women, reported with the Pelvic Floor Distress Inventory/ Colo-Rectal-Anal Distress Inventory-8. (p=.01) There was no significant difference in scores for loss (FI) of well-formed or not well-formed stools between the obese BMI≥30 kg/m^2 and non-obese (<30 kg/m^2) groups (p=.818 and .539 respectively). The score for loss of gas however was significantly greater in the obese (3.1) versus non-obese group (1.9, p=.031). Study limitations were unequal group sizes and lack of adjustment for other risks of FI between groups.

In the second study, 20 men and six nulliparous women awaiting bariatric surgery (BMI = 48.8 (8.5) kg/m^2 (mean (sd)) were matched by age and sex with 26 non-obese controls (BMI = 25.1 (2.8)) (184). AI was reported using the Cleveland Clinic Florida Incontinence score. A higher percentage of obese patients (65.4%) had AI than non-obese controls (0%). Anorectal manometry (ARM) was also performed on both groups. Contraction/squeeze pressure (mean (sd)) was significantly lower in the obese group (155.6 (64.1) mmHg compared to the non-obese group (210.1 (75.9) p=.004)) but no other ARM measure was significantly different, including resting pressure. Limitations of the study were the absence of reporting the Cleveland Clinic AI scores and lack of multivariate analyses controlling for other risk factors of AI.

Two studies showed no effect of weight loss after bariatric surgery on AI. A retrospective cohort study reviewing medical records of 116 patients (83 women and 33 men, age = 47.6 (11.9) (mean (sd)) years) showed no significant difference in AI severity or prevalence before or one year after surgery (185). One of two surgeries were performed, gastric bypass or laparoscopic sleeve gastrectomy. Weight loss was significant; overall mean BMI was 43.6 (6.9) kg/m^2 preoperatively and 30.7 (6.5) kg/m^2 one year after bariatric surgery

(p=.0001). AI was reported before and after surgery using the Wexner scale. The Wexner score was 0.1 (0.6) before bariatric surgery and 0.1 (.6) one year after surgery (p= .57). The rate of AI before bariatric surgery was 5.2% (4.8% in women and 6.1% in men) and did not significantly change after surgery and weight loss. Limitations of the study include its retrospective design and not reporting the specific prevalence rate of FI postoperatively.

In a second study, using a prospective design, 86 of 117 obese patients (age=45 years (IQR 34–54 years), 84.6% women) receiving bariatric surgery (sleeve gastrectomy) were evaluated before and after surgery for AI (186). The median time of postoperative follow-up was 15 months (IQR 12.5–17.3 months). AI was defined as a Vaizey score above 4. The FIQL scale assessed quality of life.

There was no significant change in the prevalence of AI preoperatively (12.8%) vs postoperatively (24.4%), p = 0.06). The median Vaizey score for AI was 4 (IQR 4–4)) before and after surgery (p = 0.1). No patient developed new AI, but 10 patients had worsening of AI symptoms postoperatively. Patients lost weight postoperatively. The median BMI was 41.2 kg/m2 (IQR 38.3–44.5 kg/m2) at baseline (n = 117) and 31.6 kg/m2 (IQR 27.7–32.4 kg/m2) at the end of the study (n = 98). No patient had a percent excess BMI loss (%EBMIL) < 50%, which defined success of the surgery. The prevalence of AI (AI) nearly doubled after surgery from (12.8% preoperatively to 24.4% postoperatively, p = 0.06) but was not statistically significant.

An FIQL total score was calculated and did not significantly change before and after surgery. FIQL scores for subscales of Lifestyle and Depression did not significantly improve. Coping behaviour improved postoperatively from 1.8 (1.7–2.0) to 2.0 (2.0–2.1) p< 0.0002. There were too few responses to score the Embarrassment scale. Limitations included an absence of a control or comparison group of non-surgical patients, an inability to differentiate between anal and FI as an outcome, and 26.5% of participants were lost to follow up. The FIQL scale does not have a total score, but one was calculated in this study.

Lian *et al.*(187), conducted a meta-analysis of 11 cohort studies published between 2009-2016, reporting outcomes of pelvic floor disorders in obese women before and after bariatric surgery. The total number of subjects in the 11 studies was 784 and the follow up period ranged from 6 months to 3.1 years. Pooled results of nine studies showed a significant decrease in BMI after bariatric surgery (standardized mean difference (SMD) = 1.8, 95% CI (1.3, 2.3). FI was reported using the Pelvic Floor Distress Inventory/ Colo-Rectal-Anal Distress Inventory-8 in five studies. Bariatric surgery was not associated with significant improvements in FI (SMD=0.15, 95% CI (-0.15, 0.45).

Montenegro *et al.* (188), conducted a meta-analysis of English and non-English language studies from 2007-2017 about the effect of bariatric surgery on FI. FI was analysed in nine studies and reported using the Pelvic Floor Distress Inventory/ Colo-Rectal-Anal Distress Inventory-8. The mean reduction in BMI (12.90 kg/m^2) was significant, p < 0.001 There was a 22% decrease in FI after bariatric surgery which was not statistically significant (OR=0.80, 95% CI (0.53, 1.21, p =.29). Limitations included the high heterogeneity among the studies examining FI.

In the cohort study of female nurses by Staller *et al.* (49) the risk of FI was compared among four categorical levels of physical activity determined by assigning a value for a metabolic equivalent task over a week. In an age-adjusted analysis, the there was a modest reduction (25%) in the risk of FI with increasing physical activity. In the group with the lowest level of physical activity, the hazard ratio (95% CI) for FI was 0.86 (0.80-0.93) and in the group with the lowest level of physical activity it was 0.75 (0.70-0.81).

Because wearing high heels may adversely influence musculoskeletal health, resulting in foot and ankle problems and increasing lumbar lordosis, it may also affect the activity of pelvic floor muscles. Vitton *et al.* (189), examined the severity of anal incontinence and results of 3D high resolution anorectal manometry in 338 women with anal incontinence who wore shoes with high-heels ≥3cm at least four times a week for 4 consecutive hours for at least 1 year and or no high heels. Data in the health records of the women from two years were analysed. Anal incontinence was measured using the Wexner scale. There was no significant difference in the anal incontinence score between the women who wore high-heeled shoes (mean (sd) = 12 (6)) and those who did not (11 (5)), p=NS. There was no significant difference in mean anal resting pressure, voluntary contraction, high pressure zone or sphincter defects between those who wore high-heels or not. Study limitations were the retrospective design and absence of a control group without FI.

Summary of Weight Loss and Physical Activity

- Observational studies suggest an association between FI being overweight or obese. Many studies are of women (Level of Evidence 3).
- Anorectal manometry testing and observational studies indicate there are risk factors for FI in obese or overweight individuals; most studies are of women (Level of Evidence 3).
- There is conflicting evidence about the improvement of FI symptoms after weight loss from diet programmes or after bariatric surgery for morbid obesity. Current studies of weight loss after bariatric surgery show no significant improvement in FI (Level of Evidence 3).
- FI can limit physical activity.
- Low to moderate physical activity has no association with FI (Level of Evidence 3).
- High levels of physical activity may be associated with a modest decrease in risk of FI in older women but may increase risk younger athletic women (Level of Evidence 3).
- Wearing high heels was not associated with changes in anorectal function or FI (Level of Evidence = 3).

Recommendations for Practice Related to Weight Loss and Physical Activity

- No recommendation regarding physical activity can be made for lowering FI (Grade of Recommendation C)

Recommendations for Research on Weight Loss and Physical Activity

- Additional RCTs of the effect of weight loss to reduce FI in obese men and women are needed.

Table 15-3. Studies of Weight Loss Interventions for Managing FI

Study and Country	Design and Sample	Intervention and Outcome Measures	Findings	Strengths	Limitations
Pelletier et al. 2020 (186) France	Prospective cohort/observational 86 of 117 obese patients receiving bariatric surgery completed the study. Their age = 45 years (IQR 34–54 years), and 84.6% were women.	Patients were evaluated before and after surgery (sleeve gastrectomy). The median follow-up period after surgery among the 86 patients who completed follow-up Was 15 months (IQR 12.5–17.3 months). AI was measured using the Vaizey score. The Fecal Incontinence Quality of Life scale (FIQL) assessed quality of life.	The prevalence of AI nearly doubled after surgery from (12.8% preoperatively to 24.4% postoperatively, p = 0.06) but was not statistically significant. No patient developed new AI but 10 patients had worsening of AI symptoms postop. The median Vaizey score for AI was 4 (IQR 4–4) both before and after SG (p = 0.1). The median BMI was 41.2 kg/m2 (IQR 38.3–44.5 kg/m2) at baseline (n = 117) and 31.6 kg/m2 (IQR 27.7–32.4 kg/m2) at the end of the study (n = 98). The percent excess BMI loss (%EBMIL) was 67.5 (7.4) (mean (sd). No patient had a %EBMIL < 50%, which defined success of the surgery. An FIQL total score was calculated and did not significantly change before and after surgery. FIQL scores for subscales of Lifestyle and Depression did not significantly improve. Coping behavior improved postop 1.8 from (1.7–2.0) to 2.0 (2.0–2.1) p< 0.0002. There were too few responses to score the Embarrassment scale.	Median length of followup was adequate. Preoperative AI was measured and compared to postoperative AI.	No control (or comparison group), i.e., patients without surgery. Sample attrition was 26.5% and some measures were of small numbers of participants. Inability to differentiate between anal and FI as an outcome FIQL does not have a total score but one was calculated.

Study and Country	Design and Sample	Intervention and Outcome Measures	Findings	Strengths	Limitations
Ait Said et al. 2017 (185) USA	Retrospective cohort/observational design Medical records of 116 obese patients who underwent bariatric surgery between 2013-2014 were analysed. Patients were 83 women and 33 men. Average age of sample = 47.6 (11.9) years.	One of two surgeries was completed on patients: gastric bypass or laparoscopic sleeve gastrectomy. All participants had completed 2 questionnaires about urinary incontinence (UI) and 2 about AI the day before bariatric surgery and 1 year postoperatively. AI was reported using the Wexner score.	Preoperatively, the rate of AI in the sample was 5.2%. BMI after bariatric surgery decreased from 43.9 kg/m² to 30.7 kg/m² ($p<0.0001$). The Wexner score was 0.1 (.6) (mean (sd)) before and after bariatric surgery ($p=.5660$). There was no significant change in AI prevalence or Wexner score after weight loss after bariatric surgery.	One year followup; sample had both men and women Used validated data collection tools	Retrospective design; Prevalence values of AI after bariatric surgery was not reported; Convenience sample; Unable to differentiate between FI and AI with flatus
Scozzari et al. 2013 (168) USA	Observational 32 consecutive obese women completed questionnaires and had anorectal manometry measured before and after bariatric surgery. 71 age-matched healthy non-obese women with the same inclusion criteria completed the same questionnaires whose scores were used as a control in a multivariate analysis.	The bariatric procedure was laparoscopic Roux-en-Y gastric bypass in 18 cases, laparoscopic vertical banded gastroplasty in ten, laparoscopic gastric banding in two, and laparoscopic sleeve gastrectomy in two. The questionnaires used were the Pelvic Floor Distress Inventory Short Form 20 (PFDI-20) and the Pelvic Floor Impact Questionnaire—Short Form 7 (PFIQ-7). The selected PFDI-20 and PFIQ-7 cut-off scores were 18.2 and 2.4, respectively, AI was reported using the Wexner score before and after surgery.	Median PFDI-20 total score did not show a significant change from preop 24.2 to postop 26.6, (p=ns (not statistically significant)) in obese patients. Although median total score of PFIQ-7 in obese women showed a significant improvement in the (from 4.8 to 0.0, p= 0.044) as did their urinary score, the colorecto-anal scores did not change significantly. Mean Incontinence Wexner Score was 1.1 preop and 1.0 post-op (p=ns). AI increased from 28.1 % before surgery to 40.6 % after surgery but was not not significant. There was an increase in the rate of flatus AI from 19% before surgery to 37.5 % after surgery (p=ns).	Used validated data collection tools	Unable to differentiate between FI and AI with flatus Women only; convenience sample; No comparison treatment
Markland et al. 2011 (165) USA	Secondary analysis of 338 overweight and obese females with urinary incontinence in an RCT of a weight loss program vs control group receiving education	The modified FI Severity Index (FISI) was administered at 6, 12, and 18 months in 338 women. Repeated measures analyses identified factors associated with improved FISI scores among women with baseline scores >0	No significant difference in FISI score/AI between control vs treatment groups Women who showed a decrease in AI had a lower weight and BMI at baseline		Untested modification of the FISI score Lack of adjusting for baseline AI severity in the analysis

Study and Country	Design and Sample	Intervention and Outcome Measures	Findings	Strengths	Limitations
Roberson et al. 2010 (176) USA	Observational survey Questionnaire was mailed to 404 adults who underwent bariatric surgery at one hospital during July 2002 to May 2006. 48% (n=193) of questionnaires were completed and returned of which 33 were from men. Time of followup was >700 days after surgery for both men and women.	Gastric bypass or gastric banding surgery was performed. 83% of women and 75% of men underwent a gastric bypass. The severity of self-reported AI was determined after surgery only using the Vaizey score Patients were asked about perceived changes in AI after surgery using 4 categories, much worse' worse, better' and ''much better. In the analysis, the categories of ''much worse'' and ''worse'' into one category were combined, as were ''better'' and ''much better.''	AI was worse two years after gastric bypass or gastric banding surgery than before surgery despite an average 48 kg weight loss in more than half of the patients. The mean Vaizey FI score for women was 8.4 (sd= 2.8) and for men it was mean 8.5 (sd=2.5) Worsened AI was attributed to postoperative diarrhoea.	High response rate to mailed questionnaire	Vaizey score of AI was not obtained preoperatively Change in AI was determined using non-validated questions and not a bowel diary
Burgio et al. 2007 (175) USA	Prospective cohort study 101 women, aged 20-25, with a BMI of 40 or more	Women underwent laparoscopic Roux-en-Y gastric bypass AI was assessed by asking participants 2 questions: Do you have any uncontrolled anal leakage? and If yes, specify gas, liquid, solid or a combination before and at 6 and 12 months after surgery Change in AI from before the bypass surgery to 12 mo. after was analysed	Mean BMI decreased from 48.9 (7.2) mean (sd) before surgery to 35.3 (6.5) at 6 months and 30.2 (5.7) at 12 months after surgery Prevalence of FI (solid or liquid stool) decreased from 19.4% to 9.1% at 6 months and 8.6% at 12 months (p=.018)	Follow-up was for 1 year	Absence of control group and validated questionnaire of AI Unable to differentiate between FI and AI with flatus

AI refers to anal incontinence; BMI means body mass index; FI refers to faecal incontinence; IQR refers to interquartile range; ns means not statistically significant; sd means standard deviation

6. SMOKING CESSATION

Smoking cessation is considered a possible lifestyle modification to manage FI. In healthy individuals, nicotine can cause a dose-dependent, significant decrease of total colonic transit time, accelerate recto-sigmoid transit time, reduce colonic compliance, and induce propagated colonic contractions while relaxing the descending colon (190, 191). This colonic effect is associated with a sense of defaecation urgency and prompting initiation of defaecation. However, observational studies have shown no association between cigarette smoking and FI (56, 171, 192). In a longitudinal observational study of community-living elderly men and women, smoking was not predictive of prevalent or incident FI (140). No new studies of the association of smoking or effects of smoking cessation on FI were found.

Summary of Smoking Cessation

- There is no association between cigarette smoking and FI (Level of Evidence 3). There are no studies of the effects of smoking cessation on FI

7. RECOMMENDATIONS FOR PRACTICE RELATED TO SMOKING CESSATION

- No recommendation can be made for smoking cessation in the management of FI due to a lack of evidence.

Recommendations for Research on Smoking Cessation

- Studies of the effects of smoking cessation on reducing FI are required

8. BOWEL HABIT MANAGEMENT, TRANS-ANAL IRRIGATION, AND BOWEL TRAINING FOR URGENCY

8.1. Bowel Habit Management

Conservative management for FI includes advice for attempting to establish a regular pattern of bowel elimination, and most bowel management programmes typically involve patient teaching, modifying diet/fibre and fluid intake, encouragement for adhering to a meal-time and defaecation routine, and physical activity (193-195); toileting programmes, usually for those in long-term care settings, may be added. Because peristaltic contractions of the colon that are associated with defaecation increase in frequency following awakening from sleep and meals (196, 197), the period after breakfast is considered the best time for attempting scheduled defaecation. Bowel management programmes with or without or a toileting component has been tested for their effectiveness for FI mainly in adults with neurogenic FI or in those in rehabilitation centres or long-term care institutions (nursing homes) (195). Managing FI in community-living adults with normal cognitive function through bowel habit training is understudied.

8.2. Rectal Emptying and Trans-Anal Irrigation

Emptying the rectum of faeces in between bowel movements can be part of a bowel management programme or a strategy for reducing FI. The aim is to ensure that the rectum remains empty most of the time reducing the chance of faecal leakage. Trans-anal (retrograde) irrigation systems, small enemas, suppositories, laxatives. Digital rectal stimulation and manual evacuation are techniques used to empty the rectum. Trans-anal irrigation has been studied the most and is often recommended for those with passive FI, incomplete evacuation of the rectum, and neurogenic FI (spinal cord damage, spina bifida, multiple sclerosis, stroke etc.) but it is also used by patients with FI due to other causes. The development of small irrigation systems and addition of pumps for instilling the irrigation fluid has increased the convenience of trans-anal irrigation. A typical procedure is that the patient sits on the toilet and instills water into the rectum through the anus using one of the systems, after which they defaecate or expel the fluid into the toilet.

Several observational and quasi-experimental studies, most with small sample sizes, have shown that trans-anal irrigation can reduce the number of FI episodes in about 40-60% of users, decrease the total number of daily or nightly defaecations in some cases, and improve quality of life (150, 198-200). Patients perform trans-anal irrigation daily or less than daily. Trans-anal irrigation has been used in combination with dietary fibre supplementation (150). Adverse symptoms or reasons for discontinuation include minor rectal bleeding, transient abdominal pain after irrigation, time required for the procedures, or difficulties with the procedure (150, 198-200). Group sessions for teaching and supporting patients using transanal irrigation were a cost-effective means to providing psychosocial support and improving patients' skills in the procedure.

8.3. Bowel Training for Urgency

Sensing an urge to defaecate is part of the normal process of defaecation, but some patients experience an overly strong sensation. Bowel training programmes aim to manage the response to this urge and prolong the time to defaecate while maintaining continence. However, in an RCT that compared patients who received education, including urgency resistance techniques and dietary advice, to patients who received the same education plus anal sphincter exercises with or without home or clinic biofeedback, there was no significant difference in outcomes (118).

New Evidence about Bowel Habit Management, Trans-Anal Irrigation, and Bowel Training for Urgency

One clinical study focused on bowel management (201), and three clinical studies (202-204), focused on trans-anal irrigation for FI were identified and analysed in this review. One study about trans-anal irrigation described reductions in FI after TAI was used over time (202), one study examined predictive factors for TAI adherence (203), and one study described patient preferences regarding potential outcomes of trans-anal irrigation and standard bowel management (204). Regarding bowel training, there was one expert consensus paper about bowel training to lessen urgency (205) , and one quasi-experimental study reporting that dietary fibre supplementation and diet advice decreased defaecation urgency (157).

The effectiveness of a combination bowel management intervention that offered education and skills training to perform self-management strategies for urinary incontinence (the primary outcome) and bowel incontinence for women aged 50+ years was investigated by Brown *et al.* (201). The intervention was named "Mind Over Matter; Healthy Bowels, Healthy Bladder" and was investigated using a randomized controlled design with a wait-list control group. The bowel management part of the intervention addressed pelvic floor muscle exercises (relaxation, contraction, endurance, and coordination components), dietary changes for optimization of stool consistency, and information about defaecatory position over three

sessions of two hours each. It was facilitated by a community member (neither an investigator nor a clinician) who received a two-day training session.

Of the 121 women who participated, 60% (n=73) had both urinary and bowel incontinence, and 1% had only FI; 95% completed the 4-month self-assessment of incontinence (201). More women in the treatment group (55%) than in the control group (27%) reported that their bowel incontinence improved on a modified Patient Global Impression of Improvement tool (p<.005). However, differences between the treatment and control groups in the colorectal subscale of the Pelvic Floor Distress Inventory Short Form-20 were not statistically significant (mean (SD) reduction 6.12 (15.72) vs 0.92 (14.33) points, p=0.07). The quality of life and self-efficacy scores of the treated group improved statistically significantly more than the control group. Limitations of the study were inadequate power for outcomes of FI, a non-concurrent control/comparison group, lack of monitoring fidelity of the intervention, and use of only self-report measures. The homogenous, motivated sample limits generalizability of the findings.

In a prospective cohort study, AI of patients with anal/FI and/or constipation who failed conservative therapy was examined before (baseline) and after 12 months of using trans-anal irrigation (TAI) (202). Patients were instructed in the use the trans-anal irrigation (TAI) using a catheter system with a cone shaped tip and irrigation fluid driven by gravity (Coloplast irrigation bag/Colotip®, Coloplast A/S, Humlebæk, Denmark). Of the 507 patients (83% female, median age = 56 (range 19–86) years) receiving TAI at study start, 216 (43%) patients were using it at the one year follow up. Among those who used TAI, the Wexner incontinence score decreased from 12.4 at baseline to 10.2 at the 12-month follow-up (p < 0.001) and the St. Marks incontinence score decreased from 14.9 to 12.7 (p<0.001). Quality of life and general satisfaction with bowel function, measured on an 11- point Likert-type scale developed for the study, also significantly increased over the duration of the study (202).

The main reason for not continuing TAI was an unsatisfactory outcome, which was reported by 86 (49.4%) of those who discontinued its use. Undesirable symptoms during the TAI procedure were abdominal pain (the predominant complaint) in 50 patients (23.1%), anorectal pain in 32 patients (14.9%), sweating in 28 patients (13.0%), nausea in 23 patients (10.6%), and each of the following, chills/shivering, dizziness, headache, facial flushing, and general discomfort in less than 22 (10%) of the patients.

Strengths of this study (202), were its prospective design, length of follow up, use of common scoring tools measuring bowel function and FI. Limitations included the lack of a control group and the high percentage of patients who did not use or continue TAI (>50%). The incontinence scores were unable to distinguish anal from FI, and some scoring tools lacked validity and reliability testing.

The adherence to TAI of 108 patients (87 women and 21 men; median age 55 years (range 18-83)) with constipation or FI over a four-year period was retrospectively assessed using a mailed questionnaire (203). Of these patients, 57 (53%) had FI. Patients were classified as adopters if they continued using TAI for at least one year or as non-adopters if they stopped. Overall, 48 of the 108 (43%) patients continued to use TAI at one year after training, and 70% of those performed the irrigation at least 2 to 3 times per week. The patients with FI had the best results, with 54.5% continuing the therapy. The majority of patients (41%) discontinued TAI because of its lack of efficacy. Other reasons were technical problems such as catheter expulsion, rectal balloon bursting, instilled water leakage, pain during irrigation, anal bleeding, and anal fissure in 36% of the patients. Twenty-three percent of patients thought there were too many constraints, mainly related to the time spent performing the irrigation.

There was no significant difference between the individual characteristics of the patients who discontinued TAI versus the adopters (203). The only factor predictive of discontinuation of TAI was having a first TAI training session complicated by technical problems (expulsion of catheter, fluid leakage, or no evacuation of stools during irrigation) (p = 0.02). Limitations of the study were its retrospective design, a sample with heterogeneous neurological conditions, and not presenting results about reasons for discontinuing TAI separately for those with FI.

The aim of the third study (204), was to describe the preferences of adult patients with neurogenic bowel dysfunction regarding potential outcomes or attributes of TAI and other standard approaches to bowel management. Participants (n=143) were recruited through a panel of patients in the UK who have used TAI products of one manufacturer (Coloplast; Humlebaek, Denmark). The study used a discrete choice exercise in which participants were surveyed about the amount that they were willing to pay out of pocket for a treatment benefit or attribute. The survey combined 7 device/treatment attributes and levels of benefit into 17 choice sets. Each choice question presented two TAI devices (device A or B) and a third choice that represented a standard or conventional approach to bowel management that did not include anal irrigation, which remained constant in each question. The conventional approaches were use of suppositories, laxatives, antidiarrhoeals, active monitoring of diet and fluid intake, use of incontinence pads, and use of digital evacuation to empty the bowel. Regression models were used to analyze the influence of each of the study attributes on participants' choices. Results showed that the most highly valued attributes were the reduction in risk of FI (OR =5.18) and frequency of use (OR = 4.69) (204). For example, participants were five times more likely to prefer a device that was associated with no episodes of FI compared with one that was likely to leave three episodes of FI per month and four times as likely to prefer a device that led to going to the toilet once in every 2 days rather than three times a day. Other preferences were complete avoidance of a UTI, minimizing the amount of time spent on the toilet, and using a manual pump for TAI vs an automatic one or none. Limitations were inclusion of patients who used only one manufacturer's device and exclusion of 14 patients' responses. The majority of the included patients was independent in care, limiting generalizability of results.

A consensus document about bladder and bowel training for urgency was developed by a group of clinical and research expert nurses in the International Continence Society (205). The consensus document addresses a gap of evidence to support clinicians providing this therapy. The document provides comprehensive expert advice, based on available evidence, about the steps of assessment, planning, intervention and evaluation in bowel training programmes. The document advises on how to conduct a bowel training programme to assist an individual to make lifestyle, behavioural and sometimes environmental changes to regain a controlled response to urgency and a satisfactory pattern of defaecation. A bowel training programme provides education, increases skill in progressively increasing intervals between defaecations, using urgency suppression and relaxation techniques, and performing pelvic floor muscle exercise routines, and offers positive reinforcement.

In a non-experimental pilot study by Ribas & Munoz-Duyos (157), reviewed in the previous section, about dietary fibre for FI, defaeca-

tion and FI urgency was measured in patients before and after they consumed a supplement of 500 mg of methylcellulose fibre every 8 hrs for 6 weeks and received dietary advice. Of the 61 subjects who completed the study, 50 reported urgency incontinence episodes at baseline on a bowel diary. After treatment, 37 subjects had 50% or greater reduction in defaecatory urgency and/or urge FI episodes. The number of urge FI episodes/week decreased from 3.8 (range= 0–42) at baseline to 1.7 (0–35), $p < 0.001$ after treatment.

No new studies examining the use of laxatives or suppositories to treat FI in adults with non-neurogenic FI were found.

Summary of Bowel Management, Rectal Emptying or Trans-Anal Irrigation, and Bowel Training

- A bowel management programme focused on education and skills training to perform self-management strategies including pelvic floor muscle exercises (relaxation, contraction, endurance, and coordination components), dietary changes for optimization of stool consistency, and defaecatory position reduced FI and improved quality of life and self-efficacy in women (Level of Evidence 3).
- Trans-anal irrigation reduced FI for up to one year of its use in some patients and improved quality of life (Level of Evidence 2).
- Reasons for discontinuing TAI were an unsatisfactory outcome, a variety of adverse symptoms, or difficulties with the procedure during training (Level of Evidence 2).
- Patients prefer to use a TAI system that eliminates all episodes of FI, avoids a UTI, requires less frequency of going to the toilet, lessens the amount of time spent on the toilet, and uses a manual pump (Level of Evidence 2).
- A methylcellulose fibre supplement (500 mg every 8 hrs) and dietary advice reduced the number of urge FI episodes (Level of Evidence 2).
- There is a consensus statement to guide clinicians in bowel training for managing urge FI (Level of Evidence 3).

Recommendations for Practice Related to Bowel Management, Rectal Emptying or Trans-Anal Irrigation, and Bowel Training

- Advise the patient to attempt to establish a bowel habit routine (Grade of Recommendation B/C).
- Transanal irrigation should be recommended for patients with passive FI, incomplete rectal evacuation, or FI with defaecation difficulty; it may be tried by patients with FI of other types/causes who do not respond to other initial conservative therapies and to improve self-management (Grade of Recommendation B).
- Group sessions should be considered as a way of teaching and supporting patients performing trans-anal irrigation (Grade of Recommendation C/D).
- Evacuation of the rectum using a suppository or enema in patients with passive FI or incomplete rectal evacuation is useful (Grade of Recommendation C/D).
- Bowel training for resisting defaceation urgency that includes dietary fibre supplementation and dietary advice may be useful for patients with FI associated with urgency (Grade of Recommendation C).

Recommendations for Research on Bowel Management, Rectal Emptying or Trans-Anal Irrigation, and Bowel Training

- Randomised clinical trials of the effectiveness of trans-anal irrigation compared to other bowel emptying approaches, or to usual care and other conservative therapies are needed.
- Research on bowel management approaches and effectiveness of bowel training programmes are needed.

9. MEDICATIONS

Medication treatment of FI should be allocated according to symptom profile and patient lifestyle. The goals of this section are to identify the medications that have been used to treat FI and to evaluate the evidence regarding their efficacy (Table 15-4). Medications are part of the initial conservative management of FI, and have focused on three mechanisms

1. Reduction of diarrhoea. Diarrhoea is consistently found to be a strong risk factor for and exacerbating symptom of FI.
2. Increasing resting anal canal pressure. Low resting anal canal pressure is a risk factor for passive FI, and is commonly seen following some types of anorectal surgery (e.g., ileal pouch procedures, sphincterotomy, abdomino-perineal pull-through for imperforate anus).
3. Treatment or prevention of constipation. Constipation with overflow of liquid faeces around a faecal mass or a subsequent large bowel movement when constipation resolves is frequently found to be a risk factor for FI, especially in older persons or those with neurogenic FI (206).This treatment is addressed in the section on neurological causes of FI.

9.1. Treatment of Diarrhoea-Associated FI with Antidiarrhoeal Drugs

Loperamide (synthetic opioid with μ-agonist activity) is the most studied drug specifically for diarrhoea-associated FI. The mechanism of action is slowing of gut transit, increasing fluid reabsorption and reducing secretion, as well as directly increasing resting anal pressure. Loperamide is effective in decreasing stool frequency and improving stool consistency and reducing FI to some degree. Constipation can be a side effect. In earlier work, loperamide improved continence by reducing diarrhoea in a manner equivalent to codeine and superior to diphenoxylate, a natural opioid (207). Results of a double-blind placebo- controlled cross-over trial of loperamide in 10 obese subjects taking orlistat with resulting FI, showed loperamide significantly decreased soiling and FI (208).

Studies have compared the effects of taking loperamide along with a fibre supplement and/or using biofeedback on FI. In a study of 63 patients, taking loperamide and a psyllium fibre supplement or loperamide and a placebo supplement both improved FI (151). Results suggested taking psyllium fibre in addition to loperamide did not increase the benefit of loperamine (151). Sze and Hobbs (152), showed that 46% of women treated with methylcellulose fibre (n=19) or methylcellulose plus loperamide (n=40) resolved their FI compared to 10 control women who declined study treatment.

Another study administered loperamide supplemented with methycellulose fibre for 2-4 months or biofeedback therapy for 4-6 months then a combination of the treatments to 57 women in a cross-over design (209). Results showed the combination treatment was superior in improving FI compared to both single treatments. There was no significant difference between single or combined treatments at any time point. Markland *et al.* (148), conducted a randomised, dou-

ble-blind, placebo-controlled cross-over trial comparing loperamide (followed by psyllium) and psyllium (followed by loperamide). Both treatments reduced FI. Loperamide was associated with greater frequency of constipation. The considerable variation in comparators and study design has prevented meta- analysis of studies of loperamide for FI.

Other drugs have been investigated for FI associated with diarrhoea. Cholestyramine and biofeedback therapy versus biofeedback alone were compared in 42 patients, 21 in each group, (210). FI improved only in the group adding cholestryramine to biofeedback. Sucralfate, a formulation of aluminium hydroxide used primarily for the treatment of peptic ulcers, has been shown to reduce diarrhoea, which worsens FI, in patients with radiation proctitis. Randomised controlled trials have shown no significant benefit of sucralfate for diarrhoea (211), and a worsening of FI (212), in patients with radiotherapy-induced symptoms.

9.2. Treatment to increase resting anal canal pressure

A few small studies, have examined a variety of drugs for FI from the premise of increasing resting anal canal pressure. Table 15-4 lists studies of oral and transdermal clonidine (213), (214), as well as amitriptyline (215).There was no difference in FI or anorectal function between treatment and control groups using oral clonidine (n=44) (213). An uncontrolled study (n=12 women) of the clonidine patch reported reduced stool frequency and FI with no significant changes in anorectal manometry measurements or rectal capacitance (214). Santoro *et al.* (215), carried out an uncontrolled study of oral amitriptyline (20 mg) at bedtime in 18 patients with FI, reporting that the treatment reduced the amplitude and frequency of rectal contractions and improved sphincter pressure. Phenylephrine gel, an alpha-1 adrenergic agonist, has been investigated for the treatment of passive FI. Two studies failed to show any benefit (216, 217), but three others (217-219), suggested a modest benefit. The clinical utility of phenylephrine gel seems limited, and the topical preparation was associated with local discomfort. L-erythro methoxamine gel, an alpha-1 adrenoreceptor agonist like phenylephrine, was shown to increase internal anal sphincter resting pressure (220, 221).

New Evidence about Medication Treatment

There are three new reports of a trial of loperamide with four groups (education vs oral placebo and education vs oral placebo and anal manometry assisted biofeedback vs loperamide and biofeedback) (107, 182, 222), two trials of eluxadoline (223, 224), one trial of oxymetazoline (225), and one trial of clonidine (226). A cohort study describing use of various pharmaceutical agents including loperamide and bile acid sequestrants was also included (227).

Anti-Diarrhoeal Medications

Some new studies have been more focused on specific population groups rather than mixed groups of individuals with FI found in earlier studies. For women with FI and normal stool consistency, three analyses of data from a trial comparing loperamide with other first line treatments including education and biofeedback have been reported. Jelovsek *et al.* (107), reported that in women with normal stool consistency and FI bothersome enough to seek treatment, loperamide was no different to placebo, anal exercises using manometry-assisted biofeedback were equivalent to an educational pamphlet, loperamide and biofeedback together were equivalent to oral placebo and biofeedback or loperamide plus an educational pamphlet. The authors concluded that combining loperamide, anal manometry-assisted biofeedback, and a standard educational pamphlet resulted in negligible improvement over individual therapies.

Andy *et al. (222)*, conducted a secondary analysis of the same study data to assess changes in constipation symptoms between groups. There was no difference in constipation symptoms between treatment groups, and the authors concluded that loperamide reduced the FI but did not worsen constipation.

Improvements in defaecatory symptoms were greater in those reporting improvement in FI. Richter *et al.* (182), focused on participants in the CAPABLe trial with clinically important responses to treatment. This was defined as either a minimal clinically important difference (MID) of −5 points in St. Mark's score, a ≥50% reduction in FI episodes (as reported on a bowel diary), or a combined St. Mark's MID of -5 points and ≥50% reduction in FI episodes. Those women with higher baseline severity, adherence to drug therapy, and those who were overweight were more likely to meet the minimal clinical important difference in the St. Mark's scale score.

Two trials of eluxadoline, the mu-opioid receptor agonist to treat symptoms of irritable bowel syndrome with diarrhoea (IBS-D), report on FI. However, the primary outcomes for these studies tended to be abdominal pain and stool consistency rather than FI which was reported as a secondary outcome. In pooled data from two large randomized controlled Phase 3 studies comparing two doses of eluxadoline to placebo, Lembo *et al* (223), reported no significant decrease in FI episodes, referring to data in a supplementary data table. Brenner *et al.* (224), conducted a large randomized controlled trial comparing eluxadoline to placebo and included recording of FI episode in a diary along with other symptoms including stool consistency and abdominal pain, the primary outcome measures. FI in the two groups was only reported at baseline.

Other Medications

Barak *et al.* (225), reported a double blind crossover trial of topical oxymetazoline, an alpha-agonist that increases anal resting pressure, versus placebo in a sample of 19 spinal cord injured patients with FI. Results favoured oxymetazoline over placebo in the number of incontinence episodes 12 hours after application. However, this small study was under powered, and most participants were male, which limits generalizability.

In a two-part study, Sharma *et al.* (226), evaluated rectal compliance and sensation in response to saline or atropine (muscarinic antagonist) in 44 women with urge predominant FI compared to 16 healthy controls. Women with FI were then randomized to oral placebo versus clonidine for 4 weeks in a double blinded trial. The authors suggested the acute response to atropine provided a pharmacological challenge that may predict the long-term effects of clonidine. Results revealed a subset of FI patients with reduced rectal distensibility and increased rectal sensation, which were reversible in some patients. Larger trials are needed to confirm these findings and evaluate the efficacy of clonidine in treatment of women with urge dominant FI.

There was one descriptive cohort study (227), of people referred for treatment of chronic bowel symptoms (frequent bowel movements, loose stools, faecal urgency and FI) after having colon or pelvic cancer. Treatments were variable involving medication (bile acid sequestrants, antibiotics, loperamide) and dietary interventions. Due to the heterogeneity of the sample characteristics and interventions, specific recommendations were not possible.

Table 15-4. Effectiveness of Medication Treatment for FI

Citation	Sample	Study Design	Major Findings	Adverse Events	Comments
Antidiarreals					
Jelovsek et al. 2019 (107)	300 women with at least monthly FI over preceding 3 months and normal stool consistency were recruited from 8 clinical sites. Randomized to 4 groups: • Oral placebo and education only (n=42), • Loperamide and education (n=88), • Oral placebo and anorectal manometry assisted biofeedback (n=84), • Loperamide plus biofeedback (n=86). • Intention to treat analysis included 274 women at 12 weeks and 266 women at 24 weeks.	Randomized controlled trial (CAPABLe). Electronic randomization and stratification. Researchers, interviewers and outcome evaluators blinded to biofeedback assignment. Instruments: St Mark's (Vaizey) FI severity Scale, a 7-day bowel diary (leakage episodes and pad use), Colorectal-Anal subscales of the Pelvic Floor Distress Inventory Short Form, Colorectal-Anal subscale of the Pelvic Floor Impact Questionnaire (CRAIQ), Modified Manchester Health Questionnaire severity Subscale, Modified Patient Global Impression of Improvement (PGI-I) scale for bowel function, anal sphincter tone on physical examination using the Digital Rectal Examination Scoring System and anal manometry measures. A Fruits/Vegetables/ Fibre Screener questionnaire for dietary fibre intake. Adherence: pill counts, provider-reported adherence question and modified Medication Adherence Self-Report Inventory. Other not reported listed in study publication.	Primary outcome: changes in St. Mark's scores from baseline to 24 weeks. Results: No significant differences between groups at 24 weeks on St Mark's score. Bowel diary outcomes improved in all groups. No evidence against the null hypotheses that loperamide is equivalent to placebo, that anal exercises with biofeedback is equivalent to an educational pamphlet, and that loperamide and biofeedback together are equivalent to oral placebo and biofeedback or loperamide plus an educational pamphlet	Constipation in 2 participants in each of the loperamide groups. Only one serious side effect identified as potentially related to treatment was small bowel obstruction in the placebo and biofeedback group.	Study met sample size analysis requirements, adequately powered to detect a statistically significant difference between groups base on a minimally important difference (MID) of −5 points for the change from baseline in St. Mark's score Similar rates of post-randomization withdrawals at 24 weeks among groups are reported. Four participants were ineligible after randomization
Andy et al. 2020 (222)	296 women with at least monthly FI over preceding 3 months and normal stool consistency recruited from 8 clinical sites.	Secondary analysis of CAPABLe trial data Defaecatory symptoms measured by the Patient Assessment of Constipation Symptoms (PACSYM) at baseline, 12, and 24 weeks. Response to FI treatment: a clinically important improvement of ≥ 5 points on the St. Mark's (Vaizey) scale between baseline and 24 weeks.	Primary aim: Changes constipation symptoms between groups. No difference in constipation symptoms between treatment groups. Secondary aim: changes in constipation in responders and non-responders to FI treatment. Responders (n=137) had greater improvement in constipation compared to non-responders n=129) (-0.4; 95% CI -0.5, -0.3 vs. -0.2; 95% CI -0.3, -0.0), p<0.01, mean difference = 0.2, 95% CI 0.1, 0.4	None reported	

Citation	Sample	Study Design	Major Findings	Adverse Events	Comments
Richter et al. (2020) (182)	296 women with at least monthly FI over preceding 3 months and normal stool consistency recruited from 8 clinical sites. 266 had outcome data.	Secondary analysis of CAPABLe trial data P Minimal clinically important difference as −5 points in St. Mark's score, a ≥50% reduction in FI episodes (bowel diary), and combined St. Mark's MID and ≥50% reduction in FI episodes.	Primary aim was to identify participants with clinically important responses to treatment. Women with higher baseline severity, adherence to drug therapy, and those who were overweight (vs normal/ underweight) were more likely to meet the minimal clinical important difference in St. Mark's scale score.	None reported	Predominantly white participants (79%) who were menopausal (mean age 63.7 years). The authors identify this may limit generalizability.
Lembo et al. 2016 (223)	2427 adults with IBS with diarrhoea aged 18-80 years. Data was from Phase 3 two trials (IBS-3001 and IBS-3002). Intention to treat sample was 2425.	Randomized controlled trial. Participants randomly assigned to eluxadoline (75 mg or 100 mg) or placebo twice daily for 26 weeks or 52 weeks. Instruments were the Bristol Stool Form Scale and IBS-D global symptom score. Participants also recorded number of bowel movements and whether these were associated with urgency or FI in a diary.	Primary end point was decrease in abdominal pain and improvement in stool consistency on the same day for at least 50% of the days from weeks 1 through 12 and from weeks 1 through 26. Both doses of eluxadoline were significantly superior to placebo with respect to the end points of adequate relief of IBS symptoms, scores for global symptoms, and scores on the IBS-QOL questionnaire No significant reduction in FI was found (reported in published supplemental data.	Five patients had pancreatitis, eight cases of abdominal pain with elevated hepatic enzyme levels consistent with spasm of the sphincter of Oddi.	FI was not a primary endpoint. No link to supplementary data table.
Brenner et al. 2019 (224)	346 adults with irritable bowel syndrome with diarrhoea and self- reported inadequate symptom control with loperamide	Randomized controlled trial. Double blinded, Phase 4 study. Participants randomly assigned to placebo or eluxadoline 100mg twice daily for 12 weeks. Instruments were the Bristol Stool Scale and the Worst Abdominal Pain (WAP) scale. Participants also recorded number of bowel movements, faecal urgency and FI in a diary.	Primary efficacy endpoint was the proportion of composite responders (daily WAP score improvement and BSS score less than 5 [or absence of bowel movement accompanied by greater WAP improvement compared to baseline for at least 50% of treatment days. Weekly average FI reported as part of baseline characteristics (1.1 for placebo, 1.2 for eluxadoline group.	Three patients in the placebo group (1.7%) and 1 patient in the eluxadoline group (0.6%) experienced serious treatment emergent adverse events.	No outcome data for FI reported.

Citation	Sample	Study Design	Major Findings	Adverse Events	Comments
Markland et al. 2015 (148)	Double-blind, randomised, cross-over design 80 veterans with FI or liquid or solid stool at least weekly for 3 months	Random assignment to Loperamide (2 mg) first then a supplement of psyllium fibre (3.4 mg) or psyllium first then loperamide for 4 weeks each with a 2 week washout and a 2 week non-equivalent baseline period FI frequency was reported daily on a diary for 7 days during each period	No significant difference in FI between treatment groups. Within each treatment group, FI frequency significantly decreased from baseline during the first treatment period for both treatments, but did not significantly change after the crossover to the other treatment.	Loperamide group had one adverse event, constipation and none in psyllium group	Use of a stool diary untested for validity and reliability, potential error due to subjects needing to prepare part of the supplement, possible unmeasured cross-over effects, non-equivalent baseline period, and attrition during the washout
Sze & Hobbs 2009 (152)	59 patients and 10 controls (latter recruited if declined active treatment). Outcomes: overall improvement and Pescatori score at 8 weeks	Prospective unblinded controlled study of methyl-cellulose (1-2 Tbls/d) with (n=19) or without loperamide (1-2 capsules/d) (n=40) vs. controls (n=10)	FI resolved in 27 patients (46%) using methyl-cellulose with or without loperamide vs. control	Constipation with loperamide relieved by dose alteration.	Power calculation aimed to detect 46% difference in open study.
Lauti et al. 2008 (151)	63 randomised (49 completed both phases of cross-over) consecutive referrals to specialist centre.	Double-blind randomised cross-over trial, each treatment was given to both groups for 6 weeks. Treatment A = low-residue diet sheet, placebo (1 tsp of an infant food thickener containing locust bean gum fibre/d) and loperamide as needed Treatment B = psyllium fibre (1 tsp/d), low and high residue diet sheet and loperamide as needed	FISI scores fell from baseline 31 to 18 for treatment A and 19 for treatment B. No differences between treatments in terms of FISI or FIQL.	Nil major adverse events – palatability of supplements caused 1 patient (3%) to withdraw	Loperamide was taken as needed so dose was variable; there was low fidelity of monitoring the intervention; Possible confounding from placebo that contained dietary fibre Possible carry-over effects from cross-over to other treatment
Other medications					

Citation	Sample	Study Design	Major Findings	Adverse Events	Comments
Barak et al. 2019 (225)	N= 19 spinal cord patients aged 23.7-57.2 years (Mean 42.6) with FI. SCI injury at least 3 months and less than 5 years before randomization with at least 4 incontinence events per week. 16/19 were men. Prior to randomization, patients underwent a 1 day open label anal manometry and pharmacokinetic study.	Double blind crossover trial of topical oxymetazoline 2 arms: Placebo x 4 weeks followed by oxymetazoline x 4 weeks (n=9) OR oxymetazoline x 4 weeks followed by placebo x 4 weeks (n=10). 2 week washout period between each phase	Primary outcome: number of FI episodes at 8 and 12 hours after administration, recorded on daily diaries. Change in mean faecal incontinence episodes per month (12 hours post drug application) favoured treatment over placebo [26.3 (SD ±28.4) versus 36 (SD ±39.8) (p = 0.021)]. Non-gas episodes only: mean number of episodes decreased from 10.1 (+4.3) to 6.3 (±2.1) per month (p = 0.022).	No differences between groups. Abdominal pain mean less than 1.5 on a 1-10 scale. No deaths. Secondary outcome was quality of life(Faecal Incontinence Quality of Life Scale FIQLS).	Authors acknowledge small sample but argue a clinically beneficial effect and favourable safety and tolerability profile. Sample size analysis: 17 per group with a total of 34.
Sharma et al. 2018 (226)	N=16 controls and N= 44 women with urge dominant FI. Controls mean age = 34 years, FI patient mean age = 57 years. FI patients had urge-predominant FI for > 1 year. Exclusion criteria: current or prior organic colonic or anorectal diseases, severe diarrhoea during run in phase, clinically significant cardiovascular or pulmonary disease or EKG abnormalities, symptomatic hypotension, or systolic blood pressure of <100 mm Hg at screening visit, neurological disorders, use of opiate analgesics, and pregnancy or nursing.	Two part study (RCT in Part 2). Part 1: Baseline in controls and FI patients: rectal distensibility and sensation were evaluated by barostat and sinusoidal oscillation. After randomization to IV saline or atropine, these parameters were evaluated again in controls and FI patients Part 2: Randomized double blind placebo controlled trial. FI patients randomized to oral placebo or clonidine for 4 weeks, rectal compliance and sensation re-evaluated. Clonidine treatment stratified by age and BMI. Study personal blind to assignment in each phase until database unlocked.	Baseline, rectal capacity lower mean pressure and elastance greater in FI participants, signifying reduced distensibility, Compared to placebo, atropine increased the heart rate in controls and FI and reduced the variability in rectal pressures during sinusoidal oscillation in controls. Clonidine significantly increased rectal compliance and reduced rectal capacity in FI patients. Atropine and clonidine effects on compliance, capacity pressures during sinusoidal oscillation, pressure and volume sensory thresholds were correlated.	Reported that neither atropine nor clonidine altered rectal elastance or hysteresivity (lag/return to original state) in controls and FI patients.	Controls were younger and with lower BMI than those participants with FI. A subset of FI patients have reduced rectal distensibility and increased rectal sensation which are reversible in some patients. Larger studies are needed to confirm the effect of clinical on urge dominant FI in women, and to confirm potential findings of reversible rectal features in some individuals.

Citation	Sample	Study Design	Major Findings	Adverse Events	Comments
Larsen et al. 2019 (227)	60 patients with chronic bowel symptoms after treatment for colon or pelvic organ cancer referred to the department of gastroenterology over a 2 year period.	Prospective cohort study	Median time from cancer treatment was 5.5 years (range 1-36 years). Symptoms included frequent bowel movements (65%), loose stools (87%), urgency for defaecation (57%), and FI (50%). Specific cause of bowel dysfunction found in 48 (80%) with 21 (35%) having more than one cause. Treatments included bile acid sequestrants (n =36), antibiotics (n= 33), loperamide (n =21), and dietary intervention (n= 20). Major improvement in bowel symptoms was reported by 23 (38%) patients, 27 (45%) reported some improvement.	Not reported	Heterogenous sample that received a variety of treatments based on identified cause of symptoms. No recommendations can be derived other than authors conclusion such patients may benefit from clinical evaluation and targeted treatment.
Bharucha et al. 2014 (213)	Double-blind, randomised, placebo-controlled, parallel-group study 44 women (age 18-75 years) with urge- predominant FI of 1 year or longer duration.	After a 4 week baseline (no drug) period, patients with ≥ 4 FI episodes in 4 weeks were randomly assigned to clonidine (0.1 mg bid) or placebo. Symptoms, anal pressures, rectal compliance and sensation were assessed before and after therapy. Anal sphincter injury was evaluated by endoanal magnetic resonance imaging.	Differences in FI and anorectal functions between treatment groups were not significant. However, clonidine reduced the proportion of loose stools in patients with diarrhoea and also reduced (p=0.08) the proportion of days with FI in patients with diarrhoea.	Adverse events were more common for clonidine (19 patients) than placebo (7 patients).	Of individual side effects, dry mouth was more common after clonidine than placebo.
Bharucha et al. 2010 (214)	12 women with urge-predominant FI and mixture of sphincter integrity. Outcomes: diary data, FI symptom severity score, FIQL, anorectal physiology	Open label, uncontrolled study of 4 weeks clonidine via patch (0.2mg/day)	Clonidine reduced stool frequency and proportion of patients with >50% reduction of FI episodes (9 of 12, 75%) and FI days (8 of 12, 67%). No significant changes in manometry measurements or rectal capacitance with clonidine	6 (50%) had adverse effects. 5 (42%) had skin reaction, 3 (25%) fatigue, 2 (16%) postural hypotension and 2 (16%) dry mouth.	Unclear whether effects most marked in those with baseline looser stool
Remes-Troche et al. 2008 (210)	21 patients with FI treated with cholestyramine plus biofeedback and matched cohort of 21 with FI who underwent biofeedback alone	Prospectively collected data. Median cholestyramine dose was 4 gm/d	Improved stool frequency and consistency and FI in group taking cholestyramine + biofeedback, but not biofeedback only.	Side effects in 7 (33%), constipation 4 (19%), bloating (9%) and headache 1 (5%).	Poor palatability Side effects improved with dose reduction.

Citation	Sample	Study Design	Major Findings	Adverse Events	Comments
Santoro et al. 2000 (215)	18 patients and 24 controls (latter for anal physiology measurements)	Open study of 20 mg amitriptyline for 4 weeks	FI scores reduced from median 16 (maximum 18) pre-treatment to 3. Treatment reduced amplitude and frequency of rectal contractions and improved sphincter pressure.	Dry mouth or drowsiness in 4 patients (22%) Nil withdrew	Effects suggested to be mediated by anti-muscarinic slowing of transit, and improved anorectal coordination

FI refers to FI; QOL refers to quality of life; tsp means teaspoon

Summary of Evidence for Medication Treatment of FI

- Loperimide may be helpful in women with FI and normal stool consistency, but is not superior to education and anal manometry biofeedback. Women who have more severe FI and are obese may have better outcomes (Level of Evidence 1).
- Loperamide is useful for diarrhoea-associated FI (Level of Evidence 2).
- loperamide may be superior to diphenoxylate (Level of Evidence 2).
- Use of loperamide can be similarly effective to supplementation with psyllium fibre in reducing FI (Level of Evidence 1).
- Combining loperamide with biofeedback or a standard educational pamphlet results in negligible improvement over individual therapies (Level of Evidence 1).

Recommendations for Clinical Practice Related to Medication Treatment

- Administer loperamide to women with FI and normal stool consistency. Women should be advised of the potential for constipation (Grade of Recommendation B).
- Loperamide is useful for reducing non-infectious diarrhoea-associated FI (Grade of Recommendation B).
- Loperamide, supplementation with psyllium fibre, biofeedback therapy, or education about FI may be tried for reducing FI (Grade of Evidence B).

Recommendations for Research on Medications for FI

- There is a need for further research on preparations, doses and combination therapies including medications versus single treatments for FI in various patient groups
- Larger trials are needed to confirm and evaluate the efficacy of clonidine in treatment of women with urge dominant FI. Such studies need to carefully report any adverse effects.
- FI data on eluxadoline, an opioid agonist with low bioavailability, needs to be published in studies along with other symptoms of irritable bowel syndrome with diarrhoea.

V. INTERVENTIONS FOR FI IN NEUROLOGICAL DISEASES

1. INTRODUCTION

In neurological diseases, bowel dysfunction is common. This is true in major neurological diseases including degenerative neurologic diseases e.g., Parkinson's disease (PD) and multiple system atrophy (MSA), and diseases affecting the spinal cord, i.e., spinal cord injury (SCI) and multiple sclerosis (MS). There are various approaches prevent and manage constipation, impaction and overflow FI including position during defaecation, abdominal massage, rectal evacuation, and bowel management.

2. POSITION AND MASSAGE

2.1. Defaecation Position

A position in which the knees are elevated to form a 60-degree angle with the trunk or the trunk is bent forward on the toilet or commode is typically recommended to promote defaecation in patients with bowel dysfunction due to neurological disease. There are no randomized, double-blind control studies (RCT) about the effectiveness of defaecation posture. However, studies using objective measures clearly showed that "Eastern" knee-up posture and a resulting widened recto-anal angle lessened the necessary abdominal strain and led to easier defaecation ($p<.05$), which seemed to be more physiological (228-231). This finding is reported in both normal volunteers and patients with idiopathic constipation. Adopting this position is a simple strategy without any reported adverse events. As compared with usual horizontal sitting, the recommended position decreases basal abdominal pressure ($p<.01$), lowers abdominal pressure on defaecation, and enlarges the recto-anal angle ($p<.01$), all of which promote easier defaecation. This effect might be brought about by mechanical release of the tightened recto-anal angle. A recent study by Tashiro (232) showed almost the same results.

2.2. Abdominal Massage

Manual abdominal massage is traditionally performed to facilitate bowel movement. Abdominal massage can be done by patients (at home, daily) or by a nurse (at a clinic or a hospital, not daily). Most studies employed the similar methods. For example, a recent RCT study by Okuyan (233), employed the following method of massage steps:

- When the older adult was in the supine position, a thin cushion was placed beneath the knees to loosen the abdomen and provide slight flexion in the legs
- Participants were told to breathe normally and relax the abdomen as much as possible.
- The abdominal region was then massaged for about 15 min.
- Then massage was applied in the direction of the colon in order to increase the contractions in the intestines by the deep effleurage method.
- With the kneading method, massages with palms and fingers were applied with upward pressure on the ascending colon and downward pressure on the descending colon.
- Later, the massage was continued by vibration (vibration) method in order to stimulate the nervous system and to relax the muscles. This procedure was performed as the 8-week program.

There are 13 RCTs about abdominal massage showing its effectiveness (234-237). There are also studies using objective measures showing that abdominal massage elicits spontaneous rectal contraction (peristalsis) with sensation and following defaecation (238-240). These effects might be brought about by a somato-autonomic reflex as observed in experimental settings (240-242). This somato-autonomic reflex is reported in patients with idiopathic constipation, in older adults, post-colectomy, HTLV1-associated myelopathy/spastic tropical paraparesis, stroke, spinal cord injury, and post-orthopaedic surgery population. Abdominal massage is simple without any reported adverse events.

3. RECTAL EVACUATION

3.1. Transanal enemata

Transanal enemata comprise an injection of fluid into the lower bowel by way of the rectum. The most frequent uses are to relieve constipation and for bowel cleansing before a medical examination or procedure. There are two RCTs showing the effectiveness of transanal enemata ($p<.05$) (243, 244). In one a docusate/sorbitol enema and usual (not specified) enema were superior to oral laxative macrogol (polyethylene glycol, PEG) 3350 ($p<.05$) in children with constipation (244). This result might be brought about by extending the rectal wall and stimulating sensory afferent fibers. Using a transanal enema is a simple intervention without any reported adverse events.

3.2. Trans-anal suppositories

Rectal suppositories are used into the rectum. The "torpedo" shape helps the device to travel internally, increasing its efficacy. There are five RCTs showing the effectiveness of transanal suppositories using sodium bicarbonate ($p<.05$) (245, 246). The effect might be brought about by extending the rectal wall and stimulating sensory afferent fibres which seems to be physiological. Use of trans-anal suppositories is simple and without any reported adverse events.

3.3. Retrograde continence enema (RCE) (also called transanal rectal irrigation (TAI))

A retrograde continence enema (RCE) (also called transanal rectal irrigation (TAI)) provides a large amount of water into the colono-rectal lumen from the anus, which leads to stool softening, distension of the rectal wall, and stimulation of sensory afferent fibres, promoting evacuation of rectal contents. Time is needed to achieve defaecation. RCE/TAI has been studied in adults and children with idiopathic constipation, spinal cord lesion, and spinal bifida; however, there are no RCTs investigating effectiveness. Recent large-scale systematic reviews concluded RCE/TAI as being useful without reported major adverse events (247, 248). In addition, studies using objective measures showed that RCE/TAI hastened colonic transit time (CTT) by scintigraphy, lessened rectal diameter by ultrasound, and brought about easier defaecation ($p<.05$) (248, 249).

3.4. Malone antegrade colonic (continence) enema with appendicostomy surgery (MACE)

Similar to RCE/TAI, Malone antegrade colonic (continence) enema ith (MACE) provides a large amount of water into the intestinal lumen through the ostomy opening in the colon (appendicostomy surgery is needed) but in an antegrade or forward manner, which leads to stool softening, distension of the rectal wall and stimulation of sensory afferent fibres. There is one RCT and one meta analysis/systematic review about MACE showing its effectiveness ($p<.05$) (250, 251). Two studies, using objective measures, also showed that MACE hastened colonic transit time (CTT) by scintigraphy or marker CTT test ($p<.05$) (248, 252).However, MACE needs surgery (appendicostomy), which raised caution particularly in children in some reports (253).

4. LAXATIVES, STOOL SOFTENERS, AND PROKINETIC SUBSTANCES AND DRUGS

The term laxative originates from Middle French laxatif, which itself originates from Latin laxātīvus (literally "relaxing, loosening"), possibly expressing medicines that ameliorate painful abdominal evacuation (relaxation) and hard stools (loosening). In a modern meaning, a laxative has various physiological effects that can be divided into stool softener (mainly by water-adding, which concurrently bulking stools. Softening and bulking also accelerate colonic transit time mildly) and prokinetics (directly promoting colonic transit time mainly by acting on myenteric plexus nerves, formerly called 'stimulating laxatives').

4.1. Stool softeners/ bulking agents

4.1.1. Magnesium oxide

Magnesium oxide is the oxide salt of magnesium with antacid, laxative and vascular smooth muscle relaxant activities. Magnesium combines with water to form magnesium hydroxide which reacts chemically to neutralize or buffer existing quantities of stomach acid; stomach-content and intra-oesophageal pH rise, resulting in a decrease in pepsin activity. This agent's laxative effect is the result, in part, of osmotically mediated water retention (osmotic laxative), which subsequently stimulates peristalsis presumably by distending the rectal wall and stimulating sensory afferent fibres, also with stool softening, that seem to be physiological. Magnesium ions may behave as calcium antagonists in vascular smooth muscle (relaxant), although this effect is not observed clinically. There is one RCT with favourable effects for the use of magnesium oxide. [32] This drug has few reported adverse events, but particularly in older patients, magnesium overdose/intoxication may occur; therefore, it is recommended to measure serum magnesium levels regularly if prescribing a larger dose of a drug than the Drug Formulary. In general, magnesium oxide is recommended for slow-transit and anorectal constipation with secondary overflow FI in patients with various neurological diseases. Magnesium is relatively inexpensive.

4.1.2. Macrogol (polyethylene glycol, PEG) 3350

Macrogol is an osmotically acting inert substance that passes through the gut without being absorbed into the body (254). It relieves constipation because it causes water to be retained in the bowel instead of being absorbed into the body. This agent subsequently stimulates peristalsis presumably by distension of the rectal wall and stimulation of sensory afferent fibres, also with stool softening. There is one RCT and four meta-analyses/ network analysis showing favourable effects for the use of macrogol (polyethylene glycol, PEG) 3350 (255-259). A study using objective measures also showed that macrogol hastened colonic transit time (CTT) by scintigraphy or marker CTT test (p<.05) (256). This drug has few reported adverse events. It is recommended for slow-transit and anorectal constipation with secondary overflow FI in patients with various neurologic diseases. PEG 3350 is relatively inexpensive.

4.1.3. Bisacodyl

Bisacodyl is a contact laxative; it increases fluid and salt secretion. Bisacodyl works by stimulating enteric nerves to cause peristalsis,. The action of bisacodyl on the small intestine is negligible; stimulant laxatives mainly promote evacuation of the colon. This agent subsequently stimulates peristalsis presumably by extending rectal wall and stimulating sensory afferent fibers, also with stool softening. There are three meta-analyses/ network analysis showing favourable effects of bisacodyl (257, 259, 260). Two studies using objective measures also showed that bisacodyl hastened colonic transit time (CTT) by a marker CTT test (p<.05) (261, 262). This drug has few reported adverse events.

4.1.4. Elobixibat

Elobixibat is an inhibitor of the ileal bile acid transporter (IBAT), undergoing development in clinical trials for the treatment of chronic constipation and constipation predominant irritable bowel syndrome (IBS-C). IBAT is the bile acid:sodium symporter responsible for the reuptake of bile acids in the ileum which is the initial step in the enterohepatic circulation. By inhibiting the uptake of bile acids, elobixibat increases the bile acid concentration in the gut, which accelerates intestinal passage and softens the stool. There are two meta-analyses/ network analysis showing favorable effects for the use of elobixibat (259, 260). This drug has few reported adverse events. Elobixibat is recommended for slow-transit and anorectal constipation with secondary overflow FI in patients with various neurological diseases.

4.1.5. Linaclotide

Like the endogenous guanylin and uroguanylin it mimics, linaclotide is an agonist that activates the cell surface receptor of guanylate cyclase 2C (GC-C) (263). This medication binds to the surface of the intestinal epithelial cells. Activation of GC-C increases cyclic guanosine monophosphate (cGMP), which further activates, through protein kinase 2, *cystic fibrosis* transmembrane conductance regulator (*CFTR*) facilitating water movement into the lumen softening stool. Linaclotide also inhibits activation of colonic *sensory* neurons and activating colonic motor function.

There are **3** meta-analyses/ network analyses supporting the use of linaclotide (257, 259, 260). Studies by objective measure also showed that it hastened colonic transit time (CTT) by a marker CTT test (p<.05) (264). This drug has few reported adverse events.

4.1.6. Plecanatide

Plecanatide works as a laxative by drawing water in to the gastrointestinal tract thereby softening stool and encouraging its natural passage. Similar to linaclotide, plecanatide activates guanylate cyclase-C on endothelial cells within the gastrointestinal tract. There is one meta-analysis/ network analysis supporting the use of plecanatide (259). This drug has few reported adverse events. Plecanatide is recommended for slow-transit and anorectal constipation with secondary overflow FI in patients with various neurologic diseases.

4.1.7. Lubiprostone

Lubiprostone is a bicyclic fatty acid derived from prostaglandin E1 that acts by specifically activating ClC-2 chloride channels on the apical aspect of gastrointestinal epithelial cells, producing a chloride-rich fluid secretion (265). There are one RCT and two meta-analyses/ network analyses which support the use of lubiprostone (257, 259). Studies using objective measures also showed that lubiprostone hastened colonic transit time (CTT) by a marker CTT test (p<.05) (266). This drug has few reported adverse events. Lubiprostone is recommended for slow-transit and anorectal constipation with secondary overflow FI in patients with various neurologic diseases.

4.1.8. Polycarbophil

Polycarbophil is a form of *surfactant* with amphiphilic properties. Polycarbophil is a bulk-forming laxative. Increased stool bulk helps to cause movement of the intestines. It also works by increasing the amount of water in the stool, making the stool softer and easier to pass. Calcium polycarbophil is not absorbed from the intes-

tine. There is one RCT showing favourable effects for the use of polycarbophil (267). Three studies using objective measures also showed that polycarbophil hastened colonic transit time (CTT) by a marker CTT test (p<.05) (268, 269). This drug has few reported adverse events. Polycarbophil is recommended for slow-transit and anorectal constipation with secondary overflow FI in patients with neurological diseases.

4.2. Prokinetics

4.2.1. Sodium picosulfate

Sodium picosulfate is a prodrug. It has no significant direct physiological effect on the intestine; however, it is metabolised by gut bacteria into the active compound 4,4'-dihydroxydiphenyl-(2-pyridiyl) methane (DPM, BPHM). This compound is a stimulant laxative for sensory afferent fibers and increases peristalsis in the gut. There are one RCT and three meta-analyses/network analyses supporting use of sodium picosulfate (255, 257, 259, 270). Use of sodium picosulfate is straightforward and without any reported adverse events.

4.2.2. Mosapride

Mosapride is a gastroprokinetic agent that acts as a selective 5HT4 agonist (271, 272). The major active metabolite of mosapride, known as M1, additionally acts as a 5HT3 antagonist, which accelerates gastric emptyingand is used for the treatment of gastritis, gastroesophageal reflux disease, functional dyspepsia and irritable bowel syndrome. In addition to its prokinetic properties, mosapride exerts anti-inflammatory effects on the gastrointestinal tract which may contribute to some of its therapeutic effects. By stimulating 5HT4 and 3 receptors in colonic wall, mosapride stimulates peristalsis (prokinetic effect). There is one RCT supporting the use of mosapride (273). Four studies using objective measures also showed that mosapride hastened colonic transit time (CTT) by a marker CTT test (p<.05) (274-276). Contraction of the longitudinal muscles in the colonic wall via acetylcholine (Ach) is controlled positively by serotonin (mainly 5-HT4) and negatively by dopamine (D2), vasoactive intestinal peptide (VIP) and nitric oxide (NO). This drug has few reported adverse events.

4.2.3. Prucalopride

Prucalopride, a first in class dihydro-benzofuran-carboxamide, is a selective, high affinity serotonin (5-HT4) receptor agonist with enterokinetic activities (also called as prokinetics) (263). Prucalopride alters colonic motility patterns also via selective serotonin 5-HT4 receptor stimulation: it stimulates colonic mass movements, which provide the main propulsive force for defaecation. There are 3 meta-analyses/ network analysis with favorable effects for the use of prucalopride (256, 257, 259, 260). A study using objective measures also showed that prucalopride hastened colonic transit time (CTT) by a marker CTT test (p<.05) (256). This drug has few reported adverse events. Prucalopride is recommended for slow-transit and anorectal constipation with secondary overflow FI in patients with various neurologic diseases.

4.2.4. Velusetra (investigational drug)

Velusetrag is a selective 5-HT4 receptor serotonin agonist, and is a drug candidate for the treatment of gastric neuromuscular disorders including gastroparesis, and lower gastrointestinal motility disorders including chronic idiopathic constipation and irritable bowel syndrome. It is still under investigation and not yet clinically available. There are two meta-analyses/ network analysis showing favourable effects for the use of velusetrag (259, 260), A study using objective measure also showed that velusetrag hastened colonic transit time (CTT) by a marker CTT test (p<.05) (277).

4.2.5. Nizatidine

Nizatidine is a histamine H2 receptor antagonist that inhibits stomach acid production, and is commonly used in the treatment of peptic ulcer disease and gastroesophageal reflux disease. Nizatidine *has also a cholinomimetic property, which acts as a* prokinetic drug. There is no RCT for the use of nizatidine. However, two studies using objective measures showed that nizatidine hastened gastric emptying (p<.05) by a 13C breath test and hastened colonic transit time (p<.05) leading to easier defaecation without serious adverse events (278, 279). Nizatidine can be an option for slow-transit and anorectal constipation with secondary overflow FI in patients with various neurological diseases.

5. DIETARY HERB EXTRACTS

5.1. Dai-Kenchu-To

Recently dietary herb extracts (herbal medicine) including Dai-Kenchu-To (DKT) have attracted attention because of their few adverse events (they are called 'time-tested'). A mixture of natural ingredients may have a role in reducing unwanted effects. This is particularly important to treat older adults with neurological disease. Dai-Kenchu-To is a combination of ginger, ginseng, and zanthoxylum (Sansho, Japanese pepper). Among these, an active component, hydroxy-beta-sanshool (in Sansho), mostly accounts for the lower-gastrointestinal tract contraction induced by DKT, which stimulates serotonergic 5HT3 receptors in the bowel. DKT has few reported adverse events.

There is one RCT supporting the use of DKT (280). Three studies using objective measures also showed that DKT statistically significantly hastened total colonic transit time (CTT) from 92 hours to 65.6 hours (upper normal limit, 39 hours) by a marker CTT test (p<.05) (281). A videomanometry study showed an increase in rectal contractions on defaecation after administration of DKT (p<.05) (281). DKT is recommended for slow-transit and anorectal constipation with secondary overflow FI in patients with various neurological diseases.

5.2. Rikkunshi-To

Rikkunshi-To (RKT) (also called Xiang-Sha-Liu-Jun-Zi tang (XSLJZT)**)** is a combination of eight natural materials: *Atractylodis lanceae, Poria cocos*, ginseng, *Pinellia ternata*, ginger, orange peel, *Ziziphus jujuba*, and glycyrrhiza. Among these, an active component, 10-gingerol (in ginger), mostly accounts for the gastrointestinal tract contraction induced by RKT. 10-gingerol inhibits the 5-HT2 (and 3) receptors in the myenteric plexus and induces ghrelin secretion. There is one RCT supporting the use of RKT (282), two studies using objective measures also showed that RKT hastened total colonic transit time (CTT) by a marker CTT test significantly (p<.05) (283, 284). RKT has few reported adverse events.

Summary of FI in Neurologic Diseases

- The knees-up position is recommended as the position for defaecation for anorectal constipation with secondary overflow FI in patients with various neurologic diseases if they can achieve this posture (Level of Evidence 3).
- Abdominal massage can be tried for slow transit and anorectal constipation with secondary overflow FI in patients with various neurological diseases (Level of Evidence 3).
- Transanal enemas are effective for rectal evacuation and managing anorectal constipation with secondary overflow FI in pa-

tients with various neurological diseases if patients themselves or their caregivers perform the manoeuvre (Level of Evidence 2).
- Transanal suppositories are effective for rectal evacuation and managing anorectal constipation with secondary overflow FI in patients with neurological diseases if patients or their caregivers can perform this intervention (Level of Evidence 1).
- Retrograde continence enema (RCE) (also called transanal irrigation (TAI)) is effective and managing anorectal constipation with secondary overflow FI in patients with neurological diseases if patients and /or their caregivers are able to do it (Level of Evidence 1).
- Malone antegrade colonic (continence) enema with appendicostomy surgery (MACE) is effective for managing severe slow-transit and anorectal constipation with secondary overflow FI that is resistant to other manoeuvres and drugs, and in patients with neurological disease (particularly spinal cord diseases, spinal bifida, and other diseases that cause severe bowel disorder) (Level of Evidence 1).
- The following stool softeners and bulking agents are effective in managing constipation in patients with neurogenic diseases; however, their effect on FI needs further clarification: magnesium oxide (Level of Evidence 2), macrogol (polyethylene glycol, peg) (Level of Evidence 1), bisacodyl (Level of Evidence 1), elobixibat (Level of Evidence 1), linaclotide (Level of Evidence 1), plecanatide (Level of Evidence 1), lubiprostone (Level of Evidence 1), and polycarbophil (Level of Evidence 2).
- velusetra (investigational drug) is potentially effective for constipation (Level of Evidence 4).

Recommendations for Practice Related to FI in Neurological Diseases
- Advise patients with anorectal constipation with secondary overflow FI to assume a knees up position during defaecation (Grade of Recommendation C).
- Abdominal massage should be suggested for slow transit and anorectal constipation with secondary overflow FI in patients if patients themselves or their caregivers can perform if (Grade of Recommendation C).
- Transanal enemas are recommended for rectal evacuation for anorectal constipation with secondary overflow FI if patients themselves or their caregivers are able to perform this manoeuvre (Grade of Recommendation B).
- Transanal suppositories are recommended to aid rectal evacuation in anorectal constipation with secondary overflow FI if patients or their caregivers are able to perform this manoeuvre (Grade of Recommendation A).
- Retrograde continence enema (RCE) (or transanal irrigation (TAI)) is recommended for anorectal constipation with secondary overflow FI if patients and/or their caregivers are able to do it (Grade of Recommendation B).
- The Malone antegrade colonic (continence) enema with appendicostomy surgery (MACE) is recommended only for severe slow-transit and anorectal constipation with secondary overflow FI that is resistant to other manoeuvres and drugs, and in patients with neurological diseases (particularly spinal cord disease, spinal bifida, and other diseases that cause severe bowel disorder) if patients and/or their caregivers are happy to use this procedure despite its high surgical burden (Grade of Recommendation A).
- Stool softeners and bulking agents should be considered to lessen FI in patients with neurological disease and mild slow-transit and anorectal constipation with secondary overflow FI (Grade of Recommendation C).
- Velusetra (investigational drug) may be tried when other medications fail (Grade of Recommendation C).

Recommendations for Future Research on FI in Neurological Diseases
- RCTs are needed to determine the effectiveness of the knees-up position for promoting defaecation in patients with neurological diseases.
- Because most medications have been studied for managing or preventing constipation, they need to be investigated for their effectiveness in managing or preventing FI as an outcome. Studies with RCT designs are recommended.

VI. SECONDARY INTERVENTIONS

1. BEHAVIOURAL THERAPIES: PELVIC FLOOR MUSCLE TRAINING, BIOFEEDBACK, AND ELECTRICAL STIMULATION

Pelvic floor muscle training (PFMT), biofeedback (BF), electrical stimulation of the anal mucosa (ES), and tibial nerve electrical stimulation (TNS) are secondary interventions for FI. Each is a distinctly different therapeutic technique for treating FI, and is described below. However, these three techniques are discussed together because many studies compare them to each other while other studies test combinations of these techniques (e.g., BF combined with ES) (Table 15-5).

1.1. Pelvic Floor Muscle Exercise Training

The patient is instructed to contract the pelvic floor muscles (usually maximally) including the external anal sphincter and puborectalis while keeping abdominal wall muscles relaxed and to do this multiple times each day with the goal of strengthening pelvic floor muscles. In a typical protocol the patient may be instructed to squeeze for 10 seconds while continuing to breathe deeply so that the abdominal wall muscles do not also contract. Ten to 20 such 10-sec squeezes are separated by 20 second periods of pelvic floor relaxation. Often patients are instructed to squeeze 10-20 times in a block and to repeat this block of exercises 3-5 times a day. The patient may be taught how to perform this exercise using only verbal or written instructions (285), or they may be given verbal feedback on their performance by the therapist during a digital rectal examination (286, 287). However, electronic or mechanical devices are not used to amplify the sensory information available to the patient to make them more aware of how well they are performing the exercises; this distinguishes PFMT alone from PFMT with BF.

1.2. Biofeedback

Biofeedback is distinguished from PFMT alone using electronic or mechanical devices to augment the intrinsic sensory information available to the patient on how well they are contracting and relaxing their pelvic floor muscles. The purpose of this type of training is to ensure that patients learn the appropriate way to selectively contract and relax the pelvic floor muscles while keeping abdominal wall muscles relaxed.

Another feature of many biofeedback training protocols is sensory training (rectal balloon training) or coordination training (288). Because of neurological injuries, many patients lose the ability to recognize sensations associated with the movement of stool into the rectum and may fail to contract the pelvic floor muscles to avoid stool leakage.

In sensory training, a balloon-tipped catheter is introduced into the rectum and distended with varying volumes of air or water to help the patient learn to recognize weaker distensions. Coordination training is a variant of sensory training and refers to having the patient practice contracting pelvic floor muscles in response to any sensation of rectal distention until this becomes a well-practiced habit (289).

A third type of BF training for FI (in addition to strength training and sensory training) is referred to as urgency resistance training (288). This is intended for patients who experience intense sensations of urgency to defecate prior to stool leakage. These sensations may be associated with prolonged smooth muscle contractions of the rectum leading to reflex inhibition of the external anal sphincter and puborectalis muscles and rectal evacuation (290). These smooth muscle contractions may be triggered by stress or anxiety (291), or by food ingestion (292). Urgency resistance training has the goal of desensitizing the patient to the sensation of rectal fullness or rectal contraction. This is accomplished byteaching the patient to use deep breathing or another relaxation technique to counteract anxiety and progressively inflating a balloon in the rectum to desensitize the patient to the sensation of rectal filling (293).

1.3. Electrical Stimulation

Electrical stimulation from probes placed in the anal canal as far up as the puborectalis muscle or from electrodes on the perineum adjacent to the anus has also been used to treat FI. In typical applications, stimulation is performed daily at home using a battery operated electrical pulse generator connected to the anal electrodes (287).

Different theories have been advanced to account for how this might facilitate continence (287). In the earliest applications, ES was used at intensities that triggered a contraction of the pelvic floor muscles, and patients were encouraged to try to augment the contractions produced by ES or to try to reproduce these contractions without electrical stimulation. Others have suggested that the stimulation of afferent nerves by lower intensities of ES may help by increasing the sprouting of synapses peripherally or the size of the receptive fields for these nerves in the brain (294). ES is sometimes combined with BF (295).

1.3.1. Tibial Nerve Stimulation

Tibial nerve stimulation is a form of ES in which surface electrode is placed on the skin over the tibial nerve on one ankle and referenced to another electrode on the ipsilateral foot (transcutaneous, TTNS) or a needle inserted beneath the skin close to the tibial nerve on one side and is referenced to an electrode on the ipsilateral foot (percutaneous, PTNS) (296). Typical TTNS stimulation parameters are 200 microsecond pulses at a frequency of 10 Hz and current of up to 30 mA. Typical PTNS stimulation parameters are 200 microsecond pulses at a frequency of 10-20 Hz and up to 9 mA. In the 6th ICI, Chapter 16, the Committee “Assessment and conservative management of FI and quality of life in adults” reviewed the evidence for tibial nerve stimulation available at that time and concluded: “Percutaneous tibial nerve stimulation remains an investigational treatment protocol which cannot currently be recommended for clinical practice”(1).

2. NEW EVIDENCE ABOUT PELVIC FLOOR MUSCLE TRAINING, BIOFEEDBACK, AND ELECTRICAL STIMULATION

PFMT Studies

In a RCT of 98 adults with FI Ussing *et al.* (297), provided support for a superior effect of supervised PFMT in combination with conservative treatment compared with attention-control massage treatment, which consisted of six 30 minutes sessions of massage of the neck and back over 16 weeks and conservative treatment. The primary outcome was rating of symptom changes, after 16 weeks, based on scores from the Patient Global Impression of Improvement scale.

Secondary outcomes were changes in the Vaizey incontinence score (Vaizey Score), Fecal Incontinence Severity Index, and Fecal Incontinence Quality of Life Scale.They found that participants who received supervised PFMT had 5-fold higher odds of reporting improvements in FI symptoms and had a larger mean reduction of incontinence severity based on the Vaizey score compared with attention control massage treatment.This RCT provides support for a superior effect of supervised PFMT in combination with conservative treatment compared with attention control massage treatment and conservative treatment.

Johannessen *et al.* (298), evaluated the effect of PFMT in 109 post-partum women with AI. They stratified women in a parallel two-armed RCT obstetric anal sphincter injury with primary sphincter repair and hospital affinity. The intervention group received 6 months of individual physiotherapy-led PFMT and the control group written information on PFMT. Primary outcome measures were changes in St. Mark’s scores and predictors of post-intervention AI. Secondary outcome measures were manometrymeasures of anal sphincter length and strength, endoanal ultrasound (EAUS) defect score and voluntary pelvic floor muscle contraction. There was a significant difference in the reduction of St. Mark’s scores from baseline to post-intervention in favour of the PFMT . No differences in secondary outcome measures were found between groups. The authors concluded that individually adapted PFMT reduces postpartum AI symptoms.

Biofeedback in combination with Surgery Compared to only Surgery

In an RCT including 27 women with a complaint of FI because of delivery trauma, Ghahramani *et al.* (299), evaluated the efficacy of biofeedback therapy in combination with surgery to manage FI. The patients underwent sphincteroplasty and levatorplasty via the same method by 2 colorectal surgeons. In Group I, BF was performed 3 months before and 6 months after the surgery; in Group II, BF was applied only 6 months after the surgery; and in Group III, only surgical management was performed.

The results revealed a significant difference between the preoperative and postoperative Wexner scores of incontinence in all the 3 groups. Additionally, the difference between the preoperative and postoperative scores was significant only in Group I and Group III, but not in Group II. The reduction in the Wexner score was significantly less in Group III. However, no significant difference was observed between the 3 groups concerning the mean difference of preoperative and postoperative manometry. The present study revealed no significant role for biofeedback therapy alone in the improvement of manometric evaluation. However, the Wexner score,

which is an indicator of patient satisfaction, increased with BF following sphincteroplasty.The conclusion was that currently there is no conclusive evidence for the effectiveness of BF in the treatment of FI in patients with significant sphincter defects.

Comparison of Different Biofeedback Regimes

In a RCT of 332 women and 18 men with FI Young *et al.* (300), compared the effectiveness of four different BF treatment regimes, stratifying the study population into two groups (metropolitan and rural) and then randomized into two subgroups (groups 1 and 2 within metropolitan, groups 3 and 4 within rural) with varying face-to-face and telephone BF components. All patients received standardized counselling and education, dietary modification and the use of anti-diarrhoeal medications. Group 1 received four monthly face-to-face BF treatments, groups 2 and 3 received one face-to-face BF followed by telephone BF and group 4 received a one-off face-to-face BF treatment. Primary outcomes were patient-assessed severity of FI and quality of life as assessed by the 36-item Short Form Health Survey and direct questioning of objectives. Secondary outcomes included St Mark's incontinence score, anxiety, depression and anorectal physiology measures (resting, squeeze pressures; isotonic, isometric fatigue times). All groups had significant improvements in FI, quality of life, incontinence score and mental status There were no differences in improvements in FI between groups although patient satisfaction was less with reduced face-to-face contact. There were modest improvements in isotonic and isometric fatigue times suggesting improved sphincter endurance. The authors concluded that BF is effective for FI. Although face-to-face and telephone BFis not necessary to improve FI, it is important for patient satisfaction.

Biofeedback Compared to Standard Conservative/ Medical Care

Jelovsek *et al*.(107), studied the effect of loperamide and anal muscle exercises with BF compared with oral placebo and an educational pamphlet in 300 randomly assigned women with FI. They also compared the effect of combination therapy to each individual therapy. Because oral placebo and education was compared with oral placebo and anorectal manometry-assisted BF, and loperamide plus education only, and loperamide plus anorectal manometry-assisted BF, the authors were able to compare BF with education (as a standard conservative care). At 24 weeks, there were no differences between loperamide versus oral placebo, BF versus education, loperamide and BF versus oral placebo, and BF versus loperamide plus education.

Some benefits were observed with combined treatments compared with individual treatments. Because these are common first-line treatments for FI, the authors suggested that clinicians could consider combining loperamide, anal manometry-assisted biofeedback, and a standard educational pamphlet, but this is likely to result in only negligible improvement over individual therapies and patients should be counselled regarding possible constipation.

Home Biofeedback Training

Xiang *et al.* (301), investigated if home biofeedback therapy (HBT) is non-inferior to office biofeedback therapy (OBT). Thirty patients with FI were randomized to HBT or OBT for 6 weeks. HBT was performed daily using a novel device that provided resistance training and electrical stimulation with voice-guided instructions. OBT consisted of six weekly sessions. Both methods involved anal strength, endurance, and coordination training. The study primary outcome was change in weekly FI episodes. FI improvement was assessed with stool diaries, validated instruments (FISI, FISS, and ICIQ-B), and anorectal manometry using intention-to-treat analysis.

Weekly FI episodes decreased significantly after HBT and OBT compared with baseline,. The authors concluded that HBT was non-inferior to OBT, based on significant results from the FISI and FISS scores, bowel pattern, bowel control, and quality of life (QOL) domains (ICIQ-B). Resting and maximum squeeze sphincter pressures significantly improved in both HBT and OBT groups and sustained squeeze pressure in HBT, without group differences. The authors suggest that home biofeedback is safe, effective, improves QOL, and through increased access could facilitate improved management of FI.

Electrical Stimulation

No new studies/RCTs related to ES were identified.

Table 15-5. New Evidence for the Efficacy of Biofeedback, Pelvic Floor Muscle Therapy, Electrical Stimulation, and Tibial Nerve Stimulation

First author, Year, Reference	Aims	Subjects	Study Design	Results	Comments
Sjodahl, 2014 (209)	Compare 3 conditions: EMG BF (median of 3 visits in 4-6 months); medical treatment only (1 mg loperamide 2 g fibre for 2 months); and combined BF and medical treatment	64 females aged 18+ with at least 1 episode FI in 2 weeks Excluded patients with any disease explanation for FI but allowed those with sphincter tears Analysis limited to 57 who completed study	Crossover design: Patients randomized to either BF or medical treatment in Phase 1; second treatment added in Phase 2 Anorectal manometry tested at baseline and after each treatment phase.	FI frequency did not differ between groups in Phase 1, but decreased significantly for both groups following combined treatment. Anal resting and squeeze pressures did not change significantly in either study phase.	Authors conclude that combined treatment was effective but neither BF nor medical treatment alone was effective. Study limitations: Number of BF sessions and loperamide dose are lower than most published studies. Study was not adequately powered.
Damon, 2014(302)	Compare BF to standard medical care	157 randomized but analysis was per protocol in 142 who did not drop out Trial duration was 4 months	Primary outcome was self-rating of improvement (-5 to 5). Secondary measures were diary, questionnaires, & manometry.	Significantly more BF patients met success criterion (defined as >3 on -5 to 5 scale) at 4 months.	This study supports the efficacy of home-based BF training. Limitations: data analysis in completers only (there were more drop-outs in the BF condition), and lack of long-term follow-up. A strength was that standard care followed French national guidelines and BF training protocol was developed by consensus of physical therapists.
Dehli, 2013 (303)	Compare biofeedback to dextranomer injection	126 adults with FI, minimum severity of 4 on St Mark's scale. Patients with any prior treatment for FI were excluded.	BF was performed 5 days/wk for 6 mo at home using a portable device. BF patients met with PT 5-6 times and 28/62 received supplemental ES. Anal injection of 4 ml bulking agent was repeated in 21/64 at 3 mo.	Primary assessment at 6 mo showed significant improvement in both groups but no between-group difference. Also, no difference at 24 mo. QOL also showed no between-group difference. More adverse events seen in anal injection group, but most could be prevented by antibiotic prophylaxis.	Well designed, adequately powered study showed nodifference between BF and dextranomer injection in moderately severe, treatment naïve patients. Study limitation: no minimum severity requirement for eligibility except St. Mark's score >3.

First author, Year, Reference	Aims	Subjects	Study Design	Results	Comments
Bartlett, 2015 (304)	(1) Assess accept-ability of home biofeedback (BF); (2) Compare clinic home BF to clinic-only BF	75 FI patients aged 18-80, average of 61 years	Unblinded, parallel group study of 6 wks duration All patients had 4 BF sessions in the clinic, but the home BF group practiced daily with a BF device while standard group practiced using PFMT instructions.	Supplementing BF with home practice had no overall effect but post hoc analysis found that patients younger than 61 yrs improved more when treated with home BF than with clinic-only BF; home BF was acceptable to most patients.	Daily home practice with a BF device improves FI and QOL more than standard BF with PFMT practice at home. Study limitations: Only 4 sessions of BF in clinic, which may be insufficient.
Peirce, 2013 (305)	Compare home BF to PFMT for prevention of FI in women with 3rd degree obstetric tears.	120 women with 3rd degree tears were randomized to begin EMG BF (n=30) or PFMT (n=90) prior to discharge.	All were assessed 3 months later. BF and PMTF were taught in hospital before discharge. Both groups were told to practice twice daily.	There were no between-group differences in Cleveland Clinic Continence Scores, QOL, anal canal resting or squeeze pressures.	This study shows no added value for home BF compared to PFMT. It is unclear whether either helps to prevent postpartum FI in women with obstetrical tears.
Cohen-Zubary, 2015 (306)	Compare daily electrical stimulation (ES) at home to weekly BF in the clinic on continence scores and cost.	Analysis limited to 18 in each group who completed the protocol. Eligibility required normal colonoscopy, normal ultrasound, no diabetes or other severe comorbidity.	BF was 6 weekly 30-45 min sessions for strength and sensory factors, supplemented by home PFE. ES was 25 min twice daily for 6 weeks with no clinic training.	No significant differences between groups. ES improved FI from baseline to end of treatment but BF did not. Costs were lower for ES than BF.	Authors argue that ES is at least as effective as BF, and it is less costly and more widely available.
Schwandner, 2011 (307)	Triple Therapy (3T) compared to low frequency ES	80 patients with FI of any severity including gas only	Two 20-min sessions per day for 6 months For 3T group, morning BF session included alternating between ES and voluntary Contraction. Afternoon session involved medium frequency ES triggered by voluntary contractions above a threshold determined by ability. Control group received low frequency ES in both sessions each day.	Cleveland Clinic scores improved more in 3T than in low frequency ES at 3 and 6 months QOL was also significantly better in 3T group. 54% of 3T group were continent at 6 mos. vs. none in the low frequency ES group. The attrition rate was low in this trial (8% in the 3T group vs. 15% in the low frequency ES group).	3T was superior to low frequency ES and was better tolerated. Limitation: Trial could not be blinded, and 6 mos. of twice daily practice may be more than most patients will tolerate.

First author, Year, Reference	Aims	Subjects	Study Design	Results	Comments
Schwandner, 2010 (308)	9 mos of twice daily ES combined with EMG BF (3T) compared to EMG BF only	158 patients from 8 sites were enrolled. Severity varied from loss of flatus only to solid or liquid stool loss.	For 3T protocol, see above. Control group received only EMG BF in morning and afternoon.	3T group improved significantly more than BF only group (8 points vs. 3 points) improvement on Cleveland Clinic scale from baseline to 9 months. More subjects dropped out in the BF only group. Significant differences between groups did not emerge until 6 mos. of twice daily therapy. Dropout rate was higher in BF only group.	Data show 3T is superior to EMG BF only, but the high burden of undergoing training twice daily for at least 6 mos. may be a limitation.
Leroi, 2012 (309)	Compare TTNS to sham ES	144 patients with FI >1/week and no response to conservative treatment were recruited from 9 centres in France.	Multisite RCT; Patients used battery operated stimulator twice daily at home for 3 mo. Electrodes were on calf and ankle in both active and sham groups. No current was used for sham group. Primary outcomes were frequency of FI and urgency/week. QOL and time to defer defaecation was also measured.	No significant differences between groups on any outcome. Active TTNS tended to show greater decreases in frequency of FI and urgency, but differences were not significant.	TTNS showed no evidence of efficacy in this large RCT.
George, 2013 (310)	Comparison of PTNS, TTNS, and sham TTMS in parallel groups	30 patients with >2/ week episodes of FI were randomly assigned to 3 groups.	RCT conducted at one centre. 12 treatment sessions scheduled 2/week for 6 weeks. Primary outcome was >50% reduction in FI frequency.	PTNS but not TTNS patients improved significantly more than sham group on number with >50% decrease in FI, number of FI episodes per week, and ability to defer defaecation. No differences in QOL or St Mark's scale.	Underpowered study which nevertheless suggests PTNS is superior to TTNS and sham.
Knowles, 2015 (311)	Comparison of PTNS to sham ES	Inclusion based on FI sufficiently severe to warrant intervention as recommended by PI at each of 17 sites and failure to respond to conservative treatment.227 women were randomized.	RCT comparing 12 sessions of PTNS to 12 sessions of sham (ES between 2 electrodes on one foot). Responder was defined by >50% decrease in FI frequency on diary.	Responder rates were no different (38% for PTNS, 31% for sham, N.S.). However, FI frequency decreased significantly more in PTNS group, especially in patients with urge-related FI.	This RCT fails to support the efficacy of PTNS, but the differences seen in secondary outcomes make it unclear whether PTNS may have a specific benefit for urge FI. Further research is needed.

First author, Year, Reference	Aims	Subjects	Study Design	Results	Comments
Thin, 2015 (312)	Pilot study aimed to estimate effect sizes for SNS vs. PTNS as well as acceptability of these treatments to patients	FI patients meeting NICE criteria for SNS and PTNS were randomized: 23 to SNS and 17 to PTNS (unbalanced to allow for failure of trial stimulation in 25%). Qualitative interviews were done in 5 patients from each group.	SNS and PTNS followed standard protocols. 15 30-min PTNS sessions over 5 months Assessed at baseline, 3, and 6 months after end of treatment Within group effect sizes were estimated but between-group differences were not tested.	19 patients underwent temporary SNS and 15 had permanent implants. 16 received all 15 PTNS sessions. At 6 months, ITT analysis showed 61% of SNS and 40% of PTNS patients had >50% reduction in FI. Significance of between group differences were not tested.	Both SNS and PTNS significantly improved FI. Effect sizes tended to be larger in SNS, but a definitive RCT comparing SNS to PTNS would require a sample size that is not feasible. Both treatments were acceptable to patients but some preferred one over the other.
Glazener, 2014 (313)	Assess 12 year FU of study comparing brief PFMT to standard care for UI and FI	747 women with UI 3 months after vaginal delivery. 15.7% also reported FI at study initiation.	Nurses taught PFMT in 3 home visits 5, 7, and 9 months after delivery. Controls received standard medical care. FU was at 1, 6, and 12 years.	FI rate was significantly lower after PFMT at 1 year (4% vs. 11%, p= .01), but not at 12 years (19% vs. 15%, p=.22). 52% were still using PFMT after 12 years.	Benefits of PFMT at 12 mos. were not evident 12 years later. Study limitations: 12-year follow up is of questionable relevance. FI increases with age, and in 12 years women may try other treatments.
Peirce, 2013 (305)	Compare home BF to PFMT for prevention of FI in women with 3rd degree obstetric tears	120 women with 3rd degree tears were randomized to begin EMG BF (n=30) or PFMT (n=90) prior to discharge.	All were assessed 3 months later. BF and PMTF were taught in hospital before discharge. Both groups were told to practice twice daily.	There were no between-group differences in Cleveland Clinic Continence Scores, QOL, anal canal resting or squeeze pressures.	This study shows no added value for home BF compared to PFMT. It is unclear whether either helps to prevent postpartum FI in women with obstetrical tears.
Lin, 2016 (314)	(1) Test whether FI improves with time following LARS for rectal cancer; (2) determine whether PFMT augments improvement	60 patients in Taiwan with rectal cancer were randomised to PFMT instructional DVD pamphlet or pamphlet alone.	PFMT taught just before hospital discharge. Weekly phone calls for first month in both groups. FU at 1, 3, 6, and 9 months	FI severity (CCI scale) decreased over time and was significantly less in PFMT group vs. controls at 1, 3, and 6 month FU. No difference at 9 months	Persuasive evidence that brief PFMT training plus a pamphlet and DVD accelerates improvement in FI following LARS procedure.
Laforest, 2012 (315)	Test whether BF improves functional outcomes more than PFMT following laparoscopic rectal resection for cancer	22 patients undergoing total mesorectal excision for rectal cancer was provided BF 3 mos. after surgery. Matched controls were selected from a registry.	Cohort study. BF group received 15 weekly sessions. PFMT group received one session of training. Assessed 8-46 mos. after surgery.	No differences in FI severity but BF group reported less dyschezia and greater improvement in QOL.	Authors conclude BF conferred a benefit in functional outcomes and QOL over PFMT alone. Study limitations: Cohort design does not match groups for time and attention. PFMT group may have had lower expectations because they were not study participants.

First author, Year, Reference	Aims	Subjects	Study Design	Results	Comments
Ghahramani 2016 (299)	Evaluation of the efficacy of BF in combination with surgery in the management of FI	27 women with FI because of delivery trauma	RCT. 3 groups via the permuted block randomization method. Group I, BF 3 months before and 6 months after surgery. Group II, BF only 6 months after surgery. Group III, only surgery (sphincteroplasty and levatorplasty) without BF	Significant difference between preoperative and postoperative FI Wexner scores in all groups. Sign. difference between preop and postop scores only in Group I and III, but not in Group II. No significant difference between groups in mean difference preop-postop. manometry	No significant role for BF alone in manometry improvement, but yes in Wexner (patient satisfaction). following sphincteroplasty. Important development!
Young 2017 (300)	Comparison of effectiveness of four different BF regimes	350 patients with FI (332 women, 18 men)	RCT: stratified into metropolitan and rural) then randomized into two subgroups (groups 1 and 2 within metropolitan, groups 3 and 4 within rural) with varying face-to-face and telephone BF components. All standardized counselling and education, dietary modification and anti-diarrhoeal medications. Primary outcome: 36-item Short Form Health Survey	All groups had significant improvements in FI, quality of life, incontinence score and mental status. No differences in improvements in FI between groups although patient satisfaction less with reduced face-to-face contact. Modest improvements in isotonic and isometric fatigue times suggesting improved sphincter endurance	BF effective for FI. Although face-to-face and telephone BF is not necessary to improve FI, it is important for patient satisfaction
Jelovsek 2019 (107)	Comparison of different combinations of anorectal manometry-assisted BF, loperamide, education, and oral placebo	300 women with FI at least 1x/month during last 3 months. (education n-42; placebo+BF n=84; lop+ed n=88; lop+BF n=86)	RCT: randomly assigned 0·5:1:1:1. BF six visits, including strength and sensory BF ; (placebo) lop 2 mg/day with option change). primary endpoint Vaizey score 0-24 weeks; intention-to-treat.	At 24 weeks, no differences between lop vs placebo (model estimated score change –1·5 points, 95% CI –3·4 to 0·4, p=0·12), BF vs ed (–0·7 points, –2·6 to 1·2, p=0·47), and lop and BF vs placebo and BF(–1·9 points, –4·1 to 0·3, p=0·092) or vs lop+ed (–1·1 points, –3·4 to 1·1, p=0·33)	Clinicians could consider combining lop, anal manometry assisted BF, and a standard educational pamphlet, but this is likely to result in only negligible improvement over individual therapies

First author, Year, Reference	Aims	Subjects	Study Design	Results	Comments
Xiang 2021 (301)	Investigation if home BF training (HBT) is non-inferior to office BF training (OBT)	30 (F/M = 26/4) FI patients (20 in HBT, 10 in OBT)	RCT: 6 weeks HBT daily using novel device that provided resistance training and ES with voice-guidedinstructions. OBT 6 weekly sessions. Both methods involved anal strength, endurance, and coordination training. Primary outcome change in weekly FI episodes	Weekly FI episodes decreased significantly after HBT (Δ ± 95% CI: 4.7 ly FI episodes decreased signifp = 0.003) and OBT (3.7 reased p = 0.0003). HBT non-inferior to OBT (p = 0.2). Resting and maximum squeeze sphincter pressures sign. improved in HBT and OBT and sustained squeeze pressure in HBT, without group differences	Home biofeedback is safe, effective, improves QOL, and through increased access could facilitate improved management of FI.
Ussing 2019 (297)	Investigation whether supervised PFMT in combination with conservative treatment is superior to attention-control massage treatment and conservative treatment in adults with FI (FI)	98 patients with FI (F/M 89/9)	RCT: Group I: supervised PFMT +BF + conservative treatment 6 sessions 45min each intensive PFMT. Group II: attention-control treatment + conservative treatment. 30 minutes of massage of neck and back. Participants no instructions in PFMT. Primary outcome was rating of symptom changes, after 16 weeks, based on scores from the Patient Global Impression of Improvement scale. Secondary outcome Vaizey score. Intention-to-treat.	PFMT group significantly improvement in FI symptoms based on Patient Global Impression of Improvement scale scores (unadjusted odds ratio, 5.16; 95% CI, 2.18–12.19; p=.0002). PFMT group larger reduction in the mean Vaizey Score (reduction, -1.83 points; 95% CI, –3.57 to –0.08; (p= .04). No significant differences in condition-specific quality of life.	Participants who received supervised PFMT had 5-fold higher odds of reporting improvements in FI symptoms and had a larger mean reduction of FI severity based on the Vaizey Score compared with attention control massage treatment

First author, Year, Reference	Aims	Subjects	Study Design	Results	Comments
Johannessen 2017 (298)	Evaluation effect of PFMT for postpartum AI	109 post-partum women	Parallel two-armed RCT stratified on obstetrical anal sphincter injury with primary sphincter repair and hospital affinity. Intervention group 6 months of individual physiotherapy-led PFMT and the control group written information on PFMT. Changes in St. Mark's scores and predictors of post-intervention AI were assessed by independent samples t-tests and multiple linear regression analyses, respectively. Study not blind.	Significant difference in reduction St. Mark's scores from baseline to post-intervention in favour of PFMT (2.1 versus 0.8 points, p = 0.04). No differences in secondary outcome measures between groups. Baseline St. Mark's, PFMT group affinity and EAUS defect score predicted post-intervention St. Mark's score in the imputed intention-to-treat analyses. Analysis on unimputed data showed that women performing weekly PFMT improved their AI scores > women in controls	PFMT was not commenced until patient able to perform correct voluntary pelvic floor muscle contraction (VPFMC) Individually adapted PFMT reduces postpartum AI symptoms
Horrocks 2015 (316) Similar RCT as Knowles et al. 2015 (311) (CONFIDeNT trial)	Comparison of PTNS to sham ES in patients with FI in whom initial conservative strategies have failed	Inclusion based on faecal incontinence sufficiently severe to warrant intervention as recommended by PI at each of 18 sites and failure to respond to conservative treatment. 227 women were Randomized, 115 PTNS; 112 sham PTNS	RCT comparing 12 sessions of PTNS with Urgent® PC device (Uroplasty Limited, Manchester, UK) to 12 sessions of sham (ES between2 electrodes on one foot). Responder was defined by >50% decrease in FI frequency on diary.	Responder rates were no different (38% for PTNS, 31% for sham, N.S.). However, FI frequency decreased significantly more in PTNS group, especially in patients with urge-related FI	This RCT fails to support the efficacy of PTNS, It would be difficult to recommend this therapy for the patient population studied. Further research will concentrate on particular subgroups of patients, for example those with pure urge FI

First author, Year, Reference	Aims	Subjects	Study Design	Results	Comments
Van der Wilt 2017 (317)	Comparison of PTNS to sham ES in patients with FI in whom initial conservative strategies have failed for at least 6 months. Failure to control FI with loperamide was not a specific criterion for inclusion	59 (F/M 51/8)patients > 18 years with FI to solid or liquid stool causing significant disruption to lifestyle.,	Multicentre, single-blinded RCT. PTNS n=29(24/5); sham 30(27/3). Urgent® PC. First 6 weeks, all patients underwent 30min 2x/week, and 30min 1x/week in 3 weeks thereafter. All patients 15 treatment sessions Primary endpoint reduction in median or mean number FI/week. Secondary endpoints FI severity, and disease-specific and generic QoL compared between PTNS and sham stimulation after 9 weeks treatment	> PTNS (13 of 29) than sham (6 of 30) group reduction ≥ 50 % median number FI//week (incidence rate ratio (IRR) 2·40, 95 per cent c.i. 1·10 to 5·24; P = 0·028), but not in mean number episodes/week (10 of 29 vs 8 of 30; IRR 1·42, 0·69 to 2·92; p =0·347). Absolute median number FI/ week decreased in PTNS but not in sham (IRR 0·66, mean number (IRR 0·65 (0·45 to 0·97); p = 0·034). 0·44 to 0·98; p = 0·041. Secondary outcomes pre-post sign. > in PTNS, not in sham.	PTNS may offer a small advantage in the clinical management of FI that is insufficiently responsive to conservative treatment. The key challenge will be to identify patients who may benefit most from this minimally invasive surgical procedure.

Systematic Reviews and Meta-Analyses

Table 15-6 lists the systematic reviews and guidelines documents published since January 2016 that address the use of BF, ES, and PFMT for the treatment of FI. The Cochrane review of Woodley *et al.* (318), reported hat it was uncertain whether PFMT reduced incontinence in the late postnatal period compared to usual care and that there was little evidence about PFMT effects on FI beyond 12 months' postpartum.

The review of Lal *et al.* (319), included 60 RCTs reporting on 4838 patients with mean ages ranging from 36.8 to 88 years. From the included RCTs, 32 did not identify a significant difference between the treatments compared. Contradictory results were identified in RCTs comparing BF-PFMT versus PFMT. Combination treatment of amplitude-modulated medium frequency stimulation and EMG-BF was noted to be superior to EMG-BF and low-frequency electrical stimulation alone.

Tibial Nerve Stimulation

In a double-blind RCT of 227 patients with FI in whom initial conservative strategies had failed Horrocks *et al.* (316), assessed the effectiveness of PTNS via the Urgent® PC device (Uroplasty Limited, Manchester, UK) for 30 minutes weekly for a duration of 12 treatments compared with sham ES. The primary outcome classified patients as responders or non-responders, with a responder defined as someone having achieved ≥e50% reduction in weekly FI episodes (FIEs). For the secondary outcomes, significantly greater decreases in weekly FIEs were observed in the PTNS arm than in the sham arm, comprising a reduction in urge FIEs rather than passive FIEs. No significant differences were found in the St Mark's Continence Score or any quality-of-life measures. No serious adverse events related to treatment were reported. The authors concluded that PTNS did not show significant clinical benefit over sham electrical stimulation in the treatment of FI based on number of patients who received at least a 50% reduction in weekly FIE. It would be difficult to recommend this therapy for the patient population studied.

Knowles *et al.* (311), reported on the same double-blind, multicentre, pragmatic, parallel-group, RCT of 277 adult patients in whom conservative treatments had not worked. Van der Wilt *et al.* (317), in an RCT assessed the effects of PTNS in 59 adult patients CT. The primary endpoint was reduction in the median or mean number of FI episodes per week. Secondary endpoints were changes in measures of FI severity, and disease-specific and generic quality of life. Outcomes were compared between PTNS and sham stimulation after 9 weeks of treatment. A higher proportion of patients in the PTNS (13 of 29) than in the sham (6 of 30) group showed a reduction of at least 50 per cent in the median number of FIEs/week but not in the mean number of episodes/week (10 of 29 vs 8 of 30). The absolute median number of FI episodes per week decreased in the PTNS but not in the sham

group. Scores on the Cleveland Clinic Florida FI scale decreased significantly in both groups, but more steeply in the PTNS group.

Van der Wilt *et al.*(317), concluded that PTNS may offer a small advantage in the clinical management of FI that is insufficiently responsive to conservative treatment and that the key challenge will be to identify patients who may benefit most from this minimally invasive procedure.

Table 15-6. New Systematic Reviews of the Efficacy of Biofeedback, PFMT, Electrical Stimulation, and Tibial Nerve Stimulation

First Author, Year, Reference	Aims/Scope	Analysis Sample	Conclusions Level of Evidence	Comments
Norton, 2012 (Update of Cochrane 2003) (320)	Determine effects of biofeedback (BF) and/or pelvic floor exercises (PFMT) in adults	1525 subjects in 21 studies	While there is a suggestion that some elements of BF and sphincter exercises may have a therapeutic effect, this is not certain. Larger well-designed trials are needed to enable safe conclusions.	Treatment protocols, outcome measures, and training of providers varied across trials. Risk of bias was judged to be low in 13/21 trials.
Rao, 2015 (321)	Define indications, training protocols, and efficacy of BF	731 patients (11% males) in 8 studies	BF is recommended for short-term & long-term treatment of FI; Level II recommendation; Grade B evidence.	Treatment protocols, outcome measures, and training of providers varied across trials. Risk of bias was not assessed.
Berghmans, 2015 (322)	Assess efficacy of BF alone or combined with PFE or ES	Not described 13 RCTs and Norton's Cochrane review are cited in the narrative summary.	BF PFE appears to be more effective than PFE alone, and BF ES appears to be more effective than ES alone. Level 3 evidence	
Vonthein, 2013 (295)	Assess efficacy of BF, ES, and/or BF ES	13 studies met criteria. Primary outcome was remission of FI.	BF was superior to all control groups but ES was not. BF ES was superior to BF alone or ES alone. BF ES is recommended as second line treatment for FI.	Only 3/13 trials met all quality criteria and 2/3 were by one of the authors, suggesting possible bias. 4 other studies rated as being of moderate quality. Type of ES was important: amplitude modulated medium frequency ES was superior to low frequency ES.
Rao S, Am College of Gastroenterology Practice Parameters Committee, 2004 (323)	Assess efficacy of BF for faecal Incontinence in adults Broader goals of review were evaluation of reliability of diagnosis and efficacy of treatment for all benign anorectal disorders	Not described	Pelvic floor rehabilitation with BF and PFE is superior to PFE alone in patients with faecal incontinence who do not respond to conservative measures.	
Visser, 2014 (324)	Assess efficacy of BF for FI secondary to low anterior resection for rectal cancer (LARS)	321 patients in 5 studies	Pelvic floor rehabilitation with BF and/or PFE improves functional outcomes after low anterior resection for cancer.	Quality of these studies was rated as low.
Horrocks, 2014 (296)	Assess efficacy of percutaneous and transcutaneous PTNS	375 patients in 12 studies, including 2 RCTs which had good quality Ratings Review predates large RCT of PTNS	TTNS was no better than sham in large RCT. However, in a second RCT comparing PTNS to TTNS and sham TTNS, PTNS was significantly more effective than TTNS, which was significantly more effective than sham ES.	RCT comparing PTNS to TTNS and sham was underpowered with 10 patients per arm.

First Author, Year, Reference	Aims/Scope	Analysis Sample	Conclusions Level of Evidence	Comments
Woodley 2017 (318)	Assess effectiveness of PFMT in the prevention or treatment of FI in pregnant or postnatal women	6 (quasi-)RCTs, one arm including PFMT, other arm no PFMT, usual antenatal or postnatal care, another control condition, or an alternative PFMT intervention ,	There are insufficient data on FI to state whether or not PFMT is effective to prevent or treat this problem in pregnant or postpartum women.	First, the lack of FI data was obvious. It is acknowledged that assessing the long-term effects of PFMT is challenging, as women may go on to have subsequent pregnancies,be offered a specific PFMT programme if they had taken part in the control arm of a trial or initiate their own PFMT
Lal 2019 (319)	Comparison of treatments for FI in adults	4838 patients in 60 RCTs	32 RCTs no significant difference between treatments compared. Contradictory results in RCTs comparing PTNS and TTNS vs sham stimulation, BF-PFMT vs PFMT, In two separate RCTs, combination treatment of amplitude-modulated medium frequency stimulation and EMG-BF, superior to EMG-BF and low-frequency ES alone. Combination of non-surgical treatments such as BF with sphincteroplasty sign.> continence scores compared to sphincteroplasty alone. Surgical treatments higher rates serious adverse events compared to non-surgical interventions	Current evidence no sign. differences between treatments for FI, and where differences identified, contradictory results between RCTs

Summary of Pelvic Floor Muscle Training, Biofeedback, and Electrical Stimulation

- Some studies support the hypothesis that biofeedback augmented by PFMT, when provided by an experienced therapist, is more effective than PFMT alone, but studies suggest that results may be dependent on the training and experience of the therapist (Level of Evidence 1).
- PFMT is possibly effective for the treatment of FI. Studies comparing PFMT alone to BF augmented by PFMT and ES have shown mixed results, and the optimal protocol for teaching PFMT has not been standardised, limiting the generalizability of findings (Level of Evidence 2). There is some evidence that BF may enhance the outcome of standard medical care (Level of Evidence 2).
- Home practice of BF and/or ES using battery-operated portable devices, appears to improve treatment outcomes when compared to clinic-based treatment. Younger patients may benefit more from home practice than older patients, and it may take up to 6 months to see benefits from home practice (Level of Evidence 2).
- Mixed results suggest that low frequency ES is weakly effective or ineffective when used alone, or in combination with BF. However, findings from a single group suggest that the Triple Therapy protocol involving electrical stimulation at a frequency of 3000 Hz combined with BF, when practiced twice daily for at least 6 months, may be more effective than biofeedback alone or low frequency (100 Hz) electrical stimulation alone (Level of Evidence 2).
- Despite mixed results and varying quality of studies, percutaneous electrical stimulation of the tibial nerve might be a possibly effective approach to the treatment of FI (Level of Evidence 2). There may be a small advantage in the treatment of FI when there is insufficient initial response to other conservative treatment (Level of Evidence 2).

Recommendations for Clinical Related to Pelvic Floor Muscle Training, Biofeedback, and Electrical Stimulation

- PFMT should be recommended as an early intervention in the treatment of FI as part of a conservative management bundle of interventions, based upon low cost, low morbidity, and at least weak evidence of efficacy (Grade of Recommendation B).
- Biofeedback, usually combined with PFMT and sensory training with a rectal balloon, is recommended as second line treatment for FI after other behavioural and conservative/medical management have failed to provide adequate symptom relief (Grade of Recommendation A).
- Biofeedback training may employ either pressure sensors or electromyographic (EMG) electrodes to provide feedback on pelvic floor muscle contractions. (Grade of Recommendation = C). Home biofeedback using portable battery-operated device may be recommended as an adjunct to biofeedback training in the clinic, especially for younger patients (Grade of Recommendation B).
- Based on currently available evidence it is not possible to recommended low frequency of (i.e., 100 Hz) electrical stimulation for FI. The Triple Therapy protocol for combining biofeedback with 3000 Hz electrical stimulation appears to be effective, but this recommendation is tentative pending confirmation of the findings by other research groups (Grade of Recommendation B).
- Percutaneous tibial nerve stimulation cannot currently be recommended for clinical practice (Grade of Recommendation B).

Recommendations for Research on Pelvic Floor Muscle Training, Biofeedback, and Electrical Stimulation

There is a need to conduct further RCTs to determine which specific biofeedback protocols alter physiological parameters of anorectal function with concomitant changes in bowel control. These studies should address:

- Clear description of modalities and evaluation of different components of BF
- Long term follow up
- Adherence monitoring
- Standardisation of outcome measures
- Exploration of possible synergies between urinary and FI interventions and diagnostic evaluations
- Standardisation of protocols for teaching PFMT are needed.
- Pelvic floor rehabilitation, as practiced by physical therapists for the treatment of FI, is not adequately described in the medical literature. Can this be standardized that it can be compared to biofeedback and to the PFMT protocols described in the literature?
- Compare the effectiveness of PFMT taught by verbal or printed instructions (as is commonly done) to PFMT taught during digital rectal examination.
- Standardise techniques for teaching PFMT via digital rectal examination.
- RCTs of the Triple Therapy protocol or other ways of combining electrical stimulation with biofeedback are needed.
- Investigate different modalities of ES, specifically distinguishing high frequency stimulation (e.g., 3000 Hz) from low frequency (e.g., 100 Hz) stimulation.
- Investigate ways to shorten the amount of training required to see benefits for FI.
- Percutaneous tibial nerve stimulation requires additional randomised controlled trials, specifically addressing:
  - Whether urgency associated FI is more responsive to treatment than passive FI and why this might be the case
  - Patient characteristics and physiological mechanisms associated with successful PTNS vs BF or PTNS vs ES or PTNS vs controls

VII. SPECIAL DIAGNOSIC TESTING FOR SECONARY AND TERTIARY MANAGEMENT OF FI

1. ANORECTAL FUNCTION TESTS (ANORECTAL MANOMETRY, THE RECTAL SENSORY TEST, AND THE BALLOON EXPULSION TEST)

1.1. Introduction

When the initial conservative management of FI fails to improve symptoms sufficiently, specialised diagnostic testing to assess the causes of FI and assist in stepwise selection of appropriate treatment is indicated (23, 325). Anorectal function tests (AFTs) (anorectal manometry [ARM], the rectal sensory test [RST] and the balloon expulsion test [BET]) are the most commonly used investigations for evaluation of anorectal function. ARM records mechanical activity of the distal rectum and anal canal through measurement of changes in intraluminal pressure, the RST evaluates parameters of perceived rectal filling though distension of the rectum, and the BET describes evacuation though measurement of ability to expel an intra-rectal balloon (326). Previously considered as tests performed and reported separately, recent consensus by the International Anorectal Physiology Working Group has recommended that these investigations are now considered as complementary and interpreted together to reflect the understanding that symptoms of incontinence and evacuatory difficulty are commonly generated secondary dysfunction of multiple parts of the anorectal unit (327).

1.2. Indications

Anorectal function tests are typically indicated during the assessment of patients with FI to facilitate the evaluation of rectoanal sensorimotor function, typically at the point of triage to advanced therapies. They are also indicated in the evaluation of patients with symptoms of constipation/evacuatory dysfunction (which co-exists in 41% of patients presenting with incontinence (328), during investigation of symptoms of functional anorectal pain, as part of preoperative assessment of anorectal function (where intervention may impact on the continence mechanism [e.g. sphincter repair, fistulectomy, rectopexy]) and in patients following an obstetric anal sphincter injury (327).

1.3. Test Specifications

1.3.1. Anorectal Manometry

Several ARM techniques exist. At the time of the 6th ICI, conventional ARM (reporting data from single points within the anal canal utilising catheters containing fewer than 6 sensors) prevailed (329). Although these systems are still available for use in clinical practice, the technology has advanced with the development of portable bedside systems (330, 331), and high-resolution / high-definition techniques. High-resolution anorectal manometry (HRAM) and High-definition anorectal manometry (HDAM) have the advantage of capturing data from the entire length of the anal canal and distal rectum using catheters containing between 12 to 256 sensors (332-334). These data are displayed in real time as colour contour plots which facilitate a more intuitive phenotypic interpretation. Emerging studies suggest high resolution measurements may offer diagnostic benefit over conventional ones (335, 336). Additionally, HDAM which allows 3D visualisation of pressure data, improves appreciation of functional sphincter morphology (337-340). Few data exist to suggest superiority of one catheter configuration over another, however it is generally accepted that studies should be performed with catheters that have a recording length of 6 cm and measure circumferential (as opposed to unidirectional) pressure (335).

ARM studies are typically performed in the left lateral position (even though recent evidence suggests that studies performed in the seated position may provide a more accurate description of recto-anal coordination (341, 342). A digital rectal examination prior to intubation not only excludes faecal loading, pain, and structural abnormalities; but also allows the clinician to check the patient's understanding of manoeuvre commands (push and squeeze). The catheter is then positioned so that the sensors span the length of the anal canal and distal rectum and a standard series of manoeuvres are performed which evaluate anorectal reflexes, anal tone and contractility and rectoanal coordination (see section 1.5 below) (327).

1.3.2. The Rectal Sensory Test

The RST is performed following anorectal manometry in the left lateral position and measures patient-reported sensory thresholds to ramp or phasic distension of a balloon with air (343). A commer-

cially available, latex-free balloon (often integrated within the ARM system) is placed within the rectum 3 - 5cm cm above the upper border of the anal canal. The balloon used should have a capacity of no less than 400mls and insufflation with air should be performed at a rate of between 1 - 5 mls per second.

1.3.3. The Balloon Expulsion Test

The BET measures the ability of a patient to evacuate a balloon from the rectum. Following the RST, a customised latex-free balloon mounted on a flexible catheter is placed inside the rectum and filled with 50mls of tepid water. The patient then sits on a commode and the time taken to expel the balloon is measured (344). Should local facilities exist, alternative investigations such as defaecation proctography / MR defaecography as an addition to the BET to describe evacuation in more detail.

1.4. Study Protocol

Recommendations for the performance of anorectal function tests were developed and published following consensus driven by the International Anorectal Physiology Working Group in 2019. This protocol outlines a standardised sequence of manoeuvres for all 3 AFTs and describes the suggested measurements to be reported. Of note, specific normal values were not recommended to the variability in equipment and patient population. Description of normality should be based on published data or local study of control subjects (327).

Recommended study protocol:

- *Stabilisation period:* After intubation, a 3-minute period of stabilisation is recommended to allow anal pressure to return to baseline. No measurements are reported during this manoeuvre.
- *Rest:* This evaluates anal tone and represents the composite pressure generated by the internal anal sphincter (which accounts for approximately 70% of the anal pressure during the relaxed state), external anal sphincter and the anal cushions [71] Measurements are taken while the patient is relaxed to avoid excessive contributory effects of the voluntarily controlled external anal sphincter. A 60-second period of rest is measured with quantitative measures and qualitative descriptors of anal tone reported.
- *Short squeeze:* This describes anal contraction strength which is predominantly generated by voluntary contraction of the external anal sphincter and puborectalis (345). Three short squeezes each of 5-second duration are performed. Following each short squeeze, a 30-second recovery period is allowed. The strongest manoeuvre is used for analysis and quantitative measures (the incremental increase in pressure over baseline rest) are reported.
- *Long squeeze:* This describes voluntary anal sphincter fatigability which is a commonly used as a target measurement in biofeedback (346, 347). A single 30-second squeeze is performed, followed by a 60-second recovery period. Quantitative measures of anal contractile fatiguability are recorded.
- *Cough:* This describes the reflex response of the anus to a sudden Valsalva manoeuvre (348). Two single coughs are performed, each separated by a 30-second recovery interval, with the best manoeuvre used for analysis. Quantitative and qualitative descriptions of both anal and rectal pressure are reported to describe the rectal pressure increase and reflex anal contractility.
- *Push:* This describes rectoanal coordination during simulated evacuation (349). Elevation of rectal pressure during Valsalva together with a reduction in anal pressure is considered a 'normal' rectoanal gradient, although paradoxical contraction or failure to relax the anal sphincter is frequently seen in healthy controls (350-352). Three pushes each of 15-second duration are performed, during which the patient is asked to bear down as if to evacuate. Following each push, a 30-second recovery period is observed, and the most phenotypically 'normal' manoeuvre is used for analysis. Quantitative measures of rectal pressure changes (propulsion) and anal pressure changes (if abnormal described as dyssynergia) are reported.
- *The rectoanal inhibitory reflex:* During this manoeuvre, rapid distension of the rectum is used to elicit reflex relaxation of the internal anal sphincter which manifests as a reduction of anal pressure (353). With the patient relaxed during recording of anal tone, the rectal balloon is quickly inflated and presence / absence of reflex reduction in anal pressure is qualitatively noted.
- *The rectal sensory test:* This measures consciously perceived sensory thresholds to progressive distension of an intrarectal balloon. Three measurements are described, the first constant sensation volume, the defaecatory desire volume and the maximum tolerated volume.
- *The balloon expulsion test:* This manoeuvre describes parameters of evacuation, also described as defaecation dynamics and is used to compliment the push manoeuvre during the description of recto-anal coordination. Agreement between these two tests is required before results are considered significant because a considerable number of healthy controls display abnormal patterns of rectoanal coordination by ARM (350). Quantitative features of evacuation are described.

1.5. AFT Measurements

The measurements used to describe outcomes of AFTs described in Table 1 (354). These measurements are used to describe physiological phenotypes described according to the London Classification in section 1.7 below.

1.6. The London Classification

The newly published London Classification is a diagnostic algorithm that uses the combined findings of AFTs to describe results from ARM, the RST and the BET. The classification is divided into four parts: I - disorder of the rectoanal inhibitory reflex; II - disorders of anal tone and contractility; III - disorders of rectoanal coordination and IV - disorders of rectal sensation (327). Within each part of the classification, findings are classified as major, minor, or inconclusive. Despite using newly introduced terminology, these diagnoses describe physiological phenotypes described in previously published literature. Each part of the classification is described below.

1.6.1. Disorder of the Rectoanal Inhibitory Reflex

Anorectal areflexia describes loss of the rectoanal inhibitory reflex. Classically, absence of this reflex is used as a screening tool for diagnosis of Hirschsprung's disease (355). Although anorectal areflexia is not classically associated with FI, studies have demonstrated alteration of the rectoanal inhibitory reflex morphology in patients with both idiopathic FI (356), and in patients with FI associated with neurological conditions such as scleroderma (357), and multiple sclerosis (358). Secondary anorectal areflexia (absence of the RAIR at low distension volumes) may be seen in patients with megarectum (359).

1.6.2. Disorders of Anal Tone and Contractility

Disorders of anal tone and contractility are commonly seen in patients with FI (328). Anal hypotonia is seen in approximately 10% of males and 20% of females with FI (360). It is particularly associated with symptoms of passive leakage (15), and is commonly associated with morphological abnormalities of the internal anal sphincter (361), and with rectal intussusception / prolapse (362,

363). Anal hypocontractility is typically associated with symptoms of faecal urgency (15) and may be associated with structural defects of the external sphincter (364, 365). In addition, endurance squeeze pressure (a measurement recommended to assist as an additional descriptor of sphincter fatiguability, though not utilised in the Classification) is significantly shortened in patients with incontinence (346), and is commonly used as a target for manometric biofeedback (118).

1.6.3. Disorders of Rectoanal Coordination

Although more commonly seen in patients presenting with primary symptoms of constipation, over 20% of patients with FI have functional abnormalities of evacuation (328). Recent studies have demonstrated that anorectal manometry alone is of limited accuracy for discriminating between symptomatic patients and healthy controls (350), the London Classification requires agreement between anorectal manometry and balloon expulsion for findings to be considered significant. In patients with overflow incontinence, disorders of evacuation commonly underlie their symptoms (323). Furthermore, interventions to improve emptying are commonly used to treat children and adults with incontinence secondary to incomplete evacuation (366, 367). As the London Classification is relatively contemporary, the incidence and particular importance of individual disorders of rectoanal coordination (abnormal evacuation with poor propulsion, abnormal evacuation with dyssynergia and abnormal evacuation with poor propulsion and dyssynergia) is yet to be described, however aspects of each could be considered as targets for interventions such as behavioural training with biofeedback.

1.6.4. Disorders of Rectal Sensation

Disorders of rectal sensation contribute to the development of FI. Rectal hypersensitivity is seen in 44% patients with faecal urgency (94), and may be associated with abnormal rectal compliance, not only in patients with idiopathic incontinence (94), but also in inflammatory bowel disease and fibrotic or inflammatory conditions affecting the rectal wall (e.g. post radiotherapy (368) (369). Rectal hypersensitivity can be successfully modulated with pharmacological therapies such as loperamide (370), sensory biofeedback (371), and neuromodulation (34). Rectal hyposensitivity is less commonly seen in FI, however it has been described in up to 18% of male patients with concurrent constipation (372).

New Evidence about Anorectal Function Tests

- Anorectal function tests (anorectal manometry, the rectal sensory test and the balloon expulsion test) should now be performed and interpreted as complimentary investigations
- The London Classification describes a standardized method and nomenclature for describing the results of these tests
- Emerging evidence suggests that novel metrics derived from high resolution anorectal manometry may improve diagnostic accuracy; however, these are yet to be incorporated into recommended measurement protocols

Summary of Anorectal Function Tests

- Anorectal function tests are indicated to facilitate the evaluation of rectoanal sensorimotor function prior to advanced tertiary level interventions and following an obstetric anal sphincter injury. There are several anorectal function tests available and results of three of the most common ones (anorectal manometry, the rectal sensory test and the balloon expulsion test) should be interpreted together (Level of Evidence C).
- The London Classification offers a guide for standardizing interpretation of anorectal function tests (Level of Evidence C).

Recommendations for Practice Related to Anorectal Function Tests

- Anorectal function tests should be performed as part of tertiary level diagnosis and management of FI (Grade of Recommendation C).
- Anorectal manometry should be performed and interpreted in conjunction with the rectal sensory test and the balloon expulsion test (Grade of Recommendation C).
- Use of the London Classification as a diagnostic algorithm is recommended when deciding to use anorectal function tests (Grade of Recommendation C).

Recommendations for Research on Anorectal Function Tests

- Further exploration of methods to improve accuracy of manometric measures for diagnosis of sphincter dysfunction and rectoanal coordination.
- Assess capability of anorectal function tests to predict outcomes of conservative, medical and surgical treatments for FI.
- Critical assessment of the utility of the London Classification protocol as a communication and decision making tool.

2. ENDOANAL ULTRASOUND IMAGING

Endoanal ultrasound (EAUS) is established as an important part of a colorectal diagnostic work-up (373), and is recommended as the gold standard investigation to identify anal sphincter injury by the International Urogynecological Association (IUGA) / International Continence Society (ICS) joint report (374). EAUS is usually performed with high multi-frequency (9-16 MHz), 360° rotational mechanical probe or radial electronic probe (frequency: 5-10 MHz) (373). High-resolution three-dimensional (3D) EAUS provides better visualisation performance by multiplanar reconstruction and rendering of the 3D data volume (373). With EAUS, the anal canal is divided into three levels of assessment. The upper level corresponds to the hyperechoic sling of the puborectalis muscle and the concentric hypoechoic ring of the internal anal sphincter (IAS). In males, the deep part of the external anal sphincter (EAS) is also identified at this level. The middle level corresponds to the superficial EAS (concentric band of mixed echogenicity), the conjoined longitudinal layer, the IAS, and the transverse perineal muscles. The lower level corresponds to the subcutaneous part of the EAS (375).

Alternative ultrasound modalities (transperineal/TPUS and endovaginal/EVUS) can be used for the investigation of sphincter integrity in FI (373, 376-382). Advantages of these procedures include wider, absence of distortion of the anal canal, better patient acceptability, and the possibility for functional studies and for the assessment of levator ani muscle injuries (373, 383).

2.1. Endoanal Ultrasonography in FI

EAUS is currently the gold standard for the morphological assessment of the anal canal in FI and is a simple, well-tolerated and inexpensive technique. Most studies reveal high accuracy in identifying sphincter defects. EAUS can differentiate between incontinent patients with intact anal sphincters and those with sphincter lesions (defects, scarring, thinning, thickening, and atrophy) due to vaginal delivery or anal surgery (e.g., haemorrhoidectomy, fistula surgery or sphincterotomy) (373, 374).

Tears are defined by an interruption of the circumferential fibrillar echo texture. Scarring is characterized by loss of normal architecture, with an area of amorphous texture that usually has low reflectivity. Number, circumferential (radial angle in degrees or in hours of the clock site) and longitudinal (proximal, distal or full length) extension of the defect should be reported.

3D EAUS is used and accepted for sphincter evaluation in FI, improving diagnostic accuracy and knowledge of physiological and pathological sphincter alterations. It allows measurement of length, thickness, and the area of sphincter defect in the sagittal and coronal planes in addition to the volume of sphincter damage (375). Two scoring systems have been proposed to define the severity of the sphincter damage (384, 385). Both systems have demonstrated good correlation between the extent of sphincter defect and the degree of FI. EAUS has an important role in detecting clinically occult anal sphincter injuries after vaginal delivery (386-388). FI related to occult sphincter lesions is likely to occur even in an elderly population of women who experienced vaginal deliveries earlier in life (late-onset FI) (389). US imaging is useful to evaluate the result of treatments (e.g., sphincteroplasty, bulking agents, injections) (390-392).

2.2. Endoanal Ultrasonography in Anorectal Surgery

Haemorrhoidectomy, fistulectomy or fistulotomy, anal dilatation, or internal lateral sphincterotomy can cause FI, due to anal sphincter injury. Clinical severity of FI after anorectal surgery is related to EAUS features. More frequently, in patients with higher clinical severity score the IAS is always affected and thicker (393). EAUS has been used to select the surgical treatment in patients with FI and to assess the clinical efficacy of the treatment. In a multicentre observational study on the implantation of prostheses in patients with FI, EAUS was used preoperatively to select cases (either intact sphincters or IAS lesions extending for less than 60° of the anal circumference), intraoperatively to perform the implants into the intersphincteric space and postoperatively to evaluate the results of surgery and complications (prostheses dislodgement) (394, 395).

3D-EAUS can quantify how much sphincter can be safely divided during fistulotomy. In a prospective, consecutive study, there was a strong correlation between preoperative 3D-EAUS measurements of fistula height with intraoperative and postoperative 3D-EAUS measurements of IAS and EAS division. Fistulotomy limited to the lower two thirds of the EAS is associated with excellent continence and cure rates (396).

2.3. Endoanal Ultrasound and Obstetric Anal Sphincter Injury (OASI)

Obstetric anal sphincter injury (OASI) is a term used to define trauma to the perineum during vaginal childbirth that includes third- (injury to perineum involving the anal sphincter complex – EAS and IAS) and fourth-degree (injury to perineum involving the anal sphincter complex and anal epithelium) tears. Within 2 months of delivery, the incidence of any degree of anal sphincter defect in primiparous women is reported to be as high as 27% -35% using EAUS. Between 4% -8.5% of multiparous women have a new sphincter defect (397). When women sustain an OASI, they are at increased risk of developing FI either immediately following childbirth or later in life. The true prevalence of FI related to OASI may be underestimated. The reported rates of FI following the primary repair of OASI range between 15% and 61%, with a mean of 39% (397). There is some evidence to suggest that EAUS performed after vaginal birth and before the tear has been repaired could lead to improved primary repair of the IAS and EAS resulting in reduced rates of FI and improved quality of life for women. One randomised trial of 752 primiparous women compared clinical examination (routine care) to the use of EAUS prior to perineal repair. EAUS was associated with a reduction in the rate of severe FI at greater than six months postpartum (risk ratio RR 0.48) (398). More high quality randomised controlled trials are needed before the routine use of EAUS on the labour ward can be supported. Cost and training required to implement EAUS requires consideration.

Data are controversial for asymptomatic patients. There are no cost-benefit studies of EAUS in this setting, nor any data on whether asymptomatic patients could benefit from it. Currently, there is no recommendation about screening women later after vaginal delivery for occult sphincter defects. EAUS may have a role after perineal repair in the evaluation of residual injury and in the management of subsequent pregnancies (399). There are no systematic reviews or randomised controlled trials to suggest the best method of follow-up after OASI.

Studies show a high frequency of endosonographic sphincter defects after primary repairs in between 54% -93% of women (400, 401). These data emphasize the importance of adequate repair of OASI and demonstrates that repair can be difficult or underestimated. The current guidelines of the United Kingdom Royal College of Obstetricians and Gynecologists (RCOG) do not make recommendations about using EAUS for confirming a complete primary repair (RCOG Guideline, 2007). According to this guideline, if a woman experiences FI at follow-up after repair, referral for EAUS should be considered. A persistent ultrasound-detected defect in the anal sphincter muscles after OASI is associated with FI (402). Reconstruction of the entire length of the EAS is crucial. Incontinence after primary repair of OASI is related to relative length of reconstructed EAS and to the extent of the ultrasonographic defects demonstrated by 3D-EAUS (403). In a prospective study assessing long term function and morphology of the anal sphincters and the pelvic floor after primary repair of OASI, women who experienced deterioration of continence over time following repair had a significantly shorter anterior EAS at 3D-EAUS. EAS length correlated with increased severity of FI (404).

A decision about the mode of delivery of pregnancy after OASI based on symptoms, anal manometry, and EAUS helps in preserving anal sphincter function and avoiding unnecessary Caesarean sections (405). In a descriptive study on a cohort of women who had OASI from 2006 to 2013, vaginal delivery was recommended to asymptomatic women with normal investigations (EAUS and anal manometry) and elective Caesarean section was recommended for women with faecal symptoms, anal sphincter defects of more than 30° or low resting or incremental anal pressures. Caesarean section was done in 22 women and 28 women delivered vaginally. Worsening of FI symptoms and reduction in anal pressures were not observed in either the planned vaginal delivery or elective Caesarean section groups. There were no new sphincter defects or recurrent OASI in any of the women in the study group.

EAUS can be useful to select patients that could benefit from rehabilitation. Therapy may be less effective in patients with sphincter lesions, and there is a linear relationship between post-rehabilitative scores of FI severity and severity of sphincter defects (406).

Currently, there is no evidence to support the use of real time elastography in the diagnostic workup of FI. There was an absence of a correlation in elastogram colour distributions of the IAS and EAS with major clinical and functional parameters (407).

2.4. Alternative Ultrasound Modalities (Transperineal and Endovaginal) in FI

Transperineal and endovaginal ultrasound have been evaluated as alternatives to EAUS for the investigation of sphincter integrity in FI (373, 376-379). Advantages of these procedures include the availability of commonly used transducers, absence of distortion of the anal canal, better patient acceptability and possibility for functional studies (380). Two-dimensional transperineal US (2D-TPUS) is performed with conventional convex transducers (main frequency between 3 and 6 MHz, field of view at least 70°) applied in the perineum between the mons pubis and the anal margin (373). Perineal ultrasound provides an overall assessment of all anatomical structures in the midsagittal plane (bladder, urethra, vaginal walls, anal canal and rectum) between the posterior surface of the symphysis pubis (SP) and the posterior part of the levator ani (LA). Imaging is usually performed at rest, on maximal Valsalva manoeuvre and on pelvic floor muscle contraction (dynamic assessment). Three/four dimensional (3D/4D) TPUS are performed with volumetric probes. The most important clinical application of 3D-TPUS is the assessment of LA injuries (408). The disconnection of the muscle from its insertion on the inferior pubic ramus and the pelvic sidewall, a consequence of overstretching during the second stage of labour, is defined as LA avulsion (409, 410).

Three-dimensional endovaginal US (3D-EVUS) is performed with a multi-frequency (9-16 MHz), 360° rotational mechanical probe. The pelvic floor is divided into four levels of assessment (411). At level I, the bladder base and the inferior third of the rectum are visualized. Level II corresponds to the bladder neck, the intramural region of the urethra and the anorectal junction. Level III corresponds to the midurethra and the upper third of the anal canal and Level IV to the perineal muscles, the perineal body, the distal urethra and the middle and distal third of the anal canal. 3D-EVUS provides information on the LA/ levator hiatus integrity (373).

There are limited studies that directly compare these techniques with EAUS (381, 382). Although the sensitivity for the detection of sphincter defects ranges from 44% for EVUS to 50% for TPUS, they can be used in combination with EAUS, to provide additional information on pelvic floor muscles and levator hiatus damage. In a prospective, observational study, defects of the pubovisceral muscle (PVM) were identified with 3D-EVUS in 27% of women with FI who had undergone vaginal delivery. Severity of incontinence was related to the extent of damage of the PVM and to the enlargement of the levator hiatus (383). These findings were not confirmed in a retrospective study where there was no statistically significant association of FI with worsening of LA deficiency among patients with major FI(412).

TPUS may be used as screening modality for the detection of occult anal sphincter injuries after vaginal delivery. In a prospective, randomised controlled trial, the occult tear rate increased from 3.5% (clinically detected) to 11.5% by US technique (413). Future studies should focus on technique standardisation and method as well on the predictive value of both EVUS and TPUS compared with EAUS in the detection of sphincter defects.

New Evidence about Ultrasonography for OASIS

Three-dimensional EAUS remains the most accurate diagnostic imaging modality for diagnosis and classification of sphincter defects after childbirth (414). This method makes it possible to detect small sphincter defects that otherwise would have gone unnoticed, as 30% of patients with sphincter injuries are asymptomatic. EAUS has the strongest association with FI symptoms after OASIS compared to introital US or TPUS (415, 416). With low positive predictive values, 2D-TPUS and 3D-EVUS are not accurate modalities for the assessment of anal sphincter complex in women with OASI (386, 415). 3D-TPUS shows good agreement with the gold-standard 3D-EAUS and a high sensitivity in detecting residual defects (386, 414). The optimal cut-off number of slices on tomographic ultrasound imaging for external and internal anal sphincters allows for standardization of a significant defect. Significant obstetric anal sphincter injuries (OASI) have been defined as visible defects of at least 30° in at least 4/6 slices using tomographic ultrasound imaging (TUI) with TPUS (417, 418). TPUS without TUI technique has proven to be effective as well (419). OASI have been graded as a 3a tear if the EAS was abnormal in <4/6 slices, 3b tear if the EAS was abnormal in ≥ 4/6 slices and 3c/4 tear if both the EAS and the IAS were abnormal in ≥ 4/6 slices. In a study on 215 women who sustained OASI, TPUS-based grading of OASIS showed fair agreement with clinical grading of the Royal College of Obstetricians and Gynecologists guidelines (420).

In women with a history of OASI, EVUS and TPUS are suitable to screen for an intact sphincter if EAUS is not available. In a cross-sectional study (421), including 563 women who delivered their first child, defects of EAS and IAS were found on TPUS in 10% and 1% of cases after normal vaginal delivery, in 32% and 7% of cases after forceps delivery and in 15% and 4% of cases after vacuum delivery, respectively. No defects were found after Caesarean section. EAS and IAS defects were associated with increased risk of development of FI. Of the ultrasonographic sphincter defects, 80% were not recorded as OASI at delivery. When defects are found, women should have EAUS to verify the diagnosis (415). Even after postpartum, diagnosis and primary repair, 25-50% of patients will have persistent FI due often to sub optimal repair of the anal sphincter tears. Ultrasound has demonstrated a high rate of residual defects after reconstruction (392, 415-417, 419).

In a retrospective review of 1495 women with OASI, EAUS demonstrated that primary repair was unsuccessful in the majority of cases (422). Sphincter defects detected using all ultrasound methods were associated with lower anal pressures (416). The extent of the residual EAS defect was the most relevant factor correlating with FI (418). Defects measured with EAUS and TPUS six months postpartum correlated to initial OASI grade and symptoms of FI (417). Women who had a higher tear grade, i.e., OASIS 3c/4, had more symptoms, lower maximal resting and squeeze pressures and more residual external and internal sphincter defects in comparison with those who had a 3a/3b tear (418). The offer of a sonographic follow-up at 10-12 weeks after vaginal delivery in high-risk women (maternal age ≥ 35, vaginal birth after Caesarean, forceps, prolonged second stage, overt OASI, shoulder dystocia and macrosomia) may help to reduce morbidity arising from anal sphincter tears (423). With a neonatal head circumference of 34cm or more (cut-off value), probability for FI was 33%, while below that value it was just 2% (424). Mediolateral episiotomy does not seem to be protective against clinically or sonographically diagnosed OASI. It should be considered only when shortening the second stage of labour is indicated due to fetal distress, and not as a means of OASI prevention.

EAUS allows a significantly better detection of symptomatic OASI compared to clinical examination alone (400). Missed OASI at delivery had worse functional outcomes than primary repair immediately following delivery (425). In a matched retrospective cohort study (426), comparing missed to recognized and repaired OASI, the consequences of undiagnosed tears were higher anal and urinary incontinence symptoms. All missed OASI had a shorter perineal body and larger sphincter defect on EAUS. In the EPIC multicentre randomised controlled trial (427), women

with asymptomatic OASI diagnosed by EAUS were planned to Caesarean section or a vaginal delivery. At 6 months after the second delivery, there were no significant differences in anal and urinary continence or sexual function between the two groups. These results do not support advising elective caesarean section for this indication.

It has been reported that 10% to 30% of woman with vaginal childbirth sustain LA avulsion (428), more commonly among those who had undergone forceps-assisted delivery. In women who had either first- and second-degree perineal tears or episiotomy, 3D-EAUS/EVUS showed signs of abnormal pelvic morphometry (429). Partial avulsion of the right or left puborectalis muscle was 16.2% in women affected by second-degree tears. Women receiving Kristeller manoeuvre during labour had a higher incidence of either right or left puborectalis muscle avulsion (429). A systematic review (430) reported that vaginal delivery was associated with a higher number of LA injuries, puborectalis defects, increase in bladder neck mobility and enlargement of the hiatal area than Caesarean section as determined by 3D-TPUS evaluation. Transperineal ultrasound demonstrated that LA avulsion is strongly associated with pelvic organ prolapse (POP). In contrast it doesn't increase the risk of stress urinary incontinence, overactive bladder and AI (431).

New Evidence about Endoanal Ultrasonography in Anorectal Surgery

Intersphincteric injectable bulking agents or implants are one of the current treatment options for FI after failure of behavioural and medical therapy (432). Preoperative 3D-EAUS has been recommended for patient selection and to exclude coexistent clinical conditions that may negatively affect outcomes. Postoperatively, 3D-EAUS has been used to demonstrate the normal localization or displacement of the prosthesis (432-434). A systematic review and meta-analysis, including a total of 889 patients in 23 articles, investigated the midterm outcomes of treatment with injectable bulking agents to identify predictive factors for improvement in incontinence (432). Meta-regression revealed that implants intact on EAUS were predictive of greater improvement in incontinence.

Endoanal ultrasound is a recommended preoperative investigation for anal fistulae which aims to provide the best chance of healing and preservation of continence function (435, 436). A retrospective analysis of 339 patients, EAUS had significant effects on functional outcome and FI after fistula surgery (435). 3D-EAUS is an accurate and reproducible modality for the assessment of type and height of anal fistulae, reducing the potential risk of FI and recurrence associated with the surgical treatment (436).

Patients with chronic anal fissure can be treated with sphincterotomy after failure of medical therapy. Preoperative measurements of the IAS by 3D-EAUS help the surgeon to plan the length of sphincterotomy. Open left lateral internal sphincterotomy extended for about 20% of total left lateral IAS length seems to be safe and effective in the treatment of chronic anal fissure achieving a high success rate without compromising anal continence.

Rectal prolapse can be associated with FI that may not completely resolve after surgical treatment. Preoperative EAUS has a role in grading anal sphincter integrity in rectal prolapse and in predicting improvement in the continence state after surgery (437). Higher grades of sphincter injury are associated with less improvement in continence than lower grades (437).

Summary of Endoanal Ultrasonography

- EAUS has the strongest association with FI symptoms after OASIS compared to introital US, 3D-EVUS or 2D-TPUS (Level of Evidence 3).
- 3D-TPUS shows good agreement with the gold-standard 3D-EAUS and a high sensitivity in detecting residual sphincter defects (Level of Evidence 3).
- Sphincter defects measured with EAUS and TPUS six months postpartum correlated to initial OASI grade and symptoms of FI (Level of Evidence 3).
- 3D-TPUS demonstrated that LA avulsion is strongly associated with pelvic organ prolapse. LA evulsion doesn't increase the risk of stress urinary incontinence, overactive bladder and FI (Level of Evidence 3).
- Detection of intact bulking agent on postoperative 3D-EAUS is predictive of improvement in incontinence after treatment with injectable bulking agents (Level of Evidence 2).

Recommendations for Practice Related to Ultrasound Imaging

- In women with asymptomatic OASIS diagnosed by EAUS, elective caesarean section to prevent AI is not recommended in the second delivery (Grade of Recommendation A).
- Sonographic follow-up at 10-12 weeks after vaginal delivery in high-risk women (maternal age ≥ 35, vaginal birth after cesarean, forceps, prolonged second stage, overt OASIS, shoulder dystocia and macrosomia) may help to reduce morbidity arising from anal sphincter tears (Grade of Recommendation 3).
- Mediolateral episiotomy is not protective against clinically or sonographically diagnosed OASIS. It should be considered only when shortening the second stage of labour is indicated due to fetal distress, and not as a means of OASIS prevention (Grade of Recommendation 2).

3. DEFAECOGRAPHY

3.1. Introduction

Defaecography, also referred to as evacuation proctography, is the radiological assessment of the voluntary rectal evacuation of semi-solid contrast material, and it provides information on both static and dynamic anorectal structure and function. Conventional fluoroscopic defaecography is an established tool for the diagnosis of evacuation disorders. MRI defaecography has the advantage of evaluating all pelvic components, although it is less utilized than fluoroscopic defaecography due to its higher cost and unnatural examination posture in the supine position.

Defaecography has been widely used in the diagnosis and management of evacuation disorders including pelvic floor incoordination, rectocele, rectal intussusception and so forth. The technique has been less often utilized in the assessment of FI until the advent of laparoscopic ventral rectopexy (LVR) (438-440). LVR improves FI through the anatomical correction of rectal intussusception (internal rectal prolapse) although there are conflicting data (441). Since LVR has been shown to be effective in the treatment of FI in patients with rectal intussusception and complicated rectocele, defaecography has become more important in diagnosing these conditions.

3.2. Examination Techniques of Fluoroscopic Defaecography
There has been no universally agreed standard method for the conduction of defaecography, but the Pelvic Floor Consortium of the American Society of Colon and Rectal Surgeons and other five societies published "Consensus Definition and Interpretation Templates for Fluoroscopic Imaging of Defaecatory Pelvic Floor Disorders" (442). Usually, a viscous barium contrast material is injected into the rectum of the patient in the left decubitus position. The semisolid contrast material can be made by mixing barium with flour, oatmeal or mashed potato, whilst ready-made barium paste can be used where it is commercially available. The volume of the injected material is either fixed at around 150ml or up to the volume at which the patient feels the urge to defaecate.

A radiopaque marker should be placed on the perineal body as a point of anatomical reference (442), while other radiopaque markers can be placed on pubic symphysis and the apex of the coccyx to facilitate interpretation. Vaginal contrast should be used to provide relevant clinical information regarding pelvic organ prolapse, whilst bladder contrast does not need routine use (442). Small-bowel contrast can assist in the identification of enterocele but is not recommended for the routine evaluation of pelvic organ prolapse, including enterocele (442).

During fluoroscopic defaecography, the patient sits on a commode attached to the footboard of the fluoroscopy table and lateral views of the film are taken at rest and maximum squeeze. Then rapid film sequences are taken during evacuation, followed by a film taken after the completion of the evacuation at maximum straining cine-defaecography.

3.3. Parameters To Be Studied at Fluoroscopic Defaecography
The anorectal junction is the distally tapered point of the rectal contrast column caused by posterior impression of the puborectal muscle. The anorectal angle (ARA) is measured by the angle between a line parallel to the posterior wall of the ampullary portion of the rectum and a line drawn along the anal canal (442). In healthy subjects, the ARA at rest is approximately 85 to 96 degrees, which becomes more acute by 10 to 15 degrees during maximum squeeze and becomes more obtuse during straining in comparison to the angle at rest (442). The degree of perineal descent should be described routinely as either "present" or "absent" if the anorectal junction drops by more than 2 cm. Perineal descent should then be further quantified in centimetres by measuring the movement of the anorectal junction from its position at rest toward the point of maximum descent with defaecation of contrast (442). The pubococcygeal line (PCL) should be the reference point from which to quantify prolapse of abdominal organs (442).

Normal subjects should be able to evacuate more than two thirds of rectal contrast material within 30 seconds. After maximal evacuation or after maximal patient effort, the degree of rectal emptying should be quantified relative to initial rectal contrast volume ("1/3 volume evacuated," "2/3 volume evacuated," and "complete evacuation") (442). In addition to assessing the functional aspect of rectal evacuation, defaecography can also reveal the structural aspects including rectal intussusception, rectocele, sigmoidocele and enterocele. Rectal intussusception is defined as the invagination of the rectal wall into itself. It should be quantified as either "intrarectal," "intra-anal," or "external". An additional scoring system (Oxford Scale) (443), to quantify the degree of rectal intussusception might be useful, but Paquette *et al.* (442), reported that "experts voted against mandating its routine use in clinical practice as the bare minimum reportable threshold." Rectocele is defined as the outpouching of the anterior rectal wall beyond the normally expected anterior rectal wall at straining. It should be quantified in centimetres by measuring the maximal displacement of the anterior rectal wall from the expected resting position during defaecation. Further characterization should include information regarding rectocele emptying, rectal emptying, need for digitation or pressure to achieve complete emptying, and degree of concomitant displacement of the posterior vaginal wall, if any (442).

All middle compartment structures and herniatione into the rectovaginal septum, such as enteroceles, sigmoidoceles, or peritoneoceles, should be described by observing their movement in relationship to the PCL in centimetres (442). Sigmoidocele and enterocele are defined as the herniation of the lining of the peritoneum by the sigmoid colon or the small bowel, respectively, into the rectovaginal septum and may push on the anterior rectal wall. Additional details should include size and location in relationship to the vagina by specifying the lowest extent of the hernia as being to the "top of vagina," "middle of vagina," or "on pelvic floor" (442). Dobben *et al.*(444), reported good reproducibility for enterocele, rectocele and their severity grading as well as fair to moderate reproducibility for rectal intussusception in a prospective assessment of inter-observer agreement for defaecography in FI.

3.4. Clinical Utilitys of Fluoroscopic Defaecography
Defaecography can be useful in the diagnosis and management of FI by measuring perineal descent and ARA, evaluating involuntary leakage of the contrast material as well as diagnosing rectal intussusception and rectocele. Perineal descent may be a sign of weak pelvic floor muscles and possible pudendal neuropathy, which may be associated with FI. An obtuse ARA implies weakening of the puborectal muscle and possibly the entire pelvic floor muscles. In a study by Piloni *et al.* the mean ARA at rest differed significantly between patients with FI and those without (445),. The normal range of ARA, however, is wide, and some patients with normal ARA are incontinent to stool, whilst some with abnormally obtuse ARA are continent. Paradoxically, Kollmann *et al.* reported that a wide anorectal angle at rest in preoperative defaecography was the only independent predictor of favourable outcome of sacral nerve stimulation in 54 patients with idiopathic FI in multivariate analysis (favorable 134.1 ± 13.9° vs. unfavorable 118.6 ± 17.1°) (446).

Continent subjects with normal anal sphincter function can easily retain the contrast material in the rectum while sitting on a commode. The involuntary leakage of material during its injection or on sitting before evacuation indicates weak anal sphincters. This finding can be utilized to evaluate whether patients are actually incontinent to semisolid stool or not when their complaints are equivocal. In a study by Savoye-Collet *et al.* of 50 women with FI, 24 showed a leakage of barium paste in upright position during defaecography (447). The finding of the involuntary leakage is beneficial in evaluating surgical outcomes by performing defaecography before and after the operation. Versluis *et al.* reported a significant correlation between the continence score and the finding of the involuntary leakage on defaecography performed before and after dynamic graciloplasty (448). This finding can be utilized in pre-operative evaluation for stoma closure to predict FI in patients with diverting stoma after surgery such as intersphincteric resection of the rectum or restorative proctocolectomy (449).

Karasick, stated that the major indication for performing defaecography in patients with FI is to diagnose rectal intussusception (450). There is controversy regarding the correlation between symptoms and defaecographic findings. Abnormal findings of defaecography can be seen in many normal subjects without symptoms (451, 452), whilst there are some convincing and increasing evidence that

rectal intussusception is associated with FI where this cannot be explained by anorectal physiology and endoanal ultrasound (443, 453-458), Hawkins *et al.* demonstrated in 147 consecutive patients that increasing grades of rectal intussusception were associated with increasing severity of FI (454). Tsunoda et al. also reported that the degree of anterior rectal intussusception descent was significantly associated with the severity of FI in 80 patients (459).

One possible mechanism of FI in rectal intussusception is thought to be the intermittent activation of the rectoanal inhibitory reflex by the redundant mucosa and faecal trapping in the rectum allowing post-defaecatory leakage (443). Harmston *et al.* demonstrated a significant reduction in the mean maximum resting pressure in association with increasing grade of rectal intussusception, concluding that the effect of rectal intussusception on continence occurs mainly through a reduction of internal anal sphincter tone (453). Surgical correction of rectal intussusception can be found in the chapter of "Surgery for FI."

Whether a rectocele can cause FI remains controversial. Collinson *et al.* claimed that one of the causal mechanisms is faecal trapping in the rectocele that allows post-defaecatory leakage to occur (443). Formijne *et al.* performed LVR in patients with combined rectocele and enterocele, and the proportion of patients with FI significantly decreased from 63% to 18% after surgery (460). However, when Wong *et al.* performed LVR in 84 patients with symptomatic complex rectocele, there was no significant improvement in FI, whilst vaginal discomfort and obstructed defaecation symptoms improved significantly (441). Tsunoda *et al.* reported an equivocal result that FI improved in two-thirds of patients, while four patients developed new-onset of FI when they performed transanal repair of rectocele in 30 patients with symptomatic rectocele (461).

Defaecography was not included as a diagnostic examination for FI in the guidelines of the American College of Gastroenterology in 2014 (23), or by the American Society of Colon and Rectal Surgeons in 2015 (22). On the other hand, it is mentioned, albeit briefly, in recent review papers for the management of FI (326, 462, 463). Since D'Hoore *et al.* (438), reported LVR for the treatment of total rectal prolapse, there has been increasing evidence that FI can be improved with ventral rectopexy by surgically correcting rectal intussusception. (437, 439, 440, 464). A consensus meeting on ventral rectopexy has reported that symptomatic high-grade rectal intussusception and complex rectocele are the relative indications for ventral rectopexy after the failure of maximal conservative therapies in patients with obstructed defaecation and/or FI (465). Thus, rectal evacuation disorders including rectal intussusception, which are diagnosed by defaecography, were incorporated into the algorithm of surgery for FI by 6th International Consultation on Incontinence in 2017(466).

3.5. Magnetic Resonance Defaecography

Magnetic resonance defaecography (MRD) can also provide information on both static and dynamic anorectal structure and function. It has advantages over conventional fluoroscopic defaecography (FD) in the avoidance of radiation exposure as well as its ability to evaluate other pelvic organs including vagina, uterus, bladder and small intestine (467, 468). MRD has been utilized not only for evacuation disorders but also for FI in their management (469). Its disadvantage is that it is usually performed in the supine position and is not physiological. Upright MRD with an open-configuration may solve this problem, but is not widely available and therefore infrequently utilized (467).

Similar to FD, the protocols for MRD vary by institutions, but some standardized techniques, recommended landmarks, parameters to be evaluated and their interpretations have been reported (467). The Society of Abdominal Radiology Pelvic Floor Dysfunction Disease Focused Panel has recommended a structured reporting template, which can be accessed from its webpage (470).

The most important aspect of MRD is that patients are required to make their best efforts to expel the rectal gel completely, which might be more difficult in the supine than in the upright position. Inadequate effort may lead to the failure to empty the rectum, resulting in the underestimate of rectal intussusception, rectocele and enterocele. Pilkington *et al.* demonstrated that MRD underestimated pelvic floor abnormalities including rectal intussusception compared with FD, especially when the rectal evacuation was poor (471),. Some studies have shown that FD is superior to MRD in detecting rectal intussusception either in the supine (472), or in the upright position (376), whilst some have reported that MRD better detects rectal intussusception than FD (473) and that both are equivalent in its diagnosis (474). Ramage et al.(475), has concluded in a meta-analysis of 16 studies including 1,703 patients that MRD has a lower detection rate than FD for rectocele (61.8 vs 73.7%; OR 0.48, 95% CI: 0.30–0.76, $p = 0.002$) and rectoanal intussusception (37.9 vs 57.1%; OR 0.32, 95% CI: 0.16–0.66, $p = 0.002$).

Therefore, FD seems more useful than MRD for the management of FI, because FD is superior to MRD in diagnosing rectal intussusception and rectocele, which could be the cause of FI.

New Evidence from the Current Review about Defaecography

- Regarding examination techniques and parameters to be studied, "Consensus Definition and Interpretation Templates for Fluoroscopic Imaging of Defecatory Pelvic Floor Disorders" was published by the Pelvic Floor Consortium of the American Society of Colon and Rectal Surgeons and other five societies (442).
- A meta-analysis demonstrated that the weighted mean rate of improvement of FI was 60.2% by abdominal rectopexy for rectal intussusception, reinforcing the possibility that rectal intussusception can be a cause of FI (437).
- There were two studies which demonstrated that rectal intussusception and its severity were associated with FI and its severity (454), (476).
- There were two studies that reported that preoperative defaecographic findings could predict the outcomes of surgery for FI: one was for sacral nerve stimulation (446), and the other was for laparoscopic ventral rectopexy (477).
- A structured template for reporting the results of MR defaecography, was recommended by the Society of Abdominal Radiology Pelvic Floor Dysfunction Disease Focused Panel (470).
- A meta-analysis demonstrated that MR defaecography had a lower detection rate than fluoroscopic defaecography for rectocele and rectoanal intussusception (475), suggesting that fluoroscopic defaecography might be more useful than MR defaecography for the management of FI.

Summary of Defaecography

- The importance of defaecography has further increased for the management of FI, since the advent of laparoscopic ventral rectopexy, which has been shown to improve FI through the

surgical correction of rectal intussusception and/or complex rectocele (Level of Evidence 2).
- Findings of defaecography could be used to predict the outcomes of sacral nerve stimulation and laparoscopic ventral rectopexy for the treatment of FI (Level of Evidence 3).
- Fluoroscopic defaecography seems more useful than MR defaecography for the management of FI because the former is superior to the latter in diagnosing rectal intussusception and rectocele (Level of Evidence 2).

Recommendations for Practice Related to Defaecography
- Perform defaecography for the diagnosis and management of FI by measuring perineal descent and anorectal angle (Grade of Recommendation C), evaluating involuntary leakage of the contrast material, (Grade of Recommendation C) as well as diagnosing rectal intussusception and rectocele (Grade of Recommendation B).
- Perform defaecography in patients with FI, when their symptoms cannot be explained by anorectal physiology and endoanal ultrasound with rectal intussusception and/or rectocele being suspected from symptoms and anorectal examinations (post-defaecatory passive FI) (Grade of Recommendation B).
- Perform defaecography in patients with FI, who have failed to maximum conservative therapies, and are possible candidates for laparoscopic ventral rectopexy (Grade of Recommendation B).
- Perform fluoroscopic defaecography rather than MR defaecography for the diagnosis of rectal intussusception and rectocele (Grade of Recommendation B).

Recommendations for Research on Defaecography
- Identify patients with rectal intussusception and/or rectocele, who would most benefit from ventral rectopexy by combining symptoms, clinical characteristics and defecographic findings.
- Establish the position for defaecography in the algorithm for the management of FI.

4. MAGNETIC RESONANCE IMAGING (MRI)

4.1. Introduction

MRI is a non-ionizing radiation technique which can provide high resolution images through the anal canal and pelvic floor. There are two kinds of MRI modalities that are used for the management of FI: one is static MRI, known as anal MRI, and the other is dynamic MRI, known as MRI defaecography (468). Anal MRI is used to evaluate the structures of anal sphincters and pelvic floor muscles, while MRI defaecography is used to diagnose dynamic pelvic floor disorders such as rectocele and rectal intussusception (See section above). This section focuses on the role of anal MRI for the management of FI.

Anal MRI provides detailed information of the anal sphincters and pelvic floor anatomy (478). It can be used to detect injuries of internal and external anal sphincters, which might be associated with FI. The spatial resolution of MRI, however, is less than that of endoanal ultrasonography (EAUS), and therefore, accuracy for detecting anal sphincter defects is reported to be slightly below that of EAUS (479-482). Moreover, experience with MRI techniques is less than EAUS because of its availability as well as paucity of dedicated radiologists in this field. Consequently, the role of MRI for the assessment of FI is limited in clinical practice, and it remains second line behind EAUS for the evaluation of anal sphincter integrity (483, 484).

Anal MRI is superior to EAUS for quantifying anal sphincters and pelvic floor muscles and delineating the presence of their atrophy (485). It is particularly useful in specialist situations where anatomy is complex or deranged, for example in anorectal malformations or following surgery (486). MRI is also more useful than EAUS in detecting pubovisceral muscle avulsions, which could be associated with FI after vaginal delivery (487). MRI is increasingly employed as a research tool to investigate the pathophysiology and mechanisms of defaecation (326).

4.2. Examination Methods of MRI

An expert consensus on MRI protocols was reported in 2017 by the pelvic floor-imaging working group of the European Society of Urogenital Radiology (ESUR) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) (488). It was produced to standardize indications, patient preparation, sequences acquisition, interpretation and reporting of MRI for diagnosis and grading of pelvic floor disorders. A consensus-based terminology report was also published by the International Urogynecological Association (IUGA) and the International Continence Society (ICS) in 2017 to standardize terminology for female anorectal dysfunction (478). This joint report included terminology of MRI for anal sphincters and pelvic floor.

Static MRI provides detailed information of the anal sphincters and pelvic floor anatomy (478). Current state-of-the art MR imaging of the pelvic floor includes imaging at a magnetic field strength of 1.5 Tesla (T), using pelvic or phased-array coils and T2-weighted fast-spin echo (FSE) sequences. Based on T2-weighted FSE sequences, muscles including external anal sphincter (EAS) are relatively hypointense, ligaments and fascia hypointense, while fat and smooth muscle including internal anal sphincter (IAS) are hyperintense. MRI can be performed with endoluminal (endoanal or endovaginal) coils or surface phased-array coils placed external to the patient. The spatial resolution can be enhanced by using endoluminal coils. In combination with T2-weighted FSE sequences, endoluminal coils provide improved signal-to-noise ratio (SNR) and high-resolution images (489).

4.3. Normal Anal Sphincter Anatomy on MRI

Anal sphincter anatomy is best depicted on high resolution angled T2-weighted images which maximise the contrast between muscle and adjacent fat. It is possible to measure muscle volume and length on the resulting images which may have some clinical utility. For example, in a series of 100 healthy volunteers, Rociu *et al*. reported that age- and sex -related differences were demonstrable on endoanal MRI, and women had a significantly shorter EAS than men (490).

The normal IAS is formed by smooth muscle in direct continuation with the circular muscle of the distal rectum. The IAS demonstrates intermediate signal intensity on T1- and T2-weighted images. The EAS is comprised of skeletal muscle and demonstrates low signal on T2-weighted images. Tirumanisetty *et al*. demonstrated in their normal value study of 112 asymptomatic healthy women that 92% had normal appearing IAS and EAS, while 96% had a normal appearing puborectal muscle (491).

It should be noted that the inferior edge of the EAS may be open posteriorly and anteriorly, which should not be confused for a tear (468). The complex anatomy of the EAS has been elucidated by

MRI techniques including diffusion tensor imaging, fibre tracking and spin-tag MRI. Using these sequences, Mittal *et al*. demonstrated a purse-string morphology of the EAS on contraction, with decussation of muscle fibres within the perineal body to the contralateral transverse perineal and bulbospongiosus muscles (492). This understanding could potentially question the fundamental premise behind lateral episiotomy and overlapping sphincteroplasty, as both of these surgical techniques assume that the EAS is a circular muscle. The subcutaneous EAS often does not form a complete ring on axial sections, stating that the variational gaps at posterior or anterior commissures can be misinterpreted as sphincter defects (493),.

4.4. Anal Sphincter Defects on MRI

The ability of MRI to detect anal sphincter defects has been addressed by several studies. In general, those reporting higher accuracy have utilized an endoanal coil, although large scale comparisons with surface coils are lacking. An advantage of MRI is multiplanar image acquisition which facilitates evaluation of the sphincter complex in multiple orientations, improving diagnostic accuracy, although 3-dimensional (3D) EAUS can also produce multiplanar images. One pitfall of MRI evaluation of the anal sphincter complex is that variations in normal anatomy may be misdiagnosed as sphincter defects by the unwary.

The IAS is typically of higher signal than the EAS on T2 weighted images and defects manifest as either discontinuity or thinning, with replacement of the normal smooth muscle by fibrous tissue. IAS defects are often found in combination with EAS defects, especially in women presenting with incontinence following obstetric sphincter tear. Solitary IAS defects are more common in iatrogenic cases of incontinence, for example after surgery for anal fistula and anal fissure.

Akin to EAUS, EAS defects manifest as discontinuity in the normal intermediate signal muscle structure, often with associated low signal fibrosis. Secondary changes to the architecture of adjacent structures (for example, the longitudinal muscle and perianal fat) may provide supportive evidence of a sphincter tear. There is evidence that MRI is accurate in detecting EAS defects potentially suitable for anal sphincteroplasty in patients presenting with FI, and accuracy of 95% has been reported for EAS tears (494-502).

In a nested case control study of 68 women with FI and 68 matched controls, Bharucha *et al*. reported that IAS injury detected on endoanal MRI was an independent risk factor for incontinence. However, neither EAS nor puborectalis injury was itself an independent risk factor (503). A retrospective cohort study in 189 women with pelvic floor dysfunction found no correlation between pubovisceral muscle avulsions detected on MRI and symptoms of FI, although there was a correlation with symptoms of pelvic organ prolapse and an inverse correlation with symptoms of obstructed defaecation (487). A retrospective study in 119 women undergoing external phased array coil MRI and anal manometry found that a patulous anal canal (which cannot be identified with endoanal MRI) was associated with more severe anal injury as documented by reduced squeeze pressure increment (504).

4.5. Anal Sphincter Atrophy on MRI

MRI has higher accuracy in identifying EAS atrophy compared with EAUS (485, 505). The ability of MRI to accurately detect EAS atrophy has been demonstrated in a number of studies (494, 495, 497, 506). For example, in a study of 25 women undergoing surgical EAS repair, Briel *et al*. (497), compared pre-operative MRI evaluation of sphincter atrophy with histological analysis of full thickness muscle biopsies. Atrophy on MRI was defined as muscle thinning or fatty replacement. Against the histopathological reference, MRI achieved a sensitivity of 89% and specificity of 94% for sphincter atrophy. Importantly, the same group reported a clear association between EAS atrophy on MRI and significantly poorer outcome following EAS repair (506), emphasizing the clinical importance of this observation. The work also showed that atrophy was only be detected on MRI and not using EAUS. There is good evidence that the longer-term functional outcome following sphincteroplasty for obstetric-related EAS defects is inferior in those with neuropathy-associated EAS atrophy (485, 505-508).

In a retrospective cohort study of 158 women with pelvic floor symptoms undergoing external phased array coil MRI, Kessels *et al.* reported a correlation between severe EAS atrophy and FI, as well as a link between the severity of EAS atrophy and increasing age and body mass index (BMI). There was, however, no statistically significant correlation between the presence of sphincter defects and FI (509).

4.6. Post-Surgical Sphincter Evaluation on MRI

MRI has been found useful in assessing patients with defaecatory dysfunction after surgical correction of anorectal malformations, both in children (486, 510, 511) and adults (512). An increased anorectal angle, misdirection of the neorectum and peritoneal fat herniation between the neorectum and striated muscle complex are associated with an increased incidence of FI. MRI is superior to EAUS in demonstrating the amount and quality of any residual EAS.

Using clinical scoring and MRI, Gangopadhyay *et al*. compared three surgical procedures in 130 children after surgery for anorectal malformations. It was concluded that MRI was a valuable modality for postoperative structural analysis of patients with anorectal malformations and was also useful for predicting the long term functional outcome of FI (486).

New Evidence about MRI

An expert consensus on MRI protocols was reported by the pelvic floor-imaging working group of the European Society of Urogenital Radiology (ESUR) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR). It was produced to standardize indications, patient preparation, sequences acquisition, interpretation and reporting of MRI for diagnosis and grading of pelvic floor disorders.

A consensus-based terminology report was published by the International Urogynecological Association (IUGA) and the International Continence Society (ICS) to standardize terminology for female anorectal dysfunction. This joint report included terminology of MRI for anal sphincters and pelvic floor.

Summary of MRI

- MRI can be used to diagnose defects of internal and external anal sphincters as well as pubovisceral muscle avulsions, which might be associated with FI (Level of Evidence 3).
- MRI is accurate in detecting external anal sphincter defects potentially suitable for anal sphincteroplasty in patients presenting with FI (Level of Evidence 3).
- Endoanal MRI has higher accuracy than surface coil MRI for detecting anal sphincter injuries. Its spatial resolution, however, is still less than that of endoanal ultrasonography (EAUS), and therefore, accuracy for detecting anal sphincter defects is slightly below that of EAUS (Level of Evidence 3).
- MRI is superior to EAUS for assessing external anal sphincter atrophy, which may correlate with symptoms of FI and predicts

poorer outcome after anal sphincteroplasty (Level of Evidence 2).
- MRI is useful in assessing children and adult patients with defaecatory dysfunction after surgical correction of anorectal malformations (Level of Evidence 2).

Recommendations for Practice Related to MRI
- Perform MRI to diagnose anal sphincter defects which might be associated with FI, if endoanal ultrasonography (EAUS) is unavailable or its results are inconclusive (Grade of Recommendation C).
- Perform MRI to evaluate external anal sphincter atrophy, which might be associated with FI or before anal sphincteroplasty (Grade of Recommendation B).
- Perform MRI in patients with anorectal malformations and/or previous anal sphincter surgery, which might be associated with FI (Grade of Recommendation C).

Recommendations for Research on MRI
- Improve the spatial resolution of MRI, so that its diagnostic accuracy becomes comparative or superior to endoanal ultrasonography (EAUS) in detecting anal sphincter defects.
- Further evaluate the usefulness of MRI in diagnosing external anal sphincter atrophy for the management of FI, particularly as selection criteria for anal sphincteroplasty in patients with obstetric anal sphincter injuries.

5. TYPES OF NEUROPHYSIOLOGICAL TESTING FOR FI

5.1. Introduction

Neurophysiological testing in patients presenting with incontinence appears to be diminishing in practice because of improvements in clinical sphincter imaging and as a result of the understanding that some neurophysiological parameters have only minimal influence on decision-making (513). Despite the rise of sacral and tibial nerve neuromodulation in selective management of incontinent patients, there is no clear guideline for specific predictive neurophysiological testing (514, 515) relegating its specific use in complicated cases of incontinence secondary to particular neurological diseases and following spinal injury. A consensus paper suggested that neurophysiological testing should be performed in all incontinent patients who either have reduced anal pressure with no obvious explanation or who have a neurological

disease although this is not supported by any references (516).

The following are the typically described neurophysiological test modalities in FI:
- Electromyography (EMG)
- Pudendal terminal motor latency (PNTML)
- Sacral latency test (SLT)
- Somatosensory evoked potentials (seps) of pudendal nerve
- Motor evoked potentials (meps)
- Anorectal reflex assessment
- Autonomic nervous system (ANS) testing

Somatic motor testing assesses skeletal muscle motor innervation plus sensory innervation from cutaneous sites to the muscle spindles. This testing incorporates all forms of electromyography (EMG), PNTML studies, motor nerve conduction studies, and motor evoked potentials. Somatosensory testing includes somatosensory evoked potentials and sensory neurography. ANS testing assesses visceral afferent pathways at peripheral, spinal and supraspinal levels.

5.2. Electromyography

In the past the specific use of this EMG technology in FI was for the differentiation of patients with potential voluntary sphincter defects from those without sphincter defects thought to be reparable but who had an attendant presumptive neurological cause for their incontinence. Concentric needle electromyography (CN-EMG) is performed with single-use needles employed at multiple sites. Inherent differences exist at rest in sphincter musculature when compared with peripheral (non-sphincteric) musculature showing basal resting activity whereas non-sphincter musculature is electrically silent (517, 518). The technique can help identify neurogenic from myopathic causes of anal sphincter dysfunction (503). There is no correlation between severity of EMG findings and degree of incontinence (519). Denervation is diagnosed as a reduction in the number of continuously firing low-threshold motor unit potentials (MUPs). CN-EMG has disappeared with improved accurate sphincter imaging; however, it may have a specific place in those patients where ultrasonography and/or MR imaging is equivocal.

Single fibre EMG (SF-EMG) has a smaller recording surface with a pickup of activity from a smaller muscle volume than that recorded with CN-EMG, recording generally 1-3 single muscle fibres from the same MU. Single fibre (needle) EMG is not routinely performed due to the associated discomfort. Surface EMG has no value in assessing neurogenic aspects of sphincter function (but may be used as part of biofeedback therapy) (18).

5.3. Pudendal Nerve Conduction Testing

Pudendal nerve conduction testing measures the nerve conduction velocity in the pudendal nerve as latency time between direct stimulation of the pudendal nerve and external anal sphincter (EAS) contraction. There is a customised (Dantec Electronic Tonsbaaken 16-18 DK-2740 Skovlunde, Denmark) St. Mark's electrode that has been designed. Prolongation of the pudendal nerve terminal motor latency (PNTML) is common after vaginal delivery and with aging (520-522). The technique tends to underestimate the degree of pudendal neuropathy since the latency measured reflects the function of the most rapidly conducting nerve fibres (523). Unlike needle EMG, it does not show direct neurological damage.

It has been suggested that the delay in PNTML is associated with a worse overall prognosis of external anal sphincter repair for patients presenting with FI (507, 524) although there is little available evidence to suggest that PNTML measurement alters specific surgical decision-making or outcomes after surgery (525). In addition, the measurement is influenced by body habitus and clinician factors (526, 527). There is little available evidence that the presence or extent of a pudendal neuropathy correlates with objective incontinence (513), or with the specific response to biofeedback therapy with or without the presence of an external anal sphincter defect (528).

5.4. Sensory System Testing

Anorectal sensitivity plays a significant role in the defaecation process and in maintaining faecal continence. Variation in anorectal sensibility is also important in pain disorders and in irritable bow-

el syndrome. Basic sensory testing of light touch and pinprick and sensation of bladder filling is standard. The ano-cutaneous sensation of the perianal area and in the anal canal below the dentate line is conveyed by the efferent fibres of the pudendal nerve (S2-S4) (529).

5.5. Anal Mucosal Electrosensitivity

Anal mucosal electrosensitivity (MES) testing was originally described independently by

Roe *et al.* (530), and Sigel (531), using two electrodes with a constant square wave of current with variable intensity. It is unknown precisely which receptors are involved in this standardised and reproducible response (532). Incontinent patients invariably have a high MES whereas patients with anal sphincter defects, (with or without FI), show an increased MES with the highest values found in patients with a combined internal anal sphincter and external anal sphincter defect.

New Evidence about Neurophysiological Testing

Assessing Anorectal Reflexes

Assessment of the rectoanal inhibitory reflex is an accepted part of anorectal physiology testing. Absence of the reflex is suggestive of anorectal pathology, including previous anorectal resectional surgery, anal hypotonia, faecal loading or megarectum. The possibility of an aganglionosis needs to be considered (533).

Summary of Neurophysiological Testing

- Neurophysiological testing in patients with FI is diminishing in practice because of improvements in clinical sphincter imaging, and its contribution to making a diagnosis or selecting treatments is minimal (Level of Evidence 4).
- Basic sensory testing of light touch and pinprick, the rectoanal inhibitory reflex, and sensation of bladder filling is a standard part of the clinical assessment of FI (Level of Evidence 4).
- CN-EMG testing can be used to help distinguish neurogenic from myopathic causes of anal sphincter dysfunction (Level of Evidence 3).
- PNTML is not useful in the preoperative assessment of patients before sphincteroplasty or sacral nerve stimulation as it does not alter specific surgical decision-making or outcomes after surgery (Level of Evidence 4).

Recommendations for Practice Related to Neurophysiological Testing

- Specialised neurophysiological testing is not recommended for routine secondary assessment of patients with FI because it has limited value over other diagnostic tests (Grade of Recommendation C).
- Basic sensory testing of light touch, pinprick, and the rectoanal inhibitory reflex is recommended as part of initial and secondary clinical assessment of FI, especially in patients suspected to have Hirschsprung's disease (Grade of Recommendation C).
- PNTML is not recommended for preoperative assessment of patients before sphincteroplasty or sacral nerve stimulation (Grade of Recommendation C).
- EMG can be used to help identify neurogenic from myopathic causes of anal sphincter dysfunction (Grade of Recommendation B).
- CN-EMG may have a specific role when ultrasonography and/or MR imaging is equivocal (Grade Recommendation C).

Recommendations for Research on Neurophysiological Testing

- Assess reproducibility of testing of anorectal sensation on predicting outcome of surgical and conservative/medical treatment for FI in large patient samples.

VIII. QUALITATIVE RESEARCH ON THE EXPERIENCE OF FI AND QUALITY OF LIFE

Qualitative studies about an individual's experience of FI and its impact on quality were included for the first time in the 5th ICI (116). Qualitative studies provide an in-depth description of the patients' experience as they live with and manage their FI. These studies typically use small purposeful sample sizes that generate a large amount of text data to accomplish their aims. The sample sizes in the 5 new studies included in this review ranged from 3 to 102 individuals and used descriptive, narrative, and phenomenological qualitative methods to explore participants' experiences.

1. CRITERIA FOR EVALUATION

Given that qualitative research employs different methods than quantitative research, a framework for making decisions about the quality, levels of evidence, and limitations of these studies was developed for the 5th ICI review (116). This framework was informed by literature on quality and rigour in qualitative research and is included in this update and the criteria and scheme used by the ICI for quantitative research studies (534-543). This framework was used to critique studies, identify their strengths and limitations, and assign an evidence level.

1.1. Type of Study – The Qualitative Evidence Pyramid

1. Qualitative meta-synthesis
2. Interpretive designs including phenomenology, grounded theory, ethnography.
3. Descriptive qualitative designs using content analysis (including inductive and deductive content analysis approaches, analysis of focus group data, photovoice, participatory action research, single or multiple case studies).
4. Surveys with semi-structured open-ended questions.

1.2. Criteria for Evaluation of Qualitative Studies

a) There is a clear research purpose or questions appropriate for qualitative inquiry.
b) The purpose or questions are linked with a critical review of the literature and key studies are included identifying a gap or misunderstanding of the phenomenon.
c) There is a guiding frame of reference for the study that fits the phenomenon being studied.
d) There is congruence between the method and the research purpose.
e) The sampling plan is purposeful and is consistent with the purpose and method.
f) The sample size is appropriate for the purpose and sampling strategy.
g) Inclusion and exclusion criteria are described and appropriate for the purpose.
h) Data collection techniques and sources are appropriate for the purpose, method and sample.
i) The analysis plan is appropriate for the purpose and method.
j) Data are sufficiently analysed and interpreted and is reported in a way that the meaning is apparent. The interpretation or description is distinguishable from the original data collected.
k) The participants' voices are evident in and demonstrate the meaning of categorical, thematic or conceptual findings.
l) Concepts, categories and themes are well developed and linked to each other and to the data.
m) The results offer new insight into the phenomenon studied and transferable to similar contexts.
n) Reflexivity is addressed within the context of the study.
o) Evidence of an audit trail of how key decisions were made is clear. Strategies to achieve rigor are described.
p) Study specific limitations are summarized.
q) Ethical considerations are discussed.

1.3. Levels of Evidence for Qualitative Studies

- **Level 1:** A study meets the following Criteria for Evaluation of Qualitative Studies: a, d-f and h-m. These are typically the studies listed as type 1 and 2 in the Qualitative Evidence Pyramid.
- **Level 2**: A study meets the following Criteria for Evaluation of Qualitative Studies: a, d-f and h-m. Level 2 studies are ones listed as types 3-4 in the Qualitative Evidence Pyramid.
- **Level 3:** The Study does not meet the majority of the Criteria for Evaluation of Qualitative Studies.

1.4. Grades of Recommendation for Qualitative Studies

- **Grade A** recommendation: Excellent evidence leads practice recommendations. A Grade A recommendation is based on Level 1 studies.
- **Grade B.** Moderate evidence leading to possible practice recommendations (more evidence is needed). Grade B recommendation includes studies with evidence levels 1 and 2 studies of only level 2 studies.
- **Grade C**. Provide poor evidence from level 3 studies that does lead to practice recommendations.

2. BACKGROUND

The 5th and 6th editions of the ICI proposed a five-domain quality of life framework for people experiencing FI that was thematically derived from the findings from qualitative studies of people with FI (1, 116). The domains were 1) Living with FI related to relationships, 2) Living with FI related to time and planning, 3) Living with FI related to bodily symptoms, self-esteem, and body image, 4) Living with FI related to sexuality, and 5) Living with FI related to dietary issues.

2.1. Living with FI Related to Relationships

Both men and women report that FI poses a threat to their relationships (5, 6, 544-546). They suffered from social isolation and anxiety because of FI (5, 87, 136, 536, 537, 545, 547, 548). They reported discomfort about being in 'mixed company' and having a possible accident (5, 6). Women expressed concerns about entering new relationships due to fear and shame of having to disclose FI (87), and did not attend social events and made excuses unrelated to their incontinence (546). Individuals described trying to protect themselves from the unpredictability of their symptoms and kept up a facade to keep FI a secret from others (87, 540). They also reported that it was a sensitive topic to discuss with others and was strongly associated with the emotions of guilt and shame (546). Humour was used as a resource to avoid humiliation and embarrassment in dealing FI and relationships, even though feelings of shame and humiliation persisted (5, 6, 87, 536, 546). Individuals expressed concern about who to tell about their FI and when. Family, close trusted friends, or co-workers were told because the secret could not be completely concealed (5, 6, 545). Support from spouses was very important (5, 6, 545, 547). Adaptation to FI was attributed to loving, empathic, unconditional support from significant others (549).

Study participants reported that relationships with health care providers were unhelpful in providing advice and that misinformation or no information was commonly given (5, 6, 87, 537, 550). Women reported feeling embarrassed, humiliated, and marginalized when their FI was minimized or trivialized by rude or blaming health care providers (6, 87, 546, 547). After years of dealing with FI men and women reported that their interactions with health care providers had become confident, assertive and control-seeking in decision-making (551).

2.2. Living with FI Related to Time and Planning

Participants reported that they spend a significant amount of time planning for and worrying about accidents (5, 6, 546). "Being prepared" was a common theme. Planning and management strategies to avoid an accident included: morning bathroom rituals, changing the location of their workstation (relative to the bathroom), altering eating habits (foods and timing), taking a fibre supplement, or using anti-diarrhoeal products (5, 6, 87, 537, 545, 546, 550). Women reported the frequency of stool leakage was unpredictable and because of this they needed to be vigilant and prepared for the unexpected (6, 87). Many reported packing 'kits' of absorbent products, cleansing supplies and extra clothing as a routine part of planning to leave their home (6, 545). Space was experienced as a measure of risk exposure of FI and personal space shrank inward or expanded related to perceived comfort or lack of perceived social safety (5, 6, 536, 537, 542, 544, 545, 548, 550). Women and men experienced heightened anxiety about FI symptoms and the risk of accidents in public spaces (6, 537, 542, 545, 550). Travel was limited to familiar spaces and significant planning was required to prevent an accident (5, 6, 536, 546, 547, 550). Seeking out the location and availability of a bathroom was a major consideration in all dimensions of space outside the home (5, 6, 87, 536, 537, 542, 545, 550, 552). Work life presented complicated situations for both men and women and limited some people's ability to engage in productive work outside the home (5, 6, 548, 550, 552). Women reported postponing business meetings because of FI (6). FI symp-

toms were reported as common reason for early retirement for both men and women (5, 6, 548).

2.3. Living with FI Related to Bodily Symptoms, Self-Esteem, and Body Image

Feelings of shame and embarrassment related to FI were noted across all studies. Men and women with FI felt stigmatized and stigmatized themselves (5, 6, 545-547, 550). They reported altered body image, low self-esteem, guilt, and distress (5, 6, 87, 536, 546), and that their emotional life and self-confidence was undermined because of embarrassment (5, 6, 536, 545-547). Other negative feelings associated with living with FI included anger, frustration, injustice, guilt, shame, disappointment, hopelessness, despair and sadness (546). Poor public knowledge of FI created feelings of stigma in persons with IBD and FI (550). Additional chronic illnesses with worsening bowel control affected one's whole self-concept (551). Key concerns were the unpredictability about the type, timing and magnitude of FI events (542, 550). Some women reported the need for psychological consultations because of feeling insufficient, incompetent, or vulnerable (87, 547). Bothersome, embarrassing, or distressing bodily sensations associated with the FI included: sensations in the intestines, itching, burning, cramping, feelings of incomplete bowel movements, and odour associated with flatus and or leaked faeces. Other distressing symptoms discussed included: leaking stool without defaecation sensations, and false abrupt and urgent sensations usually indicative of defaecation (5, 6, 537, 542, 546, 550). Skin excoriation at the rectum was reported due to frequent bowel movements, soling and associated cleansing (536, 542). Urgency to have a BM and associated fear and the unpredictable nature of FI were the most troubling bodily symptoms for persons with IBD and FI (550).

To deal with FI women used a personalised approach to adapt as "life has to go on". Women were hopeful and optimistic that they would get better. They believed their incontinence would be easier to accept if they had an explanation for their symptoms (546). Men and women adapted in the presence of obstacles, downgrading aspirations and "making the best of it" (re-evaluating control) (551). Not talking about the problem and denying the FI were coping mechanisms used to protect from threat to self-esteem and prevent public embarrassment (547).

The essential theme in the phenomenological study of men managing FI was 'secret resignation': men came to expect the consequences of FI as normal (5). The essential theme in the phenomenological study of women managing FI was 'controlling the body out of control' and a similar subtheme in the Dibley and Norton study (550), of 'loss of control'. Women tried to control all aspects of their life in relationship to the incontinence and avoiding accidents (5, 536, 546, 550, 551). Women were attentive to their body image and dressed carefully to conceal pads and wore dark clothing to hide stains if an accident should happen (6, 87, 544, 550). Men and women wore only small disposable pads that were not obvious through their clothing. Large diaper-like pads were avoided because of their perceived visibility beneath clothing (5, 6, 87).

Major goals of people experiencing FI were to have fewer dietary restrictions, less faecal leakage especially during exercise, improved public toilet accessibility, more confidence in controlling FI symptoms and associated odour, and a normal daily routine (538). A sense of mastery and new self-confidence were achieved by some after years of successfully dealing with the symptoms of FI (549, 551). After 10 or more years of living with FI, men and women found comorbidity and aging posed further challenges to adaptation. By using trial and error, adaptation was ongoing (549).

2.4. Living with FI Related to Sexuality

Although asked about sexuality and intimacy, women were reticent to discuss their sexuality or the effect of their symptoms on their sexual functioning (6, 87). Among those who did, some felt there were no changes in their sexual drive (546, 547), while others reported a range of psychosocial issues including lack of sexual arousal or desire to abstinence (87, 537, 544, 546). Women reported that they arranged timing of sex to meet their needs and the needs of their husbands in relation to the symptoms of FI (547). Choice of clothing was seen as outward expression of sexuality and FI and UI restricted clothing to wearing patterned materials to avoid people detecting an accident (544). Men and women reported continually washing themselves to avoid smelling (544). Participants reported that health care professionals did not discuss sexuality even after surgeries that affected sexual functioning (544, 548).

2.5. Living with FI Related to Dietary Issues

Men and women discussed fasting or not eating for a number of hours or days as strategies to deal with FI symptoms when outside the home (5, 6, 87, 547, 550, 553). Alternating the timing of meals to avoid an accident was a common management strategy (5, 6, 536, 545, 550). Sweets, alcohol, onions, rich and spicy foods, caffeine, fruits, greasy, fat, fried foods, and dairy products were noted to affect FI and restricted (547, 553, 554). Limiting portion or meal size was another reported strategy to limit FI (6, 536). Gas-producing foods such as, pea soup, onions, cabbage, cauliflower, and dairy products were avoided as a treatment for flatus (5, 6, 536). Increasing dietary fibre and taking fibre supplements along with digestive enzymes and yogurt were noted as treatments for FI (6). Some women reported eating foods they enjoyed at home and then dealing with the consequences of FI symptoms (5, 6, 536). Some women reported using protracted voluntary constipation for up to one month as a management technique for leakage (537). Women reported a lack of available therapeutic guidance regarding dietary modifications and adopted recommendations from other gastrointestinal disorders such as IBS and lactose intolerance or approached dietary modification by trial and error (6).

New Evidence about Qualitative Research on Quality of Life Associated with FI

Five new qualitative studies were included in this review (Table 15-7). A descriptive study with a sample of 39 community-dwelling women who had experienced FI (FI) during the prior 3 months (unrelated to diarrhoea) and were not currently undergoing treatment sought to describe barriers to seeking care for FI (555). The goal was to inform the development and revision of an instrument to assess barriers to care-seeking. Data were collected during focus groups and 10 individual cognitive interviews. Twelve barriers to seeking treatment for FI were identified: lack of knowledge about the condition; lack of knowledge about treatment options; fear of the evaluation process, including the possibility that it would identify an unwanted diagnosis, and treatment; normal thinking related to FI (attributing it to aging or childbirth); avoidance/denial, hoping the symptoms would resolve on their own; life impact of the incontinence being minimal overall or in relation to other competing medical issues; embarrassment/shame; self-blame about the cause of incontinence; sigma related to talking about FI; isolation (both literal and emotional); provider barriers including interpersonal relationships, gender and previous negative experiences with providers; and access limitations including financial, transportation, need to take time off work, and the need to see a specialist. Three overarching themes were identified for the 12 barriers, with most barriers mapping onto more than one theme. The themes were the internalized self in relation to FI, perceptions about FI and its treatment, and interaction with the health care system. The study was of good

quality, although reflexivity and procedures to ensure rigour were not discussed.

A descriptive qualitative study used three focus groups of older women to explore the association between diet and FI symptoms and dietary strategies and modifications used to manage incontinence with the goal of using the information to inform the development of an age-appropriate, culturally competent, and socially acceptable dietary modification plans (134). The 21 participants were 65 years age or older, had FI at least monthly during the prior 3 months that was bothersome enough to desire treatment, independently managed their diet, and did not have a diagnosis or colorectal cancer of inflammatory bowel disease. All participants were aware that diet played a role in their FI.

Themes about the relationship between diet and FI were discovery of the relationship between FI and diet (often a lengthy process); dietary triggers for FI including foods and food groups (triggers varied widely and most women identified more than one trigger): methods of food preparation (included fried, greasy, spicy, rich and hot foods); and amount and frequency of food intake. Themes related to dietary modifications used to manage FI included modifications in the intake of specific foods or food groups, food preparation methods, and the timing and amount of food. Finally, themes related to suggestions for dietary modifications for FI management included the importance of health care provider input (given that shame may deter women from discussing dietary habits, providers should be more proactive in discussing diet), a balanced approach (weighing the benefits of dietary modification against the enjoyment of the foods given up), and sharing of individual experiences. The study was of good quality although there was limited discussion of procedures to ensure rigour and reflexivity was not discussed.

In a descriptive study with six individuals with FI and seven health care providers (3 surgeons, 2 physiotherapists, and 3 nurses), the investigators sought to determine what constituted success in managing FI from the perspectives of both patients and health care providers and to identify barriers and promoters of participating in treatment programs for FI (108). Barriers to care included themes of education (patient knowledge and helplessness and provider helplessness) and access (lack of treatment options, access to care, health care costs, inconvenience of care, patient compliance and patient expenses). Promotor themes that encouraged patients to seek treatment for the FI were its negative impact of quality of life, personal hygiene, activities and productivity; its psychological burden; motivation to participate in new treatments; positive expectations related to treatment; and satisfaction with available treatment options.

Patients varied in their definition of successfully managing FI including having greater control of bowel function, more confidence in relation to control and a reduction in the need to participate in FI hygiene behaviours. Among clinicians, definitions of success also varied with nurses identifying it as overall patient happiness or any improvement in bowel function, physiotherapists emphasizing functional outcomes, and surgeons defining success in terms of what the patient considered a successful treatment. The study was of good quality although there was no mention of reflexivity, participant voices were not heard for some themes and study limitations were only briefly discussed.

Another study using a phenomenological method explored the experience of having AI during the early postnatal period (7). Three women who had experienced FI following vaginal delivery and were less that 12 months postnatal participated in the study. Data were collected during individual face-to-face interviews with each woman. For these women, the essential structure of their lived experience was comprised of six key constituents: the changed bodily self, becoming familiar with the postnatal body, emotional engagement, putting the baby first, a sense of hope, and an evolving sense of self. Their experiences with FI involved coming to terms with unexpected changes in their body that sometimes could not be controlled or predicted and interfered with their new maternal role and relationships with others and caused anxiety and uncertainty. Symptoms could evoke embarrassment or fear of embarrassment especially in public settings and there was reluctance to disclose incontinence. All three women reported putting their baby's needs before their own. They described becoming familiar with their new body and their maternal role and were more or less hopeful about the possibility of recovering normal bowel function. The study was of good quality although there was no mention that data collection was based on data saturation or of an audit trail.

The final study used a narrative method to describe the emotional, social, and psychological consequences of FI following obstetric injury to the anal sphincter and to develop a 'word picture' describing the consequences of FI and the pathways to coping and recovery. The sample included 81 women referred to the first author for assessment as part of a potential negligence claim. Fourteen of these women later participated in face-to-face interviews. Data collected from the interviews as well as reviewing the written consultation records (which included quotations describing the consequences of the injuries as well as coping and recovery processes) were used to construct the 'word picture' which was reviewed and refined by a focus group (n=14 women; eight were part of the previously described sample) and a postal questionnaire group (n=25; 10 were part of the previously described sample).

During the interviews women described the following themes related to FI: feeling unclean; hiding my FI; fear of incontinence during sexual intercourse; feeling isolated, guilty or embarrassed; loss of dignity; failure as a mother and feeling inadequate as a mother; loss of confidence; no one to talk to about the incontinence; employment concerns; lack of understanding within the family; shock, stress, marriage fears, disfigurement, and feeling like a failure; and anger, pain, denial, disbelief, and feeling low. The frequency with which each was reported varied and is summarized in Table 15-7. The most common strategies used to cope with FI were repetitively washing to feel clean and planning daily activities and being aware of and having access to toilet facilities. Some women reported that focusing on daily tasks or returning to work helped them cope with their FI. Women also identified factors related to recovery and healing with the baby being critical to recovery. Other factors related to recovery and healing were sharing with and support from others and moving from anger to forgiveness and despair to being positive. The study was of good quality although there were some limitations related to the evaluation criteria. The background literature was not well developed, inclusion and exclusion criteria were not described, there was no mention of reflexivity and limited procedures to ensure rigour were described.

For the most part, the findings of studies included in this edition were consistent with the themes identified in the 5th and 6th consultations of the ICI (1, 116). Based on evidence from the new studies included in this addition, however, the theme related to relationships was expanded to include roles and an addition sixth theme was identified – facilitators and promoters of seeking treatment.

Summary of Qualitative Research on Quality of Life Associated with FI

Living with FI Related to Relationships and Roles

- Concern about experiencing FI is a threat to relationships (Level of Evidence 2), particularly new relationships (Level of Evidence 2), and participation in social events, particularly in mixed company (Level of Evidence 1).
- FI evokes feelings of embarrassment, shame and guilt and individuals express concern about who to tell about their incontinence and when. Family members, close trusted friends and co-workers are often told because the individual feels they cannot completely conceal their FI (Level of Evidence 2).
- Experiencing FI following childbirth can interfere with women's adaption to their new role as a mother (Level of Evidence 2). While women report that incontinence contributes to feelings of inadequacy as a mother, the baby was also identified as a factor in recovery and healing (Level of Evidence 2).
- Over time, women reported becoming more comfortable with their new body and maternal role and were more hopeful about the possibility of normal bowel function (Level of Evidence 2).
- Health care providers are perceived as unhelpful in providing advice with study participants reporting that misinformation or no information is commonly given (Level of Evidence 2).

Living with FI Related to Time and Planning

- Study participants reported spending a significant amount of time planning for and worrying about possible accidents (Level of Evidence 2). They used a variety of management strategies to avoid potential incontinent episodes and be prepared for unexpected accidents (Level of Evidence 2).
- Concerns about FI affect both travel and work life (Level of Evidence 2).
- While some women reported concerns related to work outside their homes, for those who returned to employment, work was also identified as a coping mechanism (Level of Evidence 2).

Living with FI Related to Bodily Symptoms, Self-Esteem and Body Image

- Feelings of shame and embarrassment related to FI were reported by participants across all studies (Level of Evidence 2).
- Men and women with FI felt stigmatized and stigmatized themselves (Level of Evidence 2).
- Men and women reported altered body image, low self-esteem, guilt, and distress and that their emotional life and self-confidence was undermined because of embarrassment (Level of Evidence 2).
- Low levels of public knowledge about FI contributed to feelings of stigma (Level of Evidence 1).
- Individuals with FI report a variety of bodily sensations and distressing symptoms associated with incontinence (Level of Evidence 2).
- Both men and women reported repetitively washing to feel clean and avoid smelling (Level of Evidence 2).
- Some individuals develop a sense of mastery and self-confidence after years of successfully managing their symptoms (Level of Evidence 2).
- Women with post-natal FI identified moving from anger to forgiveness and despair to positivity as factors related to recovery and healing (Level of Evidence 2).
- Women with postnatal FI coped by repetitively washing to feel clean (Level of Evidence 2).
- Aging and new comorbidities posted additional challenges to adapting to FI (Level of Evidence 2).

Living with FI Related to Sexuality

- Women were reluctant to discuss sexuality or the effect of FI symptoms on sexual functioning even when asked about sexuality and intimacy (Level of Evidence 2). Among those who did, some reported that there were no changes in their sexual drive while others reported a range of psychosocial issues including lack of sexual arousal or desire to abstinence (Level of Evidence 2).
- Study participants reported that health care professionals did not discuss sexuality (Level of Evidence 2).
- Women with postnatal FI reported fear of incontinence during sexual intercourse (Level of Evidence 2).

Living with FI Related to Dietary Issues

- Study participants reported using a variety of dietary alterations as strategies to deal with FI symptoms (Level of Evidence 2).
- Older women reported that shame deterred them from discussing dietary habits with health care providers (Level of Evidence 2).

Living with FI Related to Barriers and Prompters of Seeking Treatment

- New studies included in this review explored barriers and facilitators of treatment-seeking behaviour among participants with FI. Barriers identified included lack of knowledge about FI and its treatment, fear about testing and treatment; attributing FI to aging, inheritance or childbirth; and feelings of embarrassment, shame, self-blame and stigma. Health system barriers to seeking treatment included provider sex, previous negative experiences with health care providers and access-related factors including cost and needing to take time off from work for evaluation and treatment (Level of Evidence 2).
- Factors identified as promoting treatment seeking were motivation to participate in new treatments and positive expectations about the benefits of treatment (Level of Evidence 2). The life

impact of FI could serve as either a barrier or promotor to seeking treatment (Level of Evidence 2).
- Women reported that lack of knowledge about FI and its evaluation and treatment as well as fear about testing and treatment were barriers to seeking care (Level of Evidence 2).
- Attributing FI to aging, inheritance, or childbirth were identified as barriers to seeking treatment among women (Level of Evidence 2).
- The life impact of FI could serve as a barrier (if episodic, if other health issues were seen as more important) or facilitator of seeking treatment (if symptoms interfered with life) (Level of Evidence 2).
- Women identified embarrassment, shame, self-blame, and stigma as barriers to seeking care for FI (Level of Evidence 2).
- Women also identified provider and health care system barriers to seeking treatment for FI: Provider sex, a prior negative experience with a provider, access to health care including treatment-related costs, and needing to take time off work (Level of Evidence 2).
- Motivation to participate in new treatments, satisfaction with current treatments, and positive expectations about the benefits of treatments for FI were identified as promoting treatment-seeking behaviour (Level of Evidence 2).
- Clients with IBS and FI noted the services they would want to manage FI included access to bathrooms in both public and employment spaces (Level of Evidence 2).

Recommendations for Practice Related to Quality of Life Associated with FI
- Clinicians should actively acknowledge the problem of FI compassionately and initiate the assessment and discussion of FI symptoms as stigma, embarrassment and sensitivity associated with FI may impede communication and provision of therapeutic advice (Grade of Recommendation B).
- Clinicians need to recognize and eliminate dismissive or blaming responses as they can impair future care-seeking and contribute to patient distress and under-reporting of FI (Grade of Recommendation B).
- Providers should consider the facilitation of gender sensitive support groups to share practical knowledge of FI symptom management (Grade of Recommendation B).
- Health care providers should be aware of clinical interventions to improve symptoms (Grade of Recommendation B).
- Health care providers should inform pregnant women about the risk of anal sphincter injury during vaginal delivery and facilitate early assessment, support, and treatment of women who develop FI post-delivery (Grade of Recommendation B).
- Health care providers should support post natal women affected by FI with regard to their maternal role (Grade of Recommendation B).
- Health care providers should identify a condition-specific 'buddy', support group, or online forum for women with postnatal FI to share knowledge and provide support (Grade of Recommendation B).
- Providers should share practical management strategies, such as preparing cleansing kits and locating public restrooms, etc., with clients with FI (Grade of Recommendation A).
- Providers should promote self-efficacy by coaching clients on how to plan for and prevent unpredictable accidents and teaching strategies to go out confidently (such as, education on products, packing a change of clothes, disposable wipes, etc.) (Grade of Recommendation A).
- Providers should acknowledge and support the common feelings of shame and embarrassment by facilitating self-management (Grade of Recommendation B).
- Health care providers should raise awareness with clients and the general public that FI is not something to be tolerated and that it responds to conservative treatment (Grade of Recommendation B).
- Clinicians should educate patients regarding conservative symptom management: causes of FI, dietary modifications including fibre supplements, behavioural strategies such as pelvic floor exercises and biofeedback, anti-motility medications, use of absorbent products and ways to reduce odour and flatus (Grade of Recommendation A).
- Clinicians should consider sharing positive coping strategies identified by participants with other people managing the symptoms of FI (Grade of Recommendation B).
- Clinicians should consider patient's goals when developing a management plan for FI (Grade of Recommendation B).
- Clinicians should request completion of a daily stool diary when accurate information of FI severity is important (Grade of Recommendation A).
- Health care providers should consider referral to psychologists to manage the emotional impact of FI on self-efficacy, self-esteem and mood, as indicated and appropriate (Grade of Recommendation B).
- People with FI should be referred to, or informed of, other services for continence (Grade of Recommendation A).
- Providers should ask directly about the impact of FI on patients' sexuality (Grade of Recommendation B).
- Providers should ensure a comfortable, stigma-free climate in order to elucidate the impact of FI on sexuality and teach practical strategies (Grade of Recommendation B).
- Providers should enquire directly about dietary restrictions because some individuals may be reluctant to discuss these and not all strategies employed by people with FI are helpful or evidence-based (Grade of Recommendation B).
- Providers should teach successful dietary strategies, including: timing of food intake, restricting food amounts to minimize leakage, avoiding aggravating foods, increasing water intake, and increasing the consumption of yoghurt, high fibre foods or a fibre supplement (Grade of Recommendation B).
- Providers should ask specifically about FI, recognizing that individuals with FI may not report it (Grade of Recommendation A).
- Providers should educate patients about treatment options for FI (Grade of Recommendation B).

Recommendations for Qualitative Research on Quality of Life Associated with FI

The following topics are recommended for further research in this area

- Implementation and evaluation of gender sensitive support groups to facilitate sharing of practical management strategies for symptom management.
- Investigation of role-modelling effectiveness in adapting to FI.
- Investigation into living with FI long-term
- Investigation of interventions that promote enhanced self-efficacy, self-management, and increase incontinence health literacy.
- Evaluation of effect of public and work-based education campaigns on normalizing elimination and raising awareness that incontinence is a treatable condition.
- Determination of how goal setting and tailoring interventions for FI is effective in promoting adherence to a management plan
- Investigation of the use of humour as a therapeutic coping strategy for dealing with the symptoms of FI.
- Further exploration of the phenomenon of secret resignation as a method of coping by men and effective attitudes in treating these attitudes to assist them with improved communication with health care professionals and health care seeking
- Clinical trials about the effect of dietary strategies on FI
- Investigation of appropriate and effective interventions to educate and support men and women in adopting practices for managing FI and associated odour and urgency symptoms
- Investigation of the experience of having and managing FI in presence of other multiple chronic conditions and when the outcome of pregnancy is not delivery of a healthy baby
- Develop and test interventions that minimize stool leakage during intercourse.
- Investigate whether barriers to treatment seeking can be minimized by dissemination of information about FI and its treatment
- Exploration of attitudes and treatment goals of health professionals treating FI to identify barriers to effective treatment

Table 15-7. Qualitative Studies about FI

Authors, Reference, Country	Study Purpose/ Research Questions	Qualitative Design	Sample and Patient Type/ Diagnosis	Data Collection	Findings
Roe & May (544) UK	Explore the impact of faecal and urinary incontinence on sexuality and identify interventions for the management of incontinence on sexuality	Descriptive	27 adults Various causes of faecal incontinence	Semi-structured interviews and field notes	Themes: clothing and appearance; intimacy and caring; management techniques and relationships; life trajectory
Chevavanayagam & Norton (556) UK	Describe issues affecting quality of life of women with faecal incontinence	Descriptive	13 women Various causes of faecal incontinence unsuccessfully treated	Structured open-ended questions	Issues with toileting, psychological and emotional effects, timing of meals and proximity of toilets, skin excoriation and constant cleaning, difficulties while in public places such as shopping, maintaining an attractive appearance and wearing clothes that conceal pads and possible accidents, reduced exercise, issues with employment, restricted travel, limited socialization
Rozmovits & Ziebland (548) UK	Understand aspects of distress in colorectal cancer and explore the impact of the illness on identity and self-understanding	Descriptive	39 adults with loss of bowel control with and without colostomy or ileostomy Colorectal cancer	Narrative interviews	Loss of professional identity: temporal and special boundness Loss of ability to socialize: Considerable impact on travel, eating away from home and engaging in leisure pursuits Learning to manage a stoma: loss of dignity, privacy and independence, disruption of sexual identity

Authors, Reference, Country	Study Purpose/ Research Questions	Qualitative Design	Sample and Patient Type/ Diagnosis	Data Collection	Findings
Collings & Norton (545) UK	Discover psychosexual and psycho-social aspects of living with faecal incontinence to inform practice	Descriptive	20 women Various causes of faecal incontinence	Semi-structured interviews	Women with FI have ongoing stress and face potential humiliation. Strategies used for management include: fasting; pads; using own transportation; knowing the location of toilets. Faecal incontinence affects: skin care; shopping; eating; travel; appearance; employment; and socializing. Sex is not always affected but there may be fear and shame that deter single women from entering a new relationship.
Hansen et al. (136) USA	Investigate the meaning of food as a strategy for treating FI	Phenomenol-ogy	10 women living in the commu-nity with various causes of faecal incontinence	In-depth unstructured interviews	4 categories of diet strategies: restricting intake of food that worsen FI; avoiding gas-pro-ducing foods; limiting portion or meal size; and using diet and fluids as treatments Themes: restricting diet and eating patterns; eating and dealing with the consequences; treating faecal incontinence with food and fluids; lack of therapeutic guidance for diet modifications
Wilson & McColl (557) UK	Explore the quality of life, management strategies, reasons for and barriers of seeking help by participants experiencing faecal incontinence	Grounded theory	22 adults living in community with various causes of faecal incontinence	In-depth guided interviews	Five themes: impact of FI on self; response to faecal incontinence including adaptation or maladaptation; interactions with sig-nificant others; positive/negative life direction; interaction with health professionals

Authors, Reference, Country	Study Purpose/ Research Questions	Qualitative Design	Sample and Patient Type/ Diagnosis	Data Collection	Findings
Peden-McAlpine et al. (6) USA	Understand the experience of women with faecal incontinence and how they manage the problem on a daily basis	Phenomenology	10 women living in the community with various causes of faecal incontinence	In-depth unstructured Interviews	Lived space: comfort at home;limited travel outside the home; social isolation; availability of a bathroom a priority; anxiety about public accidents; productive work outside the home problematic Lived time: progression of symptoms over time; planning to prevent accidents; frequency of leakage and defaecation; urgency Lived relationality: faecal incontinence a threat to social acceptability and relationships; careful about disclosure of problem; humiliation and embarrassment at problem; caregiver responses rude and blaming Lived corporeality: management of symptoms aimed at regaining bodily functions; self-esteem suffered; attentive to body image Controlling the body out of control was essential theme.
Coterill et al. (87) UK	Identify question items for a tool assessing symptoms and quality of life of individuals with faecal incontinence	Descriptive	Qualitative interviews with 31 patients with Inflammatory bowel disease with FI Opinions from 7 clinical experts	Interviews with patients Comments by clinical experts	Assessment areas defined by clinical experts: type, amount and frequency of FI; ability to control flatus and stool; straining to evacuate;incomplete evacuation; ability to discriminate between flatus and stool; passive and urgent episodes of faecal incontinence; sensation during faecal incontinence episodes; ‘normal’ bowel pattern for the individual Free text comments ranking; toilet location; social life; hygiene/odour issues; coping strategies; fear, physical activities; embarrassment; bowel unpredictability Interview analysis key issues: unpredictability; coping strategies; and importance of sexual matters

Authors, Reference, Country	Study Purpose/ Research Questions	Qualitative Design	Sample and Patient Type/ Diagnosis	Data Collection	Findings
Johnsen et al. (554) Sweden	Describe problematic aspects of faecal incontinence to the experience of adults with Spina Bifida	Descriptive	11 adults with spina bifida and bowel problems	Semi-structured open-ended interviews	13 specific problem issues were identified in 4 broad categories: subjects spent a lot of time controlling their defaecation; problems communicating with nurses and physicians; involuntary faecal leakage contributed to social isolation; they did not feel secure in relationships; leisure time was determined by access to toilets; sense of helplessness and worry about smell, gaining control, accidents; sense of impurity, being socially unacceptable; poor self-image; decisions about bowel control were troubling (colostomy or voluntary constipation); and changing patterns
Norton & Chelvanayagam (558) UK	Describe the impact bowel dysfunction has on the lives of people with MS and to identify interventions that MS Society Members find helpful that may warrant further investigation	Survey with open-ended question	155 adults with multiple sclerosis	Free-text section on questionnaire	Faecal incontinence had a more profound effect on quality of life than constipation. Bowel dysfunction and bowel management had the greatest negative impact on quality of life, as much as difficulty with mobility.
Rasmussen & Ringsberg (547) Sweden	Elucidate how women experience what it is like to live with faecal incontinence due to childbirth complication and how they cope with that situation	Grounded theory	9 women with anal sphincter rupture during childbirth	Unstructured interviews	To have faecal incontinence due to a child birth complication is like being in an everlasting fight. To live with and cope with faecal incontinence is like having to fight to be like others, a fight against attitudes and having a constant striving for confirmation.
Manthey et al.(30) USA	Examine the management goals of individuals with faecal incontinence living in the community if total reduction of faecal incontinence would not be possible	Descriptive	189 community dwelling adults with various causes of faecal incontinence	Semi-structured interviews	Patients have numerous goals if cure is not possible. Having fewer leaks was most popular goal. One-third of patients can identify their own goals. Differences between men and women: men are more interested in not leaking stool at night and decreas ing the amount of stool leaked. Women rate having less urgency and decreasing size/amounts of pads of higher importance. Younger participants are more interested in elimination of leakage of stool during sex and lessening worry.

Authors, Reference, Country	Study Purpose/ Research Questions	Qualitative Design	Sample and Patient Type/ Diagnosis	Data Collection	Findings
Peden-McAlpine et al. (5) USA	Describe the life experience of men managing faecal incontinence	Phenom-enol-ogy	11 men living independently, managing frequently occurring faecal incontinence for 1 year minimum	Interviews	Essential theme: Secret Resignation -- Men accept FI as normal, limit activities outside the home, associate FI with aging, and accept the changes in their body image. Did not generally employ self-care strategies or use product
Dibley & Norton (550) UK	Understand the experiences and concerns of people with IBD and faecal incontinence To understand factors that influence help-seeking and needs or desires for continence services	Mixed methods Reflexivity, rigor, and study limitations not described by authors. New insights for persons with IBD and faecal incontinence regarding urgency and need for quick public access to toliets	28 adults with IBD Diagnosis; 583 questionnaire responses	Free-text responses to survey Interviews	7 themes: FI has intense negative emotional and psychological impact; feelings of stigma; limited life activities; 5 predominant symptoms; practical coping mechanisms; access to toilet facilities; and fear of faecal incontinence
Norton & Dibley (552) UK	Understand the experiences and concerns of people with IBD and faecal incontinence Understand factors that influence help-seeking and needs or desires for continence services	Mixed methods	Adults with IBD Diagnosis 617 questionnaire responses	Free-text responses to survey	Minority sought help for faecal incontinence because: thought nothing could be done, did not know who to ask, did not know of specialist services or thought it was too insignificant a problem. Desired services included public and social issues (e.g., employer awareness, access to toilets) and health services to cope with emotional aspect, better designed products and well-informed and sympathetic specialists

Authors, Reference, Country	Study Purpose/ Research Questions	Qualitative Design	Sample and Patient Type/ Diagnosis	Data Collection	Findings
Wilson (551) UK	Determine changes that had taken place since first study Focused on adaptation and establishing the factors for adaptation	Descriptive	5 men and 6 women with faecal incontinence of various causes	In-depth guided interviews based on topic guides directed by the initial study findings Emerging topics were explored where relevant.	The major theme identified is the quest for control. Sub-themes include: other chronic conditions: additional adversity or providing perspective (control in context), adaptation in the presence of obstacles: downgrading aspirations and making the best of it (re-evaluating control), Meaningful support: significant others (sharing control), Interaction with health professionals: from passive recipient to expert patient (taking over control); Interactions with others with FI: from advice seeker role model (inspiring control), Interaction: the generalized other (outwardly in control).
Olsson & Bereto (546) Sweden	Identify and describe the lived experience of persons living with FI and show how it affects daily life	Interpretive Phenomenol-ogy	5 women with faecal incontinence regardless of cause or severity	Unstructured interviews	Four themes: self-affirmation; guilt and shame; limitations in life; personal approach Leaked faeces, associated odour and worry about these problems occurring continue to be concerns and sources of guilt and shame
Wilson (549) UK	Report on a 10 year follow up study exam-ining the challenges associated with living with faecal incontinence and different ways of managing the condition, including the importance of social support.	Grounded Theory	3 men and 6 women with various causes of faecal incontinence	Semi-structured guided interviews	The core category was impact and response to FI. Sub-categories included: interaction with the generalized other; interaction with significant others; interaction with insiders The follow up study after 10 years of living with faecal incontinence posed challenges to adaptation. Adaptation was ongoing and faecal incontinence was not always the dominant issue. New self-management strategies were identified.
Brown et al. 2017 (555) US	To describe barriers to care seeking for FI	Descriptive	39 Community dwelling women who experienced FI unrelated to acute diarrhoea during the prior 3 months and were not currently receiving treatment (they may or may not have sought care in the past)	Six focus group (4-8 women/ group) and 10 in-dividual cognitive interviews	12 barriers to seeking care were identified that encompassed three overarching themes. The themes were: the internalized self in relation to FI, perceptions about FI, and interactions with the health care system. The 12 barriers were: (1) lack of knowledge about FI, (2) lack of knowledge about testing/ treatment, (3) fear of testing/ treatment, (4) normative think-ing, (5) avoidance/denial. (6) life impact, (7) embarrassment/ shame, (8) self-blame, (9) stigma, (10) isolation, (11) provider barriers, and (12) access limitations.

Authors, Reference, Country	Study Purpose/ Research Questions	Qualitative Design	Sample and Patient Type/ Diagnosis	Data Collection	Findings
Andy et al. 2020 (134) US	To identify dietary modifications used by older women to manage FI	Descriptive	21 women age 65 years and older with FI at least monthly over the prior 3 months that was bothersome enough to seek treatment and who controlled their own diet intake and who did not have a diagnosis of colorectal or anal cancer or inflammatory bowel disease Recruited from urogynaecology and geriatric practices.	Focus groups of 3 to 7 women	Themes identified were: discovery of the relationship between FI and diet; dietary triggers for FI including foods and food groups, methods of food preparation, and amount and frequency of food intake; dietary modifications used to manage FI which included specific foods or food groups, preparation methods, and the timing and amount of food; and suggestions for dietary modifications for FI management which included the importance of health care provider input, of a balanced approach, and sharing of individual experiences.
Helewa 2017 (108) Canada	To identify success from the perspective of patients and health care providers and barriers to promoters that could impact the success and sustainability of a percutaneous tibial nerve stimulation program	Descriptive	6 patients who failed conservative treatment for FI (cause not specified) and were interested in additional treatment; recruited from a colorectal surgery clinic	Patients: interview Clinicians: group interviews with one surgeon interviewed individually	Three broad categories of themes were identified: barriers to care, promoters of care and successful definition of FI management. Barriers to care included themes of education (patient knowledge and helplessness and provider helplessness) and access (lack of treatment options, access to care, health care costs, inconvenience of care, patient compliance and patient expenses). Promoter themes that encouraged patients to seek treatment for FI were its negative impact on quality of life, personal hygiene, and activities and productivity; its psychological burden; motivation to participate in new treatments; positive expectations related to treatment; and satisfaction with available treatments. Definitions of success varied among clinicians with nurses identifying overall patient happiness or any improvement in bowel function, physiotherapists emphasizing functional outcomes, and surgeons defining success in terms of what the patient considered a successful treatment. Patients varied in their definitions of success including greater control of bowel function, more confidence in relation to control and reduced needs to participate in ongoing FI hygiene behaviours.

Authors, Reference, Country	Study Purpose/ Research Questions	Qualitative Design	Sample and Patient Type/ Diagnosis	Data Collection	Findings
Hutchens et al. 2020 (7) UK	To describe the lived experience of having FI during the early postnatal period	Interpretive Phenomenology	3 women with FI following vaginal delivery and were within 12 months post-natal regardless of the frequency or resolution of incontinence	Individual interviews	Experiences with FI involved coming to terms with unexpected changes in their body that sometimes cannot be controlled or predicted. This interfered with their new role as mother and relationships with others and caused anxiety and uncertainty. Symptoms could evoke embarrassment or fear of embarrassment especially in public settings and there was reluctance to disclose the incontinence. All three women reported that their baby's needs before their own. The women described becoming familiar with their new body and their maternal role and were more or less hopeful about the possibility of recovering normal bowel function.

Authors, Reference, Country	Study Purpose/ Research Questions	Qualitative Design	Sample and Patient Type/ Diagnosis	Data Collection	Findings
Keighley et al. 2016 (559) UK	To describe the emotional, social and psychological consequences of FI after obstetric injury to the anal sphincter and to construct a 'word picture' to describe the consequences of FI and the pathway toward coping and recovery	Narrative	Women with FI following obstetric anal sphincter injury Three samples: (1) 81 women with FI referred for assessment as part of a potential negligence claim (2) 14 women from the first sample who completed a series of face-to-face interviews (3) a focus group of 14 women (6 from sample 1, 2 from sample 2 and 6 who were not part of either previous sample); and (4) 25 mothers with FI consisting of 15 new women and 10 from the case study sample. Data from samples 1 and 2 were used to develop the preliminary 'word picture' which was reviewed and refines by samples 3 and 4	Review of written documentation from legal consultations (sample 1) and face-to-face follow-up interviews with the 14 women in sample 2 Women is samples 3 and 4 reviewed and revised the 'word picture' developed from data collected from samples 1 and 2	Themes described during the face-to-face interviews and the frequency that they were reported: • Feeling unclean (n=14) • hiding my condition (n=13), • fear of incontinence during sexual intercourse (n=12) • feeling isolated, guilty and embarrassed n=9 for each) • loss of dignity (n=7) • failure as a mother (n=6) and feeling inadequate as a mother (n=4) • loss of confidence (n=5) • no one to talk to about condition (n=4) • employment concerns (n=3) • lack of understanding within family (n=3) • shock, stress, marriage fears, disfigurement, feeling like a failure (n=2 for each)anger, pain, denial, disbelief, feeling low (n=once each) Coping strategies described: • repetitively washing to feel clean • plan day and being aware of and having access to toilet facilities • focusing on daily tasks • returning to work Factors related to recovery and healing • the baby • having a plan • sharing • moving from anger to forgiveness and despair to being positive • support from others

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COMMITTEE 16

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I. INTRODUCTION

Treatment for faecal incontinence is based upon a number of considerations, including symptom severity, particular pathophysiological findings (e.g. structural integrity of the anal sphincter) and, for surgery, whether non-surgical measures have already failed.

As a starting point, non-surgical approaches are applicable to most patients with incontinence. These treatments, including biofeedback, pelvic floor muscle therapy, percutaneous tibial nerve stimulation, may be delivered in surgical clinics and are discussed in detail in Chapter 15. This chapter addresses treatments that are generally considered to require surgical intervention and which vary in their magnitude from minimally invasive to reconstructive surgery.

Historically, the most widely accepted surgical therapy for faecal incontinence has been overlapping sphincteroplasty, respecting the long-held functional primacy of anal sphincter integrity above other factors and the evident link between incontinence and direct sphincter damage during childbirth. This approach has changed, not least as the contribution of anal sphincter injuries is now better understood (particularly those that are not grossly evident on basic inspection), and may be less important than more subtle changes in anorectal sensorimotor function that occur with age, late pregnancy, childbirth, and other conditions.

Although sphincteroplasty is well established, paradoxically, the evidence to support its use is less robust than that supporting newer treatment options. Sphincteroplasty is useful only in cases in which there is an anatomical anal sphincter defect. Sphincteroplasty provides satisfactory results in most patients, however the results deteriorate significantly with time.

Several operations were developed to treat patients whose native sphincter was either intact but weak, or not amenable to repair. Parks conceived the postanal repair to accentuate the anorectal angle in patients with incontinence due to pelvic neuropathy. Muscle transposition procedures using either gluteus maximus or gracilis were devised to create a new sphincter (neosphincter), the latter being augmented by electrical stimulation of the neosphincter (dynamic gracilloplasty). Both failed to gain popularity outside a few pioneering centres and are rarely performed today. An artificial anal sphincter was devised as a salvage procedure for patients who had failed or were not candidates for standard therapy. A simplified magnetic bead artificial sphincter was also developed for this purpose. All have fallen from grace mainly as a consequence of surgical complications, poor long-term outcomes (or both).

Over the past 25 years, sacral neuromodulation (SNM) has become the first line surgical approach for most patients with intact or minimally disrupted anal sphincters in whom non-surgical measures have failed. A wealth of data, albeit almost all observational, attest to the general success of SNM in reducing or curing symptoms in the long-term for more than 50% patients. Such success comes with very little surgical risk but not inconsiderable direct costs. Data are awaited to address effect size in well-powered multicentre randomised trials and detailed mechanistic studies may help future selection of patients.

There has been considerable interest in the development of other minimally invasive approaches to faecal incontinence for patients with less severe symptoms. These include the use of injectable biomaterials, radiofrequency energy treatment, and pelvic sling procedures. The use of autologous muscle cells to augment residual anal sphincter function is also gaining traction, as in other areas of regenerative medicine.

Several important caveats apply to the interpretation of the results of surgery for faecal incontinence as reported in the literature. First, most reports contain only observational data, and the majority of these are uncontrolled case series. Prospective high-quality cohort studies are uncommon and often have significant issues of bias such as attrition over time; randomised controlled studies are rare, and those reported usually include insufficient numbers of patients to claim statistical power for their observations.

Secondly, there has been no standardisation of core outcomes for faecal incontinence with little sense of what defines a “successful” outcome beyond arbitrary suggestions e.g. 50% reduction in incontinence episodes. On this basis a critical review of existing outcome measures is included in this chapter.

Finally, the quality of data reported is variable, though this has generally improved in more recent studies. Chart review has been supplanted by patient questionnaires and interviews by independent data auditors. Daily continence diaries, a more stringent form of data collection, have become increasingly used (although not routine) and are now being digitalised to improve compliance. A recent systematic review has highlighted many of their limitations[1]. Notwithstanding, clinical guidelines published by the American College of Gastroenterology[2], Rome committee[3] and the American Society of Colon and Rectal Surgeons[4] provide a framework under which to consider the evidence available to support clinical decision-making regarding surgical treatments for faecal incontinence.

1. SCOPE AND REPORTING

In contemporary surgical management of faecal incontinence the surgeon has relatively few options at his/her disposal. Many procedures are now only of historical interest because they are recognised to be of limited value or, in the case of some devices, have been withdrawn from the market. While, previous iterations of this chapter have covered such procedures in considerable detail[5], this chapter has been considerably modernised. **Table 1** provides an overview of present and past surgical approaches (termed contemporary and historic for want of better descriptors) and these have been separated in the ensuing text for reader clarity. Procedures falling under the historic category have been given appropriate brevity and readers wishing to explore these interventions in more detail should refer to previous editions of the Consultation..

2. SEARCH METHODS

A PubMed search was conducted to identify studies published on the use of surgery for faecal incontinence. Keywords used were faecal (fecal) incontinence and surgery. Full text copies of studies deemed to be potentially relevant were obtained. Priority was given to systematic reviews, randomised controlled trials, and controlled clinical trials; if those were unavailable or inadequate, observational designs were considered including cohort and case-control studies. In several instances, the search was limited to poor quality observational data such as case series. Reviewers were not blinded to names of studies’ authors, institutions or publications. In view of the nature of the guideline, priority was given to the reports with large number of patients and longer follow-up periods. Particular emphasis was placed on those reporting functional outcomes including quality of life after surgery.

Table 1. Scope and reporting: contemporary and historical surgical approaches for faecal incontinence

Contemporary procedures	**Year**	**Comments**
Sphincter repair (primary)	Unknown	Repair at time of injury is optimal and is performed worldwide by obstetricians and colorectal surgeons
Anal sphincteroplasty	1923 - date	End-to-end (Lockhart Mummary); overlapping (Blaisdell 1940)
Sacral neuromodulation	1994 - date	Most commonly performed surgical procedure for faecal incontinence
Injectable biomaterials	1993 - date	Variety of agents and sites of injection
Posterior anal (puborectal) sling	1974 - date	Several slings trialled over time
Temperature-controlled RF energy	1999 - date	Reducing popularity: no published reports since 2015
Autologous cell therapies	2010 - date	Under evalauation; several ongoing clinical trials
Stoma	2000	Still recommended for end-stage faecal incontinence
Historic procedures	**Year**	**Comments**
Post-anal repair	1975-1990s	Largely abandoned due to poor results
Non-stimulated gracilis neosphincter	1952-2000s	Complexity, cost and high levels of morbidity including major perineal wound and donor site complications, as well as new onset evacuation problems, have limited current use to a very small number of patients
Electrically-stimulated gracilis neosphincter	1988-2000s	
Artificial bowel sphincter	1987-2010	Withdrawn due to infection and explantation rates as well as for commercial reasons
Magnetic anal sphincter	2012-2018	Withdrawn for commercial reasons
Pudendal neuromodulation	2010 – 2015	Several promising reports in selected patient groups not followed by commercial investment

RF = radio-frequency

Non-English language papers were noted but excluded from the review unless they contained an English language abstract providing sufficient information.

II. SURGERY FOR ADULT FAECAL INCONTINENCE

1. CONTEMPORARY PROCEDURES

1.1. Sphincter Repair

Anal sphincter repair is the term used to describe primary repair of the disrupted anal sphincter following direct trauma. The most common indication is following childbirth, and repair in this situation is usually performed by the attending obstetrician. Colorectal surgeons are more commonly involved in primary repair of injury that is the result of blunt or penetrating trauma [6]. Occasionally, the anal sphincter is damaged during anorectal surgery for other anal pathology, particularly surgery for anal fistula[7].

In Western obstetric practice, the majority of women, up to 79%, experience some form of perineal laceration at the time of vaginal delivery [8]. The obstetric injury of the perineum is classified as a *first degree* tear if confined to vaginal epithelium and perineal skin, *second degree* if the perineal muscles are torn, third degree if the anal sphincter muscles (external: EAS; internal: IAS) are torn, (3a: less than 50% EAS torn; 3b: more than 50% EAS torn; 3c: both EAS and IAS torn) or *fourth degree* if both EAS and IAS and rectal or anal mucosa are torn [9]. Third- and fourth-degree tears are collectively termed “OASIS” (obstetric anal sphincter injuries) since they involve anal sphincter mechanisms. The incidence of overt OASIS is low, with a population-based cohort study reporting 3.3% for third-degree tear and 1.1% for fourth-degree tear [10]. However, they affect quality of life (QOL) with 29% of women with OASIS reporting affected QOL due to anal incontinence after OASIS [11]. When prospectively looked for with endoanal ultrasound, the actual incidence of OASIS is higher[12, 13]. A meta-analysis of 717 vaginal deliveries found an incidence of new anal sphincter defects of 27% in primiparous and 9% in multiparous women using 2 dimensional-endoanal ultrasonography (2D-EAUS)[14]. 3D-EAUS detected anal sphincter defects in 45% of 56 primiparous women, although 30% of them were asymptomatic[15]. On the other hand, the detection of over OASIS can be improved by careful examination by experienced specialists. Andrews et al [16] demonstrated that the identification of overt OASIS increased from 11% by an accoucheur to 25% (P<0.01) when women were re-examined by an experienced doctor. **LEVEL OF EVIDENCE 2.**

Women with undiagnosed OASIS have higher rates of anal and urinary incontinence, more anal sphincter defects of greater size on endoanal ultrasound, shorter perineal body length, and more reconstructive surgeries compared to women with diagnosed and repaired OASIS [17]. In a meta-analysis of 103 studies involving 16,110 women who delivered vaginally Sideris *et al* reported that OASIS were diagnosed on ultrasound in 26%, with 19% experiencing anal incontinence. In women without clinical suspicion of OASIS (n = 3,688), sphincter defects were observed in 13% and anal incontinence experienced by 14%. Following primary repair of OASIS, 55% of 7,549 women had a persistent sphincter defect, with 38% experiencing anal incontinence [18]. **LEVEL OF EVIDENCE 2.**

A systemic review of 43 studies including 716,031 parous women reported that definite risk factors for OASIS included instrumental vaginal delivery (Risk Ratio (RR):3.4, 95% Confidence Interval (CI): 2.2 - 5.2), midline episiotomy (RR 2.9, CI:1.8 - 4.7) and a persistent occiput posterior position (RR: 2.7, CI: 2.1 - 3.6). Mediolateral epi-

siotomy did not increase its risk but was also not protective against perineal laceration (RR:1.6, CI: 0.95 - 2.5) [19]. A prolonged second stage of labour, higher neonatal birthweight and shoulder dystocia were also reported as possible risk factors [10,19]. **LEVEL OF EVIDENCE 1.**

A systematic review in 2005 [20] and a Cochrane review in 2017 [21] both concluded that routine episiotomy to reduce perineal tear is unjustified, and that a selective episiotomy policy reduces the incidence of OASIS in women where no instrumental delivery is intended. It is unknown whether routine episiotomy is useful to reduce perineal tear in women who expect instrumental delivery [21], even though two studies demonstrated that mediolateral episiotomy reduced the risk of OASIS during operative vaginal delivery[22,23]. If there is need for episiotomy, mediolateral episiotomy is recommended because of the association of midline episiotomy with increased risk of injury to the anal sphincter complex.[9]. **LEVEL OF EVIDENCE 2.**

Primary repair of an obstetric tear is correctly termed "anal sphincter repair" and is frequently performed by the obstetrician immediately after delivery, most commonly in the delivery room under local or epidural anaesthetic. However, guidelines issued by the RCOG (Royal College of Obstetricians and Gynaecologists) in the UK and by the ACOG (American College of Obstetricians and Gynaecologists) [9] in the US recommend that all such repairs should be treated as surgical procedures with adequate exposure, lighting and anaesthesia in an operating theatre or suitably equipped delivery suite. By tradition, the technique of repair has been a direct oppositional repair of the severed EAS. However, an overlapping technique, as commonly used in secondary sphincteroplasty by colorectal surgeons, has been recommended as it obliges identification and adequate mobilization of the severed ends of the EAS [24]. The IAS, if damaged, is difficult to identify separately and is usually repaired en-block with the anal canal mucosa in a 3c or 4th degree tear. However, Mahoney *et al.* [25] have shown that persistence of an IAS defect is adversely associated with continence outcome following repair of a 3rd or 4th degree tear, while Roos *et al.* [26] found that women with major tears (grade 3c or 4) were significantly more likely to have ultrasound evidence of a persisting IAS or combined IAS and EAS defect following obstetric repair; these women were more likely to have poor functional outcomes. Separate repair of the IAS is recommended when the sphincter can be separately identified using a direct appositional technique[27, 28,9]. **LEVEL OF EVIDENCE 2**.

There have been six randomised clinical trials[24, 29-33], a Cochrane review[34], and a further systematic review[35] that have compared the effectiveness of primary overlapping repair versus end-to-end repair following OASIS. The results of trials are conflicting, with four finding no difference between the two procedures, one trial showing the superiority of overlap repair and one finding the end-to-end repair to be superior. The Cochrane review of the six RCTs including 588 women showed a statistically significant lower incidence of faecal urgency and lower anal incontinence score in the overlap group. The overlap technique was also associated with a statistically significant lower risk of symptomatic deterioration of anal incontinence over 12 months. At 36 months follow-up, however, there was no difference in flatus or faecal incontinence between the two procedures. The Cochrane review concluded that more evidence is needed to establish optimum technique of repair. Norderval *et al.* [36] have shown that continence outcomes in women with OASIS were improved if the entire length of the EAS was repaired, in addition to separate repair of the IAS, if a co-existing injury was found. The guideline from the ACOG states that end-to-end or overlap repair are both acceptable for full-thickness external anal sphincter injury [9]. **LEVEL OF EVIDENCE 2**.

As colorectal surgeons are, in general, quite familiar with the anatomy of the anal canal, it has been suggested that primary anal sphincter repair might be best performed by a colorectal surgeon rather than an obstetrician. Nordenstam *et al.* [37] concluded, in a single institution study of 165 women, that technique and expertise affect the outcome of primary repair and that, if needed, the repair could be safely delayed until such expertise was available. In a similar study, Soerensen *et al.* [38] found no adverse outcome with delayed primary repair. Co-operation between obstetric and colorectal surgical colleagues can result in much improved outcomes[39]. On the other hand, the ACOG guideline states that repairing and caring for perineal lacerations are part of the obstetrician–gynaecologist's training and clinical expertise [9]. It was reported that a structured hands-on training programme for obstetric trainees improved the clinical outcomes of repairs for OASIS[40]. Instructional videos demonstrating repair techniques for fourth-degree laceration have also demonstrated the effectiveness, especially for postgraduate year 1 trainees [41]. **LEVEL OF EVIDENCE: 2.**

There have been two randomised trials of post-operative management of the bowel after primary anal sphincter repair. These have shown benefit in use of a laxative rather than a constipating regimen but no advantage to the addition of a stool bulking agent[42, 43]. **LEVEL OF EVIDENCE:2**

Some alteration in faecal continence occurs in approximately 13 - 17% of women following primiparous vaginal delivery, even in the absence of a recognised sphincter tear [12, 44, 45]. The prevalence is greater if faecal urgency is included as a symptom [13]. MacArthur *et al.* [46] found flatus incontinence in 27% of 7,879 women surveyed 12 weeks after delivery. Fenner *et al*. [47] found that women who had sustained third- and fourth-degree tears were more likely to have faecal incontinence than women without anal sphincter injury 6 months following delivery. This was more pronounced in women with a history of 4th degree tear. Women with 4th degree tear in the first delivery have a higher risk of long-term anal and faecal incontinence than women with 3rd degree tear [48]. Samarasekera *et al* [49] found long-term effects on anal continence and QOL following postpartum anal sphincter injury. Oom *et al.* [50] suggested that concomitant injury to the pelvic floor may be an associated determinant of outcome, in addition to adequacy of sphincter repair. Following repair of obstetric anal sphincter injury, patients should be referred for pelvic floor physiotherapy[51, 52] **LEVEL OF EVIDENCE: 2**

Management of subsequent labour following a previous anal sphincter tear must take account of obstetric risk factors, symptoms of incontinence and patient preferences. Harkin *et al.* [53] found an approximately 5-fold increase in the incidence of recurrent sphincter tear compared to the incidence of first sphincter injury during second labour. In a meta-analysis of 8 studies including 99,042 women, Jha *et al.* [54] reported that risk factors for recurrent OASIS in women who had suffered OASIS in their previous delivery included instrumental delivery with forceps (OR 3.1, 95%CI: 2.4–4.0) or ventouse (vacuum) delivery (OR 2.4, 95%CI: 1.8–3.3), previous fourth-degree tear (OR 1.7, 95%CI: 1.2–2.3), birth weight ≥4 kg (OR 2.3, 95%CI: 2.1–2.5) and maternal age ≥35 years (OR 1.2, 95%CI: 1.0–1.4). Caesarean delivery before the onset of the second stage of labour was found to be protective[55]. However, Nelson *et al.* [56] found that pregnancy rather than delivery was more important in predicting post-partum continence. Abramowitz *et al.* [57] have confirmed in a RCT that subsequent vaginal delivery is reasonable in asymptomatic women after a previously repaired third degree tear. **LEVEL OF EVIDENCE: 3.**

Regarding the subjective satisfaction about subsequent vaginal delivery after OASIS incurred at the previous delivery, Edwards *et al.* [58] reported that among 50 women who had experienced OASIS at their previous delivery, 41 (82%) chose a subsequent vaginal delivery after counselling. Of the 50 women, including 9 who chose caesarean delivery, 27 (54%) had no regret regarding their decision about subsequent delivery, while 18 (36%) and 5 (10%) had mild and moderate/severe regret, respectively. The regret was significantly associated with older age and prevalence of faecal incontinence after the previous delivery with OASIS.

A number of studies have examined long-term outcomes after repair of 3rd- or 4th-degree tears and all have shown an increasing prevalence of continence disorders in association with greater age. These findings parallel those in the general population of parous women who have not had a recognized tear[44, 59, 60]. Fornell *et al.* [61, 62] found that subjective and objective anal function after anal sphincter injury deteriorated with time and subsequent deliveries. A persistent defect in the IAS was also found to be an important determinant, an observation supported by Mahony *et al.* [25]. In a meta-analysis of 103 studies involving 16,110 women, Sideris *et al*. [18] reported that following primary repair of OASIS, 55% of 7549 women had persistent sphincter defect with 31% and 9 % experiencing flatus and faecal incontinence, respectively. **LEVEL OF EVIDENCE: 3**

In a study of women 10, 20 and 30 years following delivery Eogan *et al.* [63] found that onset of menopause was the most significant determent of symptoms, whereas Mous *et al.* [64] found that the incidence of faecal incontinence increased with age irrespective of menopausal status. There is some evidence that hormone replacement therapy may be of value in women who develop faecal incontinence in post menopause[62]. **LEVEL OF EVIDENCE: 3**

Summary:

- Careful examination and training are recommended to improve the detection of overt OASIS (obstetric anal sphincter injuries).

Grade of Recommendation: C

- Endoanal ultrasonography is recommended to detect occult OASIS, undiagnosed at the time of vaginal delivery.

Grade of Recommendation: C

- Primary anal sphincter repair should be treated as a surgical procedure and undertaken by an experienced operator under optimal conditions. If necessary, co-operation between obstetric and colorectal colleagues is recommended.

Grade of Recommendation: B

- A structured hands-on training programme as well as instructional videos for the repair techniques of OASIS are recommended to improve clinical outcomes.

Grade of Recommendation: C

- Primary anal sphincter repair can be performed either by end-to-end or overlapping repair.

Grade of Recommendation: B

- Separate IAS repair should be considered when divided.

Grade of Recommendation: B

- Following repair of OASIS, patients should be referred for pelvic floor physiotherapy.

Grade of Recommendation: C

- Following obstetric injury, management of subsequent deliveries should take account of patient symptoms and preferences as well as obstetric factors.

Grade of Recommendation: C

- Subsequent vaginal delivery is recommended in asymptomatic women after a previously repaired OASIS.

Grade of Recommendation: C

1.2. Sphincteroplasty

The term “anal sphincteroplasty” is used to describe secondary or delayed reconstruction of the anal sphincter injury, which has either been asymptomatic at first or was not recognised at the time of injury. Anal sphincteroplasty is also offered when the outcome of acute primary sphincter repair has been unsatisfactory. Anal sphincteroplasty is usually delayed for a minimum duration of three months after the initial injury. Anterior overlapping sphincteroplasty is the most common type of reconstruction performed because of the association with obstetric injury. In this situation, the anal sphincter muscles and perineal body are separated, leaving a horseshoe type configuration to the anal sphincter mechanism with a large defect in the anterior quadrant. Occasionally, the defect is such that the anal and vaginal mucosae have healed to form a cloacal defect. Anal sphincter defects related to previous anal fistula surgery or direct trauma are usually less complex and are not associated with a deficient perineum unless there has been an avulsion injury with significant tissue loss.

1.2.1. Indications

The decision to perform anal sphincteroplasty is based on an assessment of symptoms, anorectal function, particularly the EAS contractile function, and the anatomical extent of the sphincter defect[4, 22, 65]. When the repair is considered decades after delivery, other causes of faecal continence are first excluded e.g. inflammatory bowel disease, colorectal cancer and neurological disorders. Patients with background IBS are more likely to be symptomatic than those with a more predictable bowel habit and equivalent anal sphincter defects[66]. Other caveats are covered below.

In assessing symptoms, obtaining a consistent measure of severity of incontinence and its impact on quality of life should be considered. This can be accomplished using several validated scores. The three most commonly applied are the Cleveland Clinic Florida Fecal Incontinence Score (CCFIS)[67], the Fecal Incontinence Severity Index (FISI) [68] and the St Mark’s Incontinence Score [69]. A quality-of-life instrument, such as Fecal Incontinence Quality of Life Scale[70], may also aid a fuller understanding of outcomes, although some of the questions on this scale are rather specific to the development population. **LEVEL OF EVIDENCE: 4**

Anorectal function can be evaluated objectively using different modalities, including anorectal manometry, rectal sensation, rectal compliance and pelvic floor electrophysiology including, but not limited to, pudendal nerve terminal motor latency (PNTML)[71]. Pre-operative physiological testing is helpful in the overall management of patients with faecal incontinence. However, the value of

anal manometry and pelvic floor electrophysiological assessment as prognostic indicators for outcome following sphincteroplasty is controversial, [72]. There are no established parameters that reliably predict outcome following sphincteroplasty[73, 74].

The anatomical extent of the sphincter defect can be evaluated with either anal ultrasonography or anal MRI. Multiple ultrasound modalities can be used, including transanal transvaginal or transperineal. **LEVEL OF EVIDENCE: 3**. Results of manometry, ultrasound or any other objective measurements should be applied with recognition that these examinations are often inadequate in determining the presence and/or severity of the condition[75, 76]. **LEVEL OF EVIDENCE: 4**

For symptomatic patients with >90 degrees of anal sphincter defect, anal sphincteroplasty may be appropriate. However, this requires that the defect is believed to be the main cause (pathophysiologically) of incontinence. The finding of a sphincter defect on ultrasound, decades after an injury, may simply be a residual marker of an injury that of itself is contributing little to the current problem compared with other risk factors such as ageing, obesity, general pelvic floor laxity and neuropathy. Repair of an atrophic, denervated muscle will have no benefit (akin to anywhere else in the body where tightening of striated muscles is not perfomed). Decision making in this regard is not straight-forward and is hamperedby limitations of diagnostic tests of structure and function that measure what is measurable rather than what may be most relevant to the minute-to-minute preservation of continence. Decision making is easier if there is an obvious clinical defect leading to a visible gutter, where restoration of structural integrity is intuitive. Rectal evacuation disorders should also be excluded, since these may be worsened by tightening the barrier. For all patients, a trial of non-surgical measures should usually have failed before surgery is considered[22, 65].

Preoperatively, patients should be counselled that post-operative wound healing difficulties are common. Nevertheless, the majority of well-selected patients can expect significant improvement in continence after the procedure with a mean of 66% reporting excellent or good results in the short-term[65]. There are concerns that long-term outcomes are unsatisfactory, decreasing to between 30-80% improvement at 80 months and to 6% at 120 months [77] [see below].

Concomitant repair of a cloacal defect or vaginal fistula should be undertaken [78],[79]. There is no evidence that a defunctioning colostomy or ileostomy improves outcome [80], although some surgeons employ this in certain scenarios such as significant cloacal defects or redo repairs.

1.2.2. Technique

Anal sphincteroplasty can be performed in the lithotomy position or the prone jack-knife position. Full bowel preparation is not mandatory, although most would give at least a cleansing enema pre-operatively. The conventional incision is an inverted 'V' that may be closed as an inverted 'Y' as described by Parks and McPartlin[81]. If anterior levatorplasty or rectocele repair is contemplated, a posterior fourchette incision with the patient in the lithotomy position may have advantages[82]. The external anal sphincter is usually repaired using an overlapping technique without separate identification and repair of the IAS [22]. However, there are two studies that reported good long-term outcomes of sphincteroplasty with separate suturing of the IAS and EAS[73],[83]. **LEVEL OF EVIDENCE: 3** There has been one small randomised trial of direct versus overlapping sphincteroplasty which showed similar outcomes [84]. To prevent dehiscence and subsequent failure, the two divided ends of the external sphincters must have an adequate blood supply and the reconstructive suture cannot be under excessive tension. Occasionally the EAS defect is not full thickness and overlapping repair in such circumstances would require division of the residual intact fibres to facilitate overlap. Oberwalder et al. [85] have, in a small series of patients, found that, in such cases, imbrication of the EAS is associated with outcomes similar to formal overlapping sphincteroplasty. **LEVEL OF EVIDENCE: 3**

A limited levatorplasty can be added to lengthen the anal canal and to help support the external anal sphincter repair. Great care should be taken not to narrow the vagina excessively, which can cause dyspareunia. Women should be counselled accordingly. **LEVEL OF EVIDENCE: 4**

Other adjuncts to sphincteroplasty have been assessed. Khafagy *et al.* [86] developed an overlapping anal sphincteroplasty with the injection of bone marrow aspirate concentrate. Although the combination therapy improved the anatomical and functional results, compared with the sphincteroplasty alone, only 20 patients received the injection. Larger studies are needed. Mesh interposition, although reported is no longer recommeneded for concerns around infection and erosion. **LEVEL OF EVIDENCE: 4**

1.2.3. Outcomes

The results of anal sphincteroplasty in recent series reporting more than 50 patients are given in Table 2. Dividing them into 12 studies of short-term (< 60 months) and 11 studies of long-term (≥ 60 months) follow-up, the proportion of patients who achieved good or excellent continence after sphincteroplasty was 62% on average from the 12 studies of short-term follow-up, whilst the proportion of those who maintained the excellent or good continence after sphincteroplasty was 38% on average from the 11 studies of long-term follow-up, assuming "<30%" as "30%" in the study by Lehto *et al.* [87].

Complications from sphincteroplasty include wound infection, wound dehiscence, and urinary tract infection. A US national cohort[88] using 30-day complications recorded in registry data provided figures of 5.1%, 2.1% and 1.0% respectively for these three complications. Other large single-centre series cite higher rates. In the study by Oom *et al.* [50], 39 (23%) of patients had a postoperative complication including wound infection in 35 patients resulting in an abscess in 21 patients and a fistula in 15 patients (all required further surgical treatment). Stool impaction can be a cause of complete wound breakdown and steps should be taken to mitigate against this. Complete breakdown may require stoma formation and pateints should be informed of this risk and asked to give informed consent accordingly consented.

Initial success of sphincteroplasty is related to whether the anal sphincter defect is corrected[89, 90]. Early failure is usually associated with a persisting defect identified using endoanal ultrasound[91]. This may be amenable to a redo sphincteroplasty[90, 92, 93]. There is, however, increasing evidence that continence outcomes deteriorate with long-term follow-up (above) particularly after secondary sphincteroplasty [94], [95].Evidence regardingthe effect of age at time of operation on long-term function is conflicting [96, 97]. The long-term effects of aging and menopause coupled with atrophy of the sphincters may be relevant[22, 87, 98]. **LEVEL OF EVIDENCE: 3**

1.2.4. Sphincteroplasty and sacral neuromodulation [see also SECTION II.1.3.5]

Patients with unsatisfactory clinical outcomes following sphincteroplasty may be considered, if sufficiently symptomatic, for adjunctive sacral neuromodulation (SNM)[99]. Ratto *et al.* reported that SNM

was as effective as sphincteroplasty for the treatment of faecal incontinence due to sphincter lesions [100], and in a systematic review has also demonstrated that SNM is effective for faecal incontinence associated with an anal sphincter lesion [101]. Rodrigues *et al.* [102] reported even better outcomes of SNM than sphincteroplasty for the treatment of faecal incontinence in patients with a sphincter defect. Consequently, SNM has tended to be favoured over sphincteroplasty for faecal incontinence in patients with a sphincter defect because of the complication profile and poor long-term outcomes after sphincteroplasty . By examining the surgical interventions for faecal incontinence performed at five specialist centres in Europe and one in the US between 2000 and 2013, Ong *et al.* [103] reported a changing paradigm of SNM and sphincteroplasty for faecal incontinence, showing that 95.3% of the index operations were sphincteroplasty in 2000, while in 2013 82.6% were SNM. This might be the reason why no studies of sphincteroplasty with 50 or over patients were published between 2013 and 2018, as is shown in Table 2. However, Oom *et al.*[50] concluded in a long-term study (median: 111 months) of 120 patients that anterior sphincteroplasty resulted in acceptable to excellent outcomes in 60% of patients, emphasising the ongoing important role of sphincteroplasty as a surgical treatment for faecal incontinence. Altomare *et al.* [104] also asserted that these data did not support the replacement of sphincteroplasty with SNM in patients with faecal incontinence secondary to sphincter defects. Even in the era of SNM, sphincteroplasty still deserves a place in the treatment of faecal incontinence associated with a sphincter defect, not only by improving symptoms of faecal incontinence but also by correcting the anatomical deformity due to perineal lacerations. The choice of the surgical procedure, should be made after full discussion with patients, depending on their preference and the status of their perineal deformity.

Summary:

- Clinically overt and symptomatic cloacal defects should be surgically repaired.

Grade of Recommendation: D

- The decision to perform anal sphincteroplasty in patients without an overt cloacal defect is based on an assessment of symptoms, anorectal contractile functions, and the anatomical extent of the sphincter defect as determined by EAUS and clinical examination.

Grade of Recommendation: C

- For symptomatic patients with a < 90° anal sphincter defect, conservative therapies are recommended as first line treatments.

Grade of Recommendation: D

- For symptomatic patients with a > 90° anal sphincter defect, anal sphincteroplasty is an option after conservative therapies fail.

Grade of Recommendation: C

- An overlapping repair is recommended over end-to-end repair.

Grade of Recommendation: C

- After anal sphincteroplasty, long-term follow-up is recommended as outcomes deteriorate with time.

Grade of Recommendation: B

- In symptomatic patients with unsatisfactory clinical outcomes following sphincteroplasty, sacral neuromodulation (SNM) can be recommended.

Grade of Recommendation: B

- The choice of sphincteroplasty or SNM for the treatment of faecal incontinence associated with an anal sphincter defect is to be made after full discussion with patients, depending on their preference and the status of their perineal deformity.

Grade of Recommendation: C

1.3. Sacral Neuromodulation

SNMSacral nerve stimulation (SNM)was first applied for the treatment of faecal incontinence in patients with functional deficits of the anal sphincter but no morphologic defect in 1994 by Matzel *et al.* [123]. . The concept of recruiting residual function of an inadequate anorectal continence organ by electrostimulation of its peripheral nerve supply, i.e. the sacral spinal nerves, was adapted from the field of urology in the early 1990s[124], where it has been used since 1981[125]. The rationale for applying SNM to faecal incontinence was based on both clinical observations and anatomical considerations (from the former, the beneficial effect on bowel habits and anorectal continence function and increased anorectal angulation and anal canal closure pressure seen in urological patients; from the latter, the demonstration by dissection of a dual peripheral nerve supply of the striated pelvic floor muscles that govern these functions[124], with the sacral spinal nerves being the most distal common location of this dual nerve supply). It was hypothesised that stimulating the sacral spinal nerves could both enhance physiological function and improve the symptoms of faecal incontinence.

1.3.1. Technique

SNM has become a minimally invasive technique with low morbidity. The surgical technique can be divided into two stages. As no other predictors of SNM outcome exist at present, patients are uniformly selected for operative implantation of a permanent neurostimulation device on the basis of clinical improvement during test stimulation. This first stage, percutaneous nerve evaluation (PNE), is used to confirm a satisfactory neural response and then to evaluate the clinical effect of stimulation before implantation of a permanent device. Trial stimulation is performed for 1 – 3 weeks, a period sufficient to demonstrate its therapeutic effect: commonly considered as a decrease in the frequency of incontinence episodes (documented by bowel-habit diary) by at least 50% (and reversibility after discontinuation of stimulation if temporary electrodes are removed after the trial stimulation). Two technical options are used for PNE: a temporary, percutaneously placed, unipolar test stimulation wire (or multiple wires) that are removed at the end of this phase; or operative placement of a quadripolar lead, the so-called “foramen electrode,” close to a target nerve, usually the S3 root, less frequently that of S4. The latter approach is termed the first stage of the so called ‘two-staged’ implant[126]. This electrode can stay in place and be used for permanent stimulation if the trial is effective.

A minimally invasive technique places this foramen electrode with a modified anchoring device, the so-called “tined lead,” through a trochar. This foramen electrode implant technique has been optimized by a). introducing the regular use of a softer, curved stylet to guide the electrode placement[127] and b). standardizing the surgical steps with the key elements of the use of the curved stylet, radiological imaging and marking to define the optimal entry of the electrode

Table 2. Published results of anal sphincteroplasty since 1990, including series with 50 or more

Authors (ref)	Year	Number of patients	Follow–up months	Continent % (excellent / good)	Continent %: mean (range)
Short-term follow up					
Fleshman et al [105]	1991	55	12	72	62% (41-86%)
Engel et al [106]	1994	55	15	79	
Oliveira et al [107]	1996	55	29*	71	
Gilliland et al [108]	1998	77	24*	55$	
Young et al [109]	1998	54	18*	86$	
Karoui et al [110]	2000	74	40	47	
Osterberg et al [111]	2000	51	12	58	
Morren et al [112]	2001	55	40	56	
Tan et al [82]	2001	50	28	50	
Norderval et al [113]	2005	71	27	41	
Gleason et al [114]	2011	74	32	77	
Berg et al [83]	2019	111	45*	64	
Long-term follow up					
Londono-Schimmer et al [115]	1994	94	60	50	38% (6-80%)
Malouf et al [116]	2000	55	77	49	
Halverson and Hull [117]	2002	71	69	25	
Bravo Gutierrez et al [118]	2004	130+	120	6	
Zorcolo et al [119]	2005	93	70*	55	
Trowbridge et al [120]	2006	86	67	11	
Barisic et al [121]	2006	65	80*	48	
Maslekar et al [73]	2007	64	84*	80	
Oom et al [50]	2009	120	111*	38	
Lehto et al [87]	2013	56	89*	<30**	
Turel et al [122]	2019	146	79	49	

** Median follow-up; + 130/190 available for 10 year follow-up; $ defined as "successful"; ** Overall im-proved symptoms in regard to solid, liquid and flatus*

Summary:
Anal sphincteroplasty should be considered in symptomatic patients with a defined defect in the external anal sphincter. Overlapping EAS repair is usually performed. Results of sphincteroplasty appear to deteriorate with time. Redo sphincter repair may be feasible in patients with a poor continence outcome. Grade of Recommendation: C

into the sacral foramen and its progression through the foramen. Exact placement of the electrode is monitored by a combination of a typical appearance in imaging/fluoroscopy and achieving specific motor/sensory responses with stimulation[128]. The aim of the modified electrode placement technique is to ensure close electrode proximity to the target nerve providing a higher likelihood for optimal effect with less energy consumption (better battery longevity), more programming options with more electrode contacts close to the nerve and reduced likelihood of side-effects. This lead placement using a novel standardized flouroscopy-guided technique has been recently validated by an anatomical study demonstrating that this implantation technique enables a close contact between electrode and nerve[129]. Preliminary data indicate that with electromyographic recordings the placement of the electrode can be guided to achieve better pelvic floor muscle response to stimulation[130]. EMG-guided electrode placement confirms the upper medial quadrant of the foramen as the optimal entry point for electrode placement [131].

The therapeutic outcome for permanent SNM appears to be best when both sensory/anal motor and toe flexion responses are achieved during test stimulation[132], although threshold for motor reaction of the pelvic floor/anal sphincter during acute testing should be lower than for a potential concomitant reaction of the ipsilateral toes/forefoot[128]. For screening, both types of leads are connected to an external pulse generator, the tined lead with a percutaneous extension cable.

If the screening test is successful, the second stage is implantation of the neurostimulator. Patients with a temporary lead and a successful test require simultaneous implantation of the pulse generator and the quadripolar tined lead. Those with a tined lead foramen electrode already in place for screening will undergo removal of the percutaneous extension before placement of the pulse generator.

Bilateral placement of foramen electrodes remains the exception,

based either on improved outcome of bilateral stimulation during the screening phase[133] or on conceptual considerations[134]. A study exploring the benefit of bilateral over unilateral SNM had to be discontinued prematurely after an interim analysis of 20 patients demonstrated no additional benefit in symptom score, quality-of-life score, or findings on anorectal manometry[135].

The pulse generator is placed subcutaneously, usually in the gluteal area or under certain circumstances in the abdominal wall. It is activated and stimulation parameters are set early after surgery by telemetry; it can be deactivated by the patient with a small, handheld device commonly referred to as a "patient programmer." The patient programmer also offers the ability to vary among four preset stimulation protocols.

Recently, rechargeable and conditional magnetic resonance imaging (MRI)-safe devices have been introduced in both Europe and USA. Preliminary data indicate that the clinical effectiveness of this system appears to be similar to that of the current recharge-free device[136]. The advantages of full-body MRI-safe devices are obvious: up to 23% of SNM explantations in urology are currently due to the need for MRI[137]. Certain groups of patients, requiring regular MRI examinations for disease monitoring (such as multiple sclerosis), surveillance (such as LARS syndrome after rectal resection for cancer) or those with chronic spinal disease may benefit for the availability of MRI safe device.

Issues related to the recharging of pulse generators, device size, device longevity, treatment compliance, disease awareness and patient preference will determine patient decision making and acceptance[138].

1.3.2. Patient selection and contraindications

Over the years, the indications for SNM have gradually expanded and a variety of causes of faecal incontinence are now successfully treated with SNM. During the initial SNM experience, only patients presenting with deficient function but no morphologic defect of the striated anal sphincter and levator ani were eligible[123, 139, 140]. However, because of the high predictive value of a positive test stimulation, a more pragmatic, trial-and-error approach to patient selection evolved. Patients are now selected for SNM based upon PNE results rather than conceptual considerations of the potential mechanism of action. Test stimulation is indicated, not by an underlying pathophysiological condition, but by the existence of an anal sphincter with reduced or absent voluntary squeeze function with or without a sphincter defect. An intact nerve-muscle connection is preferably present and may be confirmed by intact anocutaneous reflex activity or by muscular response to pudendal stimulation with the St. Mark's electrode[141]. **LEVEL OF EVIDENCE: 3**

The two-stage technique offers an opportunity to test treatment efficacy before proceeding to permanent implantation, and a positive test stimulation is the only reliable method for selecting patients who will likely benefit from permanent therapeutic stimulation. Various studies have attempted to identify potential preoperative predictors that can be used to identify the ideal patient for SNM therapy. In a study by Gourcerol *et al.*[142], older age was the only variable related to success of temporary stimulation. This was confirmed in a study by Govaert *et al.*[143] but contradicted in a study by Maeda *et al.*[144] where increasing age was an independent risk factor for treatment failure. Several other studies could not confirm that patient age had any predictive value[145-147].

In another cohort analysis, the need for repeated temporary procedures was associated with failure during the screening in univariate and multivariate analysis[145]. This was confirmed by Govaert *et al.*[143]. A low threshold to obtain motor response during temporary lead placement was revealed to be associated with improved outcome only in univariate, but not in multivariate, analysis. In 244 patients undergoing test stimulation with a success rate of 78.3%, Maeda *et al.* [144] determined that low amplitude of the sensory threshold during PNE and lead placement anterior to the sacral cortex were positive predictors of PNE outcome. No other demographic, physiological or morphological variable (motor response threshold) was a negative predictive factor. Evidence of anal sphincter injury related to a greater risk of failure of SNM will be addressed in a separate paragraph in this chapter. Briefly, the results are variable but the overall conclusion is that a morphologically intact sphincter is not mandatory for successful SNM[99, 143, 148, 149].

In a cohort of 200 patients from 6 centres with permanent SNM [146] only loose stool consistency, a history of diarrhoea management by medical treatment, and low stimulation intensity were associated with improved medium-term outcome. Multivariate regression analysis confirmed that stool consistency and stimulation intensity were independent predictive factors of success or failure of SNM.

The prognostic value of preoperative anorectal physiology testing is controversial. In a cohort of 45 consecutive patients, temporary stimulation was successful in 32 (71%). At a median follow-up of 33 months, the neurostimulator remained in place in 25 (55%) and active in 23 (51%). No statistically significant differences were found in characteristics, including anorectal physiological workup, of the 32 patients who underwent implantation and the 13 who did not or in those 23 with a functioning stimulator[150]. In another study including 60 patients preoperative anal resting and squeeze pressures, rectoanal inhibitory reflex, minimum sensory threshold, and pudendal nerve terminal motor latency did not correlate to patient outcome following treatment with SNM[151].

The vast majority of studies exploring predictive factors for a successful outcome of SNM were not able to detect convincing correlations. In a single centre study, at 3-year follow-up with 33 (of 66) patients with a ≥ 30% improvement in Cleveland Clinic Incontinence score (CCIS), Roy *et al.* were unable to demonstrate any predictive factor of success, based on preoperative and postoperative assessment[147]. In a study from four European centres of 228 patients with chronic SNM, Altomare *et al.* could find no determinant of success at follow-up of ≥ 60 months[152]. Factors investigated included: demographics, technique, symptom severity and cause (age, sex, PNE vs. tined lead test, implant side, implant site, sphincter lesion, extension of sphincter lesion, incontinence type and baseline episodes of incontinence, CCIS, and St. Mark's incontinence score). Factors associated with a significantly lower failure rate over the long term included a reduction of six incontinence episodes per week and eight Cleveland Clinic and St. Mark's score points during test stimulation[152].

In a retrospective analysis of prospectively obtained data from 84 patients, Prapasrivorakul *et al.*[153] found less success at one-year follow-up in patients with a coexisting high-grade internal rectal prolapse (HIRP Oxford Grade III and IV) when compared with those without HIRP (FISI 37 to 23; $p < 0.01$ vs. 38 to 34 $p= 0.16$). In a univariate analysis, concomitant rectocele, enterocele and HIRP were found to be associated predictors of outcome of permanent SNM; in multivariate analysis only HIRP was predictive[153]. In a recent study including defecography preoperatively, the only predictive factor for a favourable outcome of SNM was an increased anorectal angle at rest. The presence of intussusception was not a predictive factor of success or failure[154].

In general, results from numerous studies on predictive factors are inconclusive and none of the variables usually considered in preoperative evaluation are of any help in selecting the appropriate patient for chronic SNM. **LEVEL OF EVIDENCE: 3**

Contraindications to SNM include abnormalities of the sacrum preventing adequate electrode placement (such as spina bifida), skin disease at the area of implantation, trauma sequelae with micturition disorders or low bladder capacity, pregnancy, bleeding complications, psychological instability, limited cognitive function that interferes with the operation of the neurostimulation device. A case series has shown the relative safety of the use of SNM in the presence of a cardiac pacemaker when monitored intraoperatively. If the distance between the devices is greater than eight inches, interference is unlikely[155, 156]. **LEVEL OF EVIDENCE: 4**

1.3.3. Mechanism of action

The mechanism of action of SNM remains uncertain. Electrode positioning is guided by clinical observation of motor striated pelvic floor musculature response to stimulation of the sacral spinal nerves. For two decades it has been postulated that the clinically observed inward bellows response indicative for a contraction of the pelvic floor musculature to sacral spinal nerves stimulation is correlated to oligosynaptic and polysynaptic reflex responses mediated by afferent input to the spinal cord[157, 158]. Recent findings challenge this idea: recordings of intramuscular needle EMG of the anal sphincter and intravaginal surface EMG with latencies measurements indicate that the inward bellows movement observed by stimulating the sacral spinal nerves is not reflex mediated, but a direct efferent stimulation resulting in pelvic floor contraction. In addition to the direct motor response, oligosynaptic reflex and polysynaptic reflex responses can occur[130].

Clinical outcome has been seen to correlate with results of anorectal physiology studies, but the effect of chronic stimulation varies greatly among published reports[141, 159]. Data monitoring colorectal and anal function are in part contradictory and inconclusive and sometimes irreproducible. The effect appears to be somatomotor[160-166], somatosensory[160, 167, 168], autonomic nervous system-based[160, 162, 166], and mediated by somatovisceral reflexes[169, 170]. The effects do not appear to be limited to the continence organ *per se*, but also to the central nervous system: corticoanal excitability in patients with faecal incontinence was found to be reduced with SNM[171]; in successfully treated patients cerebral somatosensory evoked potential (SEP) latencies were higher at baseline than in the normal population, whereas they were normal in patients with SNM failure. Success was also associated with a fall of the SEP latency to the normal range after one month of SNM at 40 Hz[172]. SNM induces changes in anal representation on the primary somatosensory cortex[173]. The effect on the CNS induced by SNM changes during its course: at its initiation, changes are seen in the contralateral frontal cortex, reflecting focus attention; subsequent changes are found in the ipsilateral caudate nucleus, an area related to learning[174]. Qualitative changes in anal, rectal and colonic motility - i.e., reduction of spontaneous rectal motility complexes[175, 176], spontaneous anal sphincter relaxation[175], reduction in antegrade transport from the ascending colon[177] or no change[178], and increased retrograde transport from the descending colon at defecation[177, 178], increase rectal perception thresholds[160, 167, 168] and improved pelvic floor contraction during SNM[168]. The findings on rectal capacity with SNM have been inconsistent: unaltered [168, 179, 180] or increased [175, 181]. No changes in gastric retention, gastric emptying, small bowel transit or colonic passage have been seen with scintigraphic measurements during SNM[182].

A review indicates that physiological functions outside the anorectum are influenced by stimulation of afferent nerve fibres via the sacral spinal nerves[159] although gating effects on corticoanal and spinobulbar pathways are almost certainly important as in the bladder[183]. The mechanism of action is most likely multifactorial and dependent on the underlying condition. **LEVEL OF EVIDENCE: 4**

1.3.4. Outcomes

The results of permanent SNM after pragmatic, trial-and-error, patient selection are shown in **Tables 3-5**. Most studies have included patients with heterogeneous pathophysiology, and they vary with regard to design and patient number, but there is general agreement regarding the test stimulation for selection for permanent implant. Quantitative measures are used to describe the clinical benefit, such as change in CCIS, days with incontinence episodes or absolute numbers of incontinence episodes per period of observation, ability to postpone defaecation (in minutes), percentage of improvement, and quality of life. Even though published reports differ with regard to patient population, a general pattern of outcome can be observed: when compared with baseline status, the clinical outcome is significantly improved. Outcome reporting increasingly includes both PP and ITT analyses.

In a first multicentre prospective trial of SNM adherent to the initial, confined spectrum of indications, Matzel *et al.*[139] reported 37 patients, 34 of whom underwent a permanent implant. Not only was the frequency of incontinence episodes and the CCIS score improved significantly, so was the ability to postpone defaecation. These effects were attained immediately. Since then, multiple case series and retrospective reports have been published, but the number of randomised controlled trials is small.

The US pivotal cohort study by Wexner *et al.* [184] confirmed the efficacy of SNM in reducing symptoms of faecal incontinence: of 112 patients with permanent SNM followed for a mean of 28 months (2-69), 83% experienced a ≥50% improvement, including 41% who gained complete continence (at 12 months). Mellgren *et al.* [185] reported on the same cohort after a mean follow-up of 3.1 years (0.2 – 6.1 years). With a complete or partial data set available in 64% of the patients, a ≥ 50% reduction of incontinence episodes was seen in 86% of these, with 40% achieving perfect continence. Symptom improvement resulted in improved quality of life, which was stable over follow-up. If a “last observation carried forward analysis” is performed, the 50% reduction of symptoms at 3 years is a 78% success rate; in a ‘modified worst-case analysis’ with all missing data classified as failure--the success rate at 3 years is 59%. Again, this same cohort was reported upon at follow-up ranging from five years (63% of patients) to more than eight years: faecal incontinence episodes per week decreased from 9.1 (mean at baseline) to 1.7 at 5 years; 89% reported a ≥ 50% improvement of incontinence (36% complete continence). After 5 years, therapy was active in 81% of the patients[185].

In a systematic review including 61 publications from 2001 to 2012, Thin *et al.*[186] found higher median rates of ≥50% improvement in incontinence episodes/week when patients’ data were analysed “per protocol” (PP) (i.e., implantation after a successful test period) than when the denominator for analysis was PNE (i.e., comparable to “intention-to-treat” [ITT] principles): short-term (median 12 months) 79% (69-83%) vs. 63% (33-66%); medium-term (25 months) 80% (65-88%) vs. 58% (51-81%); long-term (56 months) 84% (75-100%) vs. 54% (50-58%). In the ITT analysis only two studies comprising 86 patients were long-term. Perfect continence was likewise greater in the “per protocol” analysis than in the ITT: short-term 42% (21-68%) vs. 36% (8-68%); medium-term 44% (5-74%) vs. 32% (4-

72%); long-term 35% (4-52%) vs. 20% (2-48%). The CCISs were also significantly improved and remained stable over follow-up.

A summary of the published long-term outcome of SNM up to 2015 included 12 studies with a median follow-up of 85 months in 745 patients[152]. As in the report of Thin et al. [186], improvement (≥ 50% reduction in incontinence episodes) was greater on PP than on ITT analysis: median 78% (21–96%) vs. 50% (42–89%). Full continence was also greater: median 36% (4–52%) vs. 20% (2–48%).

In a meta-analysis of publications from 2000-2008, comprising 790 patients, 28 studies compared incontinence episodes per week before and with SNM, and 14 studies compared incontinence scores. Both outcome criteria were significantlyimproved. Another nine studies documented the ability to postpone defaecation, and this criterion also was significantly improved[187]. **LEVEL OF EVIDENCE: 2**

Whereas cohort studies and observation studies are numerous, only a limited number of randomised controlled trials of SNM for faecal incontinence could be included in a Cochrane review from 2015: four crossover trials and two parallel group trials[188]. In a randomised controlled trial of patients with severe faecal incontinence, Tjandra *et al.*[189] compared the effect of SNM at 12 months with that of supervised optimal medical therapy comprising pelvic floor exercises, bulking agents, and dietary manipulation. In 53 patients, permanent SNM was significantly better than conservative treatment in 60 patients: CCIS 1.2 vs. 14.1; incontinence episodes/week 3.1 vs 9.4; days with incontinence/week 1 vs. 9.4 (mean difference −5.20, 95% confidence interval [CI] −9.15 to −1.25 at 3 months; MD −6.30, 95% CI −10.34 to −2.26 at 12 months); lifestyle 3.31 vs. 2.31; coping/behaviour 2.68 vs. 1.86; depression/self-perception 3.25 vs. 2.64; embarrassment 2.76 vs. 1.78.

In a parallel group trial with 6 months' follow-up carried out by Thin *et al*., patients were allocated to receive either SNM or percutaneous tibial nerve stimulation (PTNS)[190]. Participants (N = 15) who underwent permanent SNM had had a two-week test stimulation period demonstrating at least a 50% reduction in faecal incontinence. Compared with the PTNS group, they experienced fewer episodes of faecal incontinence (MD −3.00, 95% CI −6.61 to 0.61 at 3 months; MD −3.20, 95% CI −7.14 to 0.74 at 12 months). Mean (±SD) faecal incontinence episodes per week at baseline and 3 and 6 months of follow-up with chronic stimulation were: 11.4 (12.0), 4.0 (4.0) and 4.9 (6.9), respectively, for SNM compared with 10.6 (11.2), 5.8 (6.9) and 6.3 (6.9) for PTNS. Mean (±SD) CCIS values at baseline and 3 and 6 months were: 16.2 (3.0), 11.1 (5.2) and 10.4 (5.6) for SNM versus 15.1 (2.7), 11.7 (4.4) and 12.1 (5.2) for PTNS.

Leroi *et al* [214] reported a double-blind, crossover multicentre study in 34 patients. The indication to progress from temporary to permanent SNM (N = 27) was based on at least a 50% reduction in the number of episodes of incontinence or faecal urgency per week, or both. After implantation each participant underwent a 1-3 month phase with the stimulator turned on to determine the most effective stimulation parameters. At the end of this post-implantation period, patients were randomised in a double-blind manner to on- or off-stimulation for a 2-month period, with reversal of the activation mode after 1 month. Of these, 24 of the 27 (89%) patients completed the 2-month trial. A significant decrease in median frequency of

Table 3. Chronic sacral nerve simulation (SNM) for faecal incontinence (FI): Improvement of incontinence episodes, studies with ≥ 50 patients

Author	Year	Patients (n) (Baseline)	Patients (n) (Follow-up)	Median Follow-up (month)	"Per protocol: >50% improvement Incontinence episodes / week"	"Intention-to-treat: 50% improvement Incontinence episodes / week"
Follow-up: < 12 months						
Tjandra et al [189]	2008	53	53	12 *	71	63
Hollingshead et al [191]	2011	86	86	12	81	62
Wexner et al [184]	2010	120	106	12 *	83	66 ++
Meurette et al[192]	2020	78	65	4-8	83	n.a.
Follow-up: 12-36 months						
Melenhorst et al [163]	2007	100	100	26 §	79	59
Dudding et al [193]	2008	51	48	24	65	52
Govaert et al [132]	2009	173	169	35 §	77	53
Mellgren et al [185]	2011	120	77	36 *	86	59 ++
Follow-up: > 36 months						
Altomare et al [194]	2009	60	52	74 §	n.a.	n.a.
Hollingshead et al [191]	2011	86	18	60 *	83	n.a.
Duelund-Jakobsen et al [195]	2012	158	91	46	75	n.a.
Uludag et al [196].	2011	50	50	85	84	n.a.
Mellgren et al [185]	2013	120	76	>60	89	53
Altomare et al[197]	2015	272	228	84	78	50

Modified from 186; values at specific times; § mean ++ intention-to-treat; n.a. data not available*

Table 4. Chronic SNM for FI: Cleveland Clinic Incontinence Score, studies with > 50 patients

Author	Year	Patients (n) (Baseline)	Patients (n) (Follow-up)	Median Follow-up (months)	Median Score Baseline (range)	Median Score Follow-up (range)	p- value
Follow-up (< 12 months)							
Tjandra et al [189]	2008	53	53	12 *	16 ± 1 §	1 ± 2 §	< 0.001
Brouwer et al [99]	2010	55	48	12 *	15 (13-18)	6 (4-8)	0.001
Gallas et al [198]	2011	200	130	12 *	14 (2-20)	7 (0-19)	0.001
Johnson et al[199]	2015	145	145	12 *	14 (n.a.)	3 (n.a.)	n.a.
Meurette et al[192]	2020	172	144	9-15	15.2 ± 3 §	8.8 ± 5 §	<0.0001
Follow-up 12-36 months							
Brouwer et al[99]	2010	55	31	36 *	15 (13-18)	7 (5-8)	0.001
Hollingshead et al [191]	2011	86	86	33	15 ± 3	9 ± 5	< 0.001
Michelsen et al [200]	2010	126	126	24	16 (6-20)	10 (0-20)	< 0.001
Gallas et al [198]	2011	200	54	24 *	14 (2-20)	7 (0-19)	0.001
Wong et al [201]	2011	61	61	31	14 (n.a.)	8 (n.a.)	n.a.
Duelund-Jakobsen et al[202]	2015	164	43	22	15 (3-20)	9 (0-20)	<0.001
Kirss et al [203]	2019	294	30	28	16 (0-20)	7.5 (0-20)	n.a.
Follow-up > 36 months							
Altomare et al [194]	2009	60	52	74 §	15 ± 4	5 ± 5	< 0.001
Brouwer et al [99]	2010	55	13	48 *	15 (13-18)	6 (2-8)	0.008
Faucheron et al [204]	2010	87	87	45	13 (6-19) §	8 (1-17) §	n.a.
Michelsen et al [200]	2010	126	10	72 *	20 (12-20)	7 (2-11)	< 0.001
Lim et al [205]	2011	53	41	51 §	12 (9-15)	8 (5-11)	0.001
Faucheron et al [206]	2012	57	42	63	14 (4-19)	7 (1-16)	<0.001
Damon et al [207]	2013	119	102	48 §	14 ± 3	9 ± 1	<0.0001
Maeda et al [208]	2014	108	101	60 *	16 (6-20)	8 (0-19)	<0.0001
Altomare et al [197]	2015	272	228	84	16 (13-18)	7 (4-12)	<0.001
Brochard et al [209]	2019	352	305	40	14.2 ± 3	8.4 ± 5	<0.001
Oliveira et al [210]	2019	129	n.a.	36.7*	15.9± 3	5.2 ± 4	<0.0001
Mege et al [211]	2019	352	302	40*	14.2 ± 3	8.4 ± 5	<0.0001

*Modified from 186; * values at specific time; § mean value, standard deviation; n.a. data not available*

faecal incontinence episodes was noted during the on-stimulation period. No significant difference was observed between on- and off-stimulation for frequency of urgency episodes, delay in postponing defaecation, or median number of bowel movements per week (10.2 and 11.1 for on and off, respectively). There was a trend towards greater improvement in the CCIS during on-stimulation (8.5 vs 10.5 [ns]). All 24 patients felt they had improved during the off period. In 19 participants who preferred the on period and five who preferred the off-period outcomes were reported separately: For the group of 19, the median (range) episodes of faecal incontinence per week fell from 1.7 (0-9) during the off period to 0.7 (0-5) during the on period; for the group of five, however, the median (range) rose from 1.7 (0-11) during the off period to 3.7 (0-11) during the on period.

In the crossover trial by Kahlke *et al* [215], 16 of 31 patients who had had SNM for a median of 26.8 months agreed to be randomised in a crossover design to two three-week periods each of stimulation on and off. After six weeks, the patients--still blinded to the stimulator status-- chose which stimulation period they preferred. The mode of stimulation corresponding to the selected period was then continued for 3 months (final period). All patients (N=14 of 16) selected the on mode. They experienced significantly fewer episodes of faecal incontinence per week (1 [SD 1.7]) compared with the off period (8.4 [8.7]). The CCIS was significantly higher ($P < 0.05$) during the off period (14.6 [SD 4.6]) compared with the on period (8.7 [SD 3.6]). The overall number of bowel movements per week declined significantly ($P < 0.05$) in the crossover on period (10.9 [SD 4.1]) compared with the off period (18.2 [SD 8.7]). During the final 3-month period incontinence episodes per week remained low 0.3 (SD 0.5), CCIS was 6.4 (SD 3.3), and the number of bowel movements per week was 9.4 (SD 2.6). **LEVEL OF EVIDENCE: 3**

A large proportion of patients experience altered bowel habit and faecal incontinence following anterior resection of the rectum. This has been increasingly investigated during the last decade and

Table 5: Chronic SNM for FI: Incontinence episodes, studies with > 50 patients

Author	Year	Patients (n) (Baseline)	Patients (n) (Follow-up)	Median Follow-up	Incontinence episodes/week		p- value
					Baseline	Last Follow-up	
Follow-up < 12 months							
Uludag et al [176]	2004	50	27	12 *	8 (n.a.)	1 (n.a)	< 0.001
Melenhorst et al [163]	2007	100	76	12 *	10 (n.a.) §	2 (n.c.) §	< 0.001
Tjandra et al [189]	2008	53	53	12 *	10 (13) §	3 (10) §	< 0.001
Michelsen et al [200]	2010	126	49	12 *	8 (n.a.)	1 (n.c.)	< 0.001
Wexner et al [184]	2010	120	106	12 *	9 (7) §	2 (4) §	< 0.001
Meurette et al [192]	2020	178	78	9-15*	12 ± 14 §	3 ± 8 §	< 0.001
Follow-up 12-36 months							
Uludag et al [176]	2004	50	6	24 *	8 (n.a.)	1 (n.a.)	ns
Melenhorst et al [163]	2007	100	33	36 *	10 (n.c.)	2 (n.c.)	< 0.001
Dudding et al [193]	2008	51	48	24	6 (0-81)	1 (0-59)	n.a.
Hollingshead et al [191]	2011	86	86	33	9 (7) §	1 (2) §	< 0.001
Mellgren et al [185]	2011	120	77	36 *	9 (n.a.) §	2 (n.a.) §	< 0.001
Follow-up > 36 months							
Melenhorst et al [163]	2007	100	"15 6"	"48 * 60 *"	"10 (n.a.) § 10 (n.a.) §"	"2 (n.c.) § 2 (n.c.) §"	"< 0.001 <0.001"
Altomare et al [194]	2009	60	52	74 §	4 (n.a.) §	1 (n.c.) §	0.004
Duelund-Jakobsen et al [212]	2012	147	147	46	6 (n.c.)	1 (n.c.)	< 0.001
Uludag et al [196]	2011	50	n.a.	60	8 (n.a.)	0 (n.c.)	< 0.002
Mellegren et al [185]	2013	120	76	> 60	9 (n.a.)	2 (n.a.)	<0.0001
Altomare et al [197]	2015	272	228	84	7 (4-11)	0.3 (0-3)	<0.001
Vargase et al [213]	2019	126	53	41.2*	7 (7-20) §	1,3 (0.25-3) §	<0.001

*Modified from [186]; * values at specific time; § mean value, standard deviation; n.a. data not available; n.c. not calculable*

named low anterior resection syndrome (LARS) Several studies investigating the efficacy of SNM have been published but with few patients included in each study (n=1 to 12). Huang *et al.* published the most recent review and a meta-analysis including ten studies with a total of 75 patients being implanted. There was a wide heterogeneity in the inclusion criteria and the outcome measures. All studies used CCIS to evaluate response while only three studies used the LARS score. The conclusion was that SNM may be beneficial for symptom control, however the current evidence is limited, and general recommendations cannot be made until larger multicentre studies have provided more evidence[216]. The largest series of patients was published in 2000, with 25 patients included. There was a significant reduction of both the Wexner and the LARS score after one year of treatment and a positive correlation between the clinical changes and overall satisfaction. Patients with very low anastomosis and previous radiotherapy had a less successful outcome of SNM[217]. **LEVEL OF EVIDENCE 3**

The efficacy and safety of SNM for faecal incontinence following pelvic radiotherapy have been reported in three studies[218-220]. Maeda retrospectively reviewed the outcome of 13 patients who had undergone a PNE test following pelvic radiotherapy 6,5 years previously. Seven patients went on to chronic stimulation and the frequency of incontinence episodes improved from 24(4-56) to 4 (3-6). Another study reported that the efficacy of SNM in eleven patients treated with oncological multimodal treatment for pelvic malignancies persisted at 24 months follow-up. Mege compared 19 patients with faecal incontinence after pelvic radiotherapy to 38 matched patients with faecal incontinence related to other conditions and the success rate of SNM was similar in the two groups [220]. **LEVEL OF EVIDENCE 3**

1.3.5. SNM for Patients with Anal Sphincter Lesions

An increasing body of evidence indicates that SNM may also be a treatment option for patients with sphincter defects, either unrepaired or after attempted anatomical reconstruction. This was partly addressed in section II.1.2.4. The presence of an internal anal sphincter defect on endoanal sonography is reportedly unrelated to the success of permanent SNM[145]. Since the first report that three of five patients with ultrasound evidence of sphincter disruption measuring 25–33% of the circumference benefited from chronic SNM[221], several studies have been published[148, 149, 200, 221-225]. The origins and morphologic findings regarding the extent of the sphincter gap differ in these studies but lesions up to 180° have been treated. It appears that outcome is not dependent on the radial extent[149, 221]. A significant improvement in clinical function, measured either as frequency of incontinence episodes or CCIS, has been seen in a substantial number of patients in all studies[102, 148, 151, 222, 223, 225, 226]. Follow-up is still limited. **LEVEL OF EVIDENCE: 3**

Melenhorst *et al.*[148] showed that the primary use of SNM in patients with a sphincter gap 17-33% of the circumference appeared to re-

sult in an outcome similar to its use after failed sphincter repair. In another study, SNM in 6 of 8 patients with faecal incontinence related to obstetric full-thickness anal sphincter lesions of >30-150º resulted in improved frequency of incontinence episodes (from 5.5 to 1.5 per week)[224], improved ability to postpone bowel emptying, and improved ASCRS quality-of-life scores at a median follow-up of 26.5 months[221]. No correlation between improvement and the radial extent of the sphincter defect was seen. In patients with internal and external sphincter disruption related to Crohn's disease SNM was beneficial in one study[222].

In 2012, a review of SNM for faecal incontinence associated with anal sphincter lesions identified ten publications (nine retrospective; one prospective) from 1995-2011 comprising 119 patients, of whom 106 (89%) had a definitive implant after PNE testing[227]. A lesion of the external and/or internal anal sphincter was confirmed on endoanal ultrasound. Outcome reporting was not uniform. Follow-up ranged from 4.5 to 48 months. The weighted average number of weekly incontinent episodes decreased from 12.1 to 2.3, the weighted average CCIS decreased from 16.5 to 3.8, and the ability to defer defaecation, when evaluated, increased significantly. Quality of life improved significantly in almost all studies.

In the one prospective investigation, a comparative cohort study[149], the effect of permanent SNM was reported in 53 patients with either an intact external anal sphincter (N=32, 37.5% after sphincter repair) or an external anal sphincter lesion (N=21, 81% after prior sphincter repair) of <90° (N=11) or 90-120° (N=10). Improvement in symptoms and quality of life was achieved, and outcome after 12 months was not significantly different between groups. **LEVEL OF EVIDENCE: 3**

In a single-blinded randomized controlled trial at two hospital units Rydningen *et al*. demonstrated that SNM is superior to injection therapy with Permacol in faecal incontinence following OASIS. The difference in reduction of the St Mark's score was 8.9 (95% CI: 6.1-11.7, P < 0.0001) between the two groups: St Mark's score between baseline and 6 months was reduced by 11.2 (SD 5.3) in the SNM group (n:30) vs. 2.3 (SD 5.0) in the Permacol® group (N: 28). The differences in the four scales of FIQL (lifestyle, coping, depression, embarrassment) were 0.90 (95% CI: 0.50-1.30, P < 0.001), 1.05 (0.62-1.47, P < 0.001), 0.52 (95% CI: 0.16-0.87, P = 0.005) and 0.95 (95% CI: 0.50-1.40, P < 0.001), respectively, in favour of SNM[228]. The findings of another study confirm the positive outcome of SNM PNE testing in patients with OASIS demonstrating a reduction in weekly FI episodes of 94.5%, from a median (interquartile range) of 4.8 (2.0–11.0) to 0.5 (0–2.0) (P < 0.001)[229].

A recent retrospective study including 475 patients treated during 2000-2013 indicated that the increase in the number of SNM procedures during 2000-2013 was not proportional to the change in the number of patients with sphincter injuries, suggesting that SNM has become the operation of choice for FI regardless of the underlying sphincter profile[103]. Increase in utilization and popularity of SNM is also reflected by a population-based cohort study (prospectively obtained data including 621 patients treated for FI between 2011 and 2014 in the state of New York) by a decline in numbers of sphincteroplasties performed after the approval of SNM in 2011[230].

1.3.6. SNM for specific FI aetiologies

The therapeutic potential of SNM has also been demonstrated in some, mostly small, case series and individual case reports of patients with distinct pathological conditions or well defined anorectal pathophysiology: e.g. muscular dystrophy[231]; proctocolectomy with ileoanal J-Pouch reconstruction for colitis[232]; neurological dysfunction including spinal disc prolapse[233]; rectal prolapse repair[234, 235]; rectal resection for cancer[236] with or without neoadjuvant chemoradiation[134, 237-239]; after proctectomy with colorectal or coloanal anastomosis for rectal cancer ± neoadjuvant radiochemotherapy[240]; after neoadjuvant and adjuvant chemoradiation / radiotherapy for endometrial and anorectal cancer[218, 219, 241]; after unilateral traumatic pudendal neuropathy[242]; in spina bifida[243]; in congenital faecal incontinence[244] including from anorectal malformations[245] and incontinence related to external anal sphincter atrophy[246]. **LEVEL OF EVIDENCE: 4**

1.3.7. Quality of Life

Outcome assessment has also evolved, and aspects of quality of life have been added to the evaluation (CCIS, SF-36 and Fecal Incontinence Quality of Life [FIQL] Score). The therapeutic impact of SNM is most evident when a disease-specific quality-of-life instrument, the ASCRS FIQL scale, is applied.

In the first study to apply this instrument, the multicentre clinical trial by Matzel *el al.*[139], ASCRS FIQL was significantly increased in all 4 scales; SF-36 scores improved in 7 of 8 scales, the greatest being social functioning and mental health, but only the former reached statistical significance. A similar result was published by Leroi *et al.* [214] with the French version of the ASCRS QOL (FIQL): at the final follow-up visit, improvements in lifestyle, coping behaviour, depression, and self-perception and embarrassment were significant. Hetzer *et al.* [247] demonstrated a significant improvement of the median Gastrointestinal Quality of Life Index score with permanent SNM from a baseline of 96 (range 47–128) to 107 (range: 36–128) at 6 months' post-implantation.

In many studies on outcome, quality-of-life evaluation is a secondary endpoint[99, 133, 139, 140, 160, 189, 192, 214, 233, 234, 236, 238, 248, 249]. When used, improved quality of life is consistently related to symptom relief and remains stable with longer follow-up[99, 194, 196, 247, 250]. Indeed, long-term data with a follow-up of at least 5 years indicate a significant improvement of all four scales of the FIQL score[250, 251].

In a meta-analysis[187] of 34 studies with 790 patients, SF-36 score data were analysed from 7 studies with 98 to 102 patients and ASCRS FIQL data from 9 studies comprising 199 patients: SF-36 outcome was significantly increased in all categories (physical functioning, social functioning, role physical, role emotional, mental health, vitality, general health) with one exception (bodily pain). FIQL outcome was significantly increased in all categories (lifestyle, coping/behaviour, depression/self-perception, embarrassment).

In a two-centre study of patients with permanent SNM for a median of 46 months (range: 11-122), 108 of 127 patients responded to questionnaires regarding bowel habits and quality of life. Using a non-validated score, 75.8% reported satisfaction, which in most was related to clinical improvement. However, at last follow-up 11 of 23 patients who had failed to achieve a 50% reduction in incontinence episodes reported satisfaction, and 6 of these had more incontinence episodes than at baseline[195].

Four of the randomised controlled trials discussed above, when relating quality of life to clinical efficacy of SNM, have used varying instruments: SF-12, ASCRS FIQL[189]; SF-36[252]; the French version of the ASCRS FIQL[214]; and ASCRS FIQL, SF-36 and EQ-5D[190]. Improvement was found in all, except for EQ-5D with chronic SNM. **LEVEL OF EVIDENCE: 2**

1.3.8. Cost benefit

Permanent SNM is expensive; however, its cost-effectiveness has been demonstrated in several European nations. Hetzer *et al.* [253] compared the costs of SNM with those of conservative treatment, anterior sphincteroplasty, dynamic graciloplasty, and stoma creation in 34 consecutive patients. The 5-year cumulative cost for SNM was €19,333, compared with €35,965 for a stoma (with annual costs of €5,339) and €34,953 for dynamic graciloplasty (annual costs €1,659). The equivalent cost for conservative treatment was €3,895, and the overall median real cost for an anterior sphincteroplasty was €5,327. Muñoz-Duyos *et al.* [254] analysed the direct medical costs of SNM in a series of 47 patients undergoing 57 PNEs and the consequent 29 patients with a permanent unilateral implant for a median follow-up of 34.7 (2.3-81.2) months. The cost totalled €371,434, including €317,791 for the devices. In patients without anal sphincter damage SNM provided 0.34 incontinence-free life-years and entailed additional costs of €1,054, which generates a cost-effectiveness ratio of €16,181 per quality-adjusted life-year (QALY). The nationally accepted threshold is around €30,000/QALY. The economic impact of the introduction of SNM would be to add 0.07-0.1% to the care of these patients (2008 data).

In a decision-analysis model based on prospectively collected data in 70 patients undergoing test stimulation and implantation of the permanent SNM device, incontinence episodes/week were reduced from 6 at baseline to 0.5. Dudding *et al.*[193], based on direct medical and non-medical costs, found an incremental cost-effectiveness ratio (ICER) for SNM of £25,070 per QALY gained. It cost £1,038 per year to achieve a median reduction of 238 incontinence episodes, equal to £3.61 per reduced episode. The ICER of £25,070 per QALY was within the UK nationally accepted £30,000 per QALY threshold.

In a similarly designed study based on published reports and expert opinion, Indinnimeo *et al.* [255] found that the ICER was €28,285 per QALY gained in patients with a structurally deficient anal sphincter and €30,662 per QALY in patients with an intact anal sphincter. Both were below the relevant national threshold of €40,000 per QALY gained. Budget-impact analysis demonstrated that the implementation of SNM would have an estimated impact of 0.56% over a 5-year period on the budget allocated for faecal incontinence treatment.

In a French study, clinical outcome and cost-effectiveness analyses were performed in parallel with a prospective, multicentre cohort study that included 369 consecutive patients with urge urinary and/or faecal incontinence with a follow-up of 24 months[256]. Cost-effectiveness outcomes were expressed as incremental costs per 50% of improved severity scores (incremental cost-effectiveness ratio). Based on a national health perspective the average cost of SNM for faecal incontinence was €6,581 more for the first 2 years when compared with alternative treatments (95% confidence interval, €2,077- €11,084; P = 0.006) when an improvement of more than 50% in the continence severity score was used as the criterion of effectiveness. The incremental cost-effectiveness ratio for SNM was €94,204 and €185,160 at 24 months of follow-up for urinary and faecal incontinence respectively. These findings were above the generally accepted range of cost effectiveness, but SNM was considered to offer marked health benefits for patients with faecal incontinence (measured by the severity score).

In a retrospective study of a national (> 90% of implants performed in New Zealand) cohort of 100 out of 110 patient with a permanent SNM device treated between 2008 and 2019 Varghese et al[213] described the efficacy of SNM and reported a reintervention rate of 41.5%. SNM therapy was considered expensive, costing >NZ$30,000 for implantation, increasing to >NZ$46,000 depending on number and kind of required re-interventions.

SNM requires maintenance, which comes with costs. In a structured, prospectively performed post implant follow-up program of 85 patients with permanent implant having regular visits at 3 months, 6 months, yearly thereafter for therapy monitoring and adjustments and further visit because of the need of device adjustments based on symptom changes McMullin *et al*. [257]. demonstrated at a median follow up after permanent implantation of 24 months (range: 3–108) that 27 % of the patients had an unsatisfactory outcome. The follow-up cost for these patients constituted 48.7% of the £75,702 total follow- up cost. **LEVEL OF EVIDENCE 3**.

1.3.9. Safety

SNM is a relatively safe procedure however, adverse effects are commonly reported. Painful or uncomfortable stimulation, leg cramp, superficial wound infection at the site of the implant and loss of efficacy are usually resolved with medication or reprogramming[258]. Some adverse events such as severe pain at the IPG site, lead migration or fracture, deep wound infection and battery depletion require surgical revision or explantation, The incidence of surgical revision of SNM varies in different publications and ranges from 16% to 39%, and younger age (<55 years) is the only risk factor that has been identified and associated with an increased frequency of device revision and explantation[259, 260].

In an FDA study with strict monitoring of adverse events, 334 were reported in 99 patients at three-year follow-up; 67% occurred in the first year, and most required no or minimal intervention at the time. The adverse events included pain at the implant site (28%), paresthesiae (15%), change in the sensation of stimulation (12%), implant site infection (10%), urinary incontinence (6%), diarrhoea (6%), and extremity pain (6%). Half of the infections required surgical intervention with removal of the device in 5 of 6 patients[250]. More recent data of the same patient cohort report a 39% need for device revision, replacement, or removal. With 5 years' follow-up, 26.3% of patients had a revision, replacement, or removal of the device for reasons other than battery depletion [261]. Significant differences between those who exited because of a lack of efficacy before five years and those who remained in the study were found in two areas: average percentage of improvement at test stimulation (90% vs. 80%, p=0.007) and the percentage of patients completely continent during the test stimulation (47% vs 7%; p=0.004).

Major complications are rare: one case report of a life-threatening haemorrhage after elective tined lead electrode removal has been published[262].

A review of 48 cohort studies (45 for faecal incontinence and 3 for constipation) documented the postoperative events in the 1,661 patients with test stimulation and 1,600 patients with a permanent SNM implant[263]: the review found that the incidence of suboptimal outcome was 12.1%, pain 13%, and infection 3.9%. The most common problem during test stimulation was lead dislodgement (5.3%). Systematic literature review suggests a possible underreporting of suboptimal outcome and adverse events. In one single study, the rate of adverse events reached up to 85.2% in patients with a median follow-up of 11 months: loss or lack of efficacy and pain or discomfort accounted for 88.5% of these [264]. In a review with 45 studies including 1,953 patients the pooled rate of infection was 5.1% (4.1-6.4) without significant heterogeneity between trials [265]. In a recent multicentre study with the objective to estimate incidence of infection after placement of an IPG and to identify risk factors associated

with SNM explantation, 38 cases of infection required IPG explant in a cohort of 1,930 IPG implants (1.97%). A deep pacemaker pocket (>3cm) and postoperative haematoma were factors significantly associated with infection requiring IPG explant. The most common infectious organism identified was methicillin-resistant *Staphylococcus aureus*. There was no difference in risk of infection based on choice of prophylactic antibiotics at implant[266].

In their summary of studies with long-term follow-up (70-118 months), Altomare *et al.* reported minor complications in 79 patients (PP, 29%; ITT, 19.4%), of which 64 (PP, 23.5%; ITT, 15.7%) were device related. The most common was pain at the subcutaneous site (23 patients) prompting device removal in 12 patients and replacement in seven. Removal and repositioning for dislocation or battery depletion was necessary in another 17 patients[152].

In general, the most common intervention described in the literature is repositioning of the pacemaker due to pain or migration. In a recent study the incidence of IPG site pain as a function of the site of IPG implantation was studied in patients with permanently implanted nerve stimulation systems. A total of 424 patients participated in the survey of which 80 patients (19%) had a sacral nerve stimulator. Overall, 31% of patients reported pain at IPG site (31,4% reporting moderate to severe pain, 7.6% reporting severe pain). Older age was inversely associated to IPG-related pain and the anatomical location of the IPG placement did not affect the incidence or severity of IPG site pain. However, patients with pre-implant chronic pain disorder had a higher frequency and severity of IPG site pain[267].

LEVEL OF EVIDENCE: 2

Summary:
Sacral nerve stimulation is an effective treatment in patients with severe incontinence unresponsive to conservative treatment. It may be effective as a first-line treatment in patients with an anal sphincter defect. The therapeutic benefits are sustained in the medium- to long-term. The mechanism of action is not entirely certain however effects on sensory afferents appear most probable. SNM has an effect on the peripheral and central nervous system. SNM is a relatively safe procedure, however adverse events are common and surgical revision required in up to one third of the implanted patients. **Grade of Recommendation: B**

1.4. Injectable Biomaterials

There have been several developments in the field of injection of bulk-enhancing agents into the anal canal to treat faecal incontinence (FI) since the last review. These include the use of new materials and injection techniques. Only two of these have been randomized comparisons of two or more interventions[228, 268] The remainder have been case series, one of which compared data with those from a previous series[269].

The ideal agent for injection should be biocompatible, non-allergenic, non-immunogenic, easy to inject, and should not migrate within the tissues. No agent currently has all these properties. Agents that have a diameter of 80µm are felt to be less prone to migration, but agents with a larger particle size require a larger bore needle to inject, which put them at a higher risk for leakage from the injection site.

Injectable agents for FI were first used in 1993 when Shafik treated 11 patients with injections of polytetrafluoroethylene paste into the anal submucosa[270]. Since that time there has been a steady arrival of new materials, usually after initial enthusiasm in the treatment of urinary incontinence. Most of these agents are only in use for a few years before a newer agent takes their place.

1.4.1. Types of injectable biomaterials

The following biomaterials have been used in the treatment of faecal incontinence:

- Polytetrafluoroethylene paste (Teflon)
- Autologous fat
- Glutaraldehyde cross-linked synthetic bovine dermal collagen (Contigen)
- Polydimethylsilozane elastomer silicone biomaterial (PTQ, Macroplastique)
- Microballoons with biocompatible hydrogel
- Carbon-coated zirconium oxide beads (Durasphere)
- Calcium Hydroxylaptatite Ceramic Microspheres (Coaptite)
- Dextranomer-hyaluronic acid copolymer, NASHA/Dx (Zuidex, Solesta)
- Ethylene Vinyl Alcohol EVOH
- Polyacrylonitrile cylinder (Gatekeeper)
- Polyacrylate-polyalcohol (Exantia)
- Polyacrylamide gel (Bulkamid)
- Cross-linked porcine dermal collagen (permacol)
- Polyacrylonitrile cylinder (Sphinkeeper)

1.4.2. Observational data

The multitude of case series providing outcomes for injectable biomaterials in FI are shown in **Table 6** and will not be discussed in detail here. Of 29 case series, 16 included fewer than 20 patients and none included more than 100. There was no standard methody of inclusion, injection technique or assessment. There was also wide variation in both the length of follow-up and outcome measures used. None of the case series are of high quality. Most of the studies report a modest improvement in measure of incontinence utilized. Those that measured longitudinal outcomes generally showed deterioration over time. None of the earliest biomaterials, Polytetrafluoroethylene paste (Teflon), Autologous fat, Glutaraldehyde cross-linked synthetic bovine dermal collagen (Contigen), Polydimethylsilozane elastomer silicone biomaterial (PTQ, Macroplastique), Microballoons with biocompatible hydrogel, Carbon-coated zirconium oxide beads (Durasphere), Calcium Hydroxylaptatite Ceramic Microspheres (Coaptite) are still in use for the treatment of faecal incontinence.

A recent addition to the long list of trialled materials is the polyacrylonitrile (Gatekeeper™) device. This is a shape-memory hydrophilic material that enlarges to seven times its initial diameter of 1.2 mm once in contact with human tissue. It can be manufactured into thin rods, which are injected into the intersphincteric space. An initial single-centre report showed a sustained improvement in incontinence and quality of life scores over a mean follow-up of 33 months[271]. A larger multicentre observational study reported the outcome of this device. At 12 months' follow-up, 30/54 (56%) patients achieved a greater than 75% improvement in incontinent symptoms, and 7 (13%) achieved continence. The implant extruded in three patients [272]. This technique was developed further into the SphinKeeper. Instead of using six rods, ten are placed in intersphincteric space. A combined series from St Mark's and the Royal London Hospitals in 2020 reported on 27 patients. All had passive FI. In 30% the delivery device jammed and not all of the implants were delivered. Post-operative endoanal ultrasonography showed that a median of 7 implants (0-10) were seen in each patient, with a median of 5 (0-10) postioned in the optimal intersphincteric position. Despite this, the St Mark's FI score improved by a median of 6 points and 14 patients (52%) achieved a greater than 50% improvement in symptoms. This success rate did not appear to be

related to implant position[273].

1.4.3. Randomised Controlled Trials

There have now been eight randomised trials of bulking agents for FI (Table 7), but only three of them compared an injectable biomaterial to a control/placebo. None demonstrated a clear over placebo or non-operative management.

In the first, 44 patients were randomised to receive transdermal injections of polydimethylsilozane elastomer silicone biomaterial (PTQ) or saline into the intersphincteric space[299] . Three 2.5ml injections were performed using local anaesthesia. Patients, but not investigators, were blinded to the treatment. There was no difference in percentage of patients in the two groups who had a treatment success, defined as having a CCF-FIS score <8 or the decrease in CCF-FIS scores post-treatment. The saline group tolerated treatment better and had fewer adverse effects overall. Thus, the study concluded that the use of PTQ should not be recommended.

The second is the largest study published to date, a randomized,

Table 6. Case series using injectable biomaterials

Authors (ref)	Year	Agent	# Pts.	Injection technique	# Sites	Volume	Outcomes
Shafik [270]	1993	Polytetrafluoroethylene paste (Teflon)	11	Transanal	2	0.5ml	64%
Shafik [274]	1995	Autologous fat	14	Transanal	2	50-60ml	100%
Kumar et al [275]	1998	Glutaraldehyde cross-linked synthetic bovine dermal collagen (Contigen)	17	Transanal	1-3	Up to 2ml	65% pts improved
Stojkovic et al [276]	2006	Glutaraldehyde cross-linked synthetic bovine dermal collagen (Contigen)	73	Transanal	3	1.7ml	63% improved CCF-FIS 10 to 6
Malouf et al [277]	2001	polydimethylsiloxane particles (PTQ)	10	Not stated	1-4	5-11.5ml	60% initial improvement, 20% long-term
Tjandra et al [278]	2004	polydimethylsiloxane particles (PTQ)	82	Intrasphincteric with and without ultrasound	4	2.5ml	CCF-FIS w US: 14.5 to 3 Without US: 14.5 to 11
de la Portilla et al [279]	2008	Polydimethylsiloxane particles (PTQ)	20	Transsphincteric	3	2.5 ml	CCF-FIS 13.5 to 4.5
Soerensen et al [280]	2009	Polydimethylsiloxane particles (PTQ)	33	Transsphincteric to Intrasphincteric	3	2.5ml	CCF-FIS score 12.7 to10.4 18% pts sig improved
Bartlett & Ho [281]	2009	Polydimethylsiloxane particles (PTQ)	74	Intrasphincteric	4	2.5ml	70% continent CCF-FIS=0 30% CCF-FIS 20 to 3.5
Oliveira et al [282]	2009	Polydimethylsiloxane particles (PTQ)	35	Transsphincteric to intra-sphincteric site	3	2.5ml	CCF-FIS 11 to 3.5
Feretis et al [283]	2001	Microballoons with biocompatible hydrogel	6	Transanal	3-5	0.9ml in balloon	Browning-Parks Incontinence score 16 to 5
Davis et al [284]	2003	Carbon-coated zirconium oxide beads (Durasphere)	18	Transanal	1-4	1.28ml	83% pts improved CCF-FIS 11.9 to 8.1
Altomare et al [285]	2008	Carbon-coated zirconium oxide beads (Durasphere)	33	Transsphincteric	4	8.8ml	CCF-FIS 12 to 8 AMS 89 to 73
Aigner et al [286]	2009	Pyrolytic carbon coated beads (Durasphere)	11	Intrasphincteric to submucosa	3-4	Avg. 2.82ml	CCF-FIS 12.7 to 4.91, FIQL 2/4 subscl improved
Beggs et al [287]	2010	Pyrolytic carbon coated graphite beads (Durasphere)	23	Intersphincteric	4	2.8ml	CCF-FIS 18.7 to 10.9 FIQL improved
Dehli et al [288]	2007	NASHA/Dx gel (Solesta)	4	Transanal to Submucosal	4	1.4ml	St Marks Incontinence score 19.25 to 15.75, 75% pts improved
Danielson et al [289]	2009	NASHA/Dx (Solesta)	34	Transanal to submucosa	4	1ml	# episodes/4wks 22 to 9
Danielson et al [290]	2020	NASHA/Dx (Solesta)	7	Trans anal	3-4	1ml each	20.7 FI/ 2w pre 5.3 FI/2w at 6m 4.3 FI/2w at 18m Improved SF-36

Authors (ref)	Year	Agent	# Pts.	Injection technique	# Sites	Volume	Outcomes
Al-Bayati et al [291]	2017	NASHA/Dx (Solesta)	17	Transanal	4	1ml	82% success
Ganio et al [292]	2008	Calcium Hydroxylaptatite Ceramic Microspheres (Coaptite)	10	Transsphicteric to submucosal site	4	1ml	FISS 85.6-28 FIQL improved in subscale 4
Stephens et al [293]	2010	Ethylene Vinyl Alcohol EVOH	21	Intrasphincteric	Max 8	1-2ml	FISI 32.8 to 22 CCF-FIS 11 to 6.9 FIQL 2/4 subs improved
Ratto et al [294]	2011	Polyacrylonitrile cylinder (Gatekeeper)	14	Transdermal to intrasphincteric	4	NA	CCF-FIS 12.7 to 5.1 FIQL and SF36 improvement
Ratto [272]	2016	Polyacrylonitrile cylinder (Gatekeeper)	54	Intrasphincteric	6	prosthesis	CCF-FIS 12.0 vs 5
Trenti et al [295]	2017	Polyacrylonitrile cylinder (Gatekeeper)	49	Intrasphincteric	6	prosthesis	48% responders 51% migration
Rosato et al [296]	2015	Polyacrylate-polyalcohol (Exantia)	58	Transanal to submucosal		2ml per site, total 3-9ml	60.4% met criteria of success (>=50% improvement of CCF-FIS)
Al-Abed et al [297]	2016	Cross-linked porcine dermal collagen (permacol)	30	Trans anal submucous	3	2.5ml each	CCF-FIS 12.8 to 4.9 at 12 weeks
Harran et al [298]	2017	Cross-linked porcine dermal collagen (permacol)	14	Transanal	3	2ml	CCF-FIS 12.5h) to 7.9
Grossi et al [269]	2020	Polyacrylonitrile cylinder (Sphinkeeper)	10	Intrasphincteric	10	prosthesis	CCF-FIS 13 to 4
		Polyacrylonitrile cylinder (Gatekeeper)	10	Intrasphincteric	6	prosthesis	CCF-FIS 12 to 6
Litta et al [271]	2020	Polyacrylonitrile cylinder (Sphinkeeper)	42	Intrasphincteric	10	prosthesis	CCF-FIS 12.0 to 7.6

Key: CCF-FIS Cleveland Clinic Florida Faecal Incontinence Score, FISS Faecal Incontinence Scoring System, FISI Faecal incontinence Severity Index, FIQL Faecal incontinence Quality-of-Life score

double-blinded sham-controlled trial of 206 patients randomised in a 2:1 fashion to receive NASHA Dx (Solesta) or placebo saline injection[300]. The patients and the evaluating investigators were blinded to the treatment. More patients in the treatment group had 50% or greater reduction in number of incontinence episodes (52% versus 31% of controls; p=0.009), but the change in CCF-FIS did not differ after treatment between groups (14 to 2.5 in the treatment group vs. 13 to 1.7 in placebo group). The FIQL was only significantly improved compared to placebo for the coping and behaviour subscale. Both groups had high retreatment rates: 82% of patients in the Solesta group received reinjection of product and 87% of patients in the control group had repeat sham injection. The Solesta group had significantly more adverse events, including proctalgia, rectal bleeding, pruritus, diarrhoea, constipation, fever, and two serious complications of rectal abscess and prostatic abscess. The control group had more injection site bleeding. [300]

Although the final RCT compared Solesta to biofeedback rather than placebo, it does represent a study that compares a surgical procedure with injectable biomaterial with a non-operative control. This was a large and well-designed randomised controlled trial from Norway, 126 patients were randomised to either Solesta or biofeedback training[301]. Patients were followed up to 24 months. There was no difference in improvement in St Mark's Incontinence Score between these groups at any of the follow-up times. Solesta was not superior to biofeedback retraining.

1.4.4. Randomised Comparison Trials

There have been five randomised studies comparing different surgical options. One compared SNM to Permacol, one Permacol to polyacrylamide gel (Bulkamid), two compared PTQ to Durasphere, and another compared different doses of Bulkamid.

In the trial by Rydningen *et al.,* Permacol was compared with SNM in 58 women with FI.[228] The reduction in the St Mark's score between baseline and 6 months was 11.2 (SD 5.3) in the SNM group vs 2.3 (SD 5.0) in the Permacol group (P < 0.0001). SNM also had a significantly greater improvement in all four domains of the FIQL (p<0.005). There was no difference in adverse effects. There was a clear advantage to SNM over Permacol injection

A pilot study conducted in 2008 examined two other products, cross-linked porcine dermal collagen (Permacol), and polyacrylamide hydrogel (Bulkamid) [302]. Ten patients with passive FI to liquid or solid stool who had failed conventional treatments were prospectively randomised to receive either of the two products. There was a modest reduction of the St Mark's incontinence score at 6 weeks for both groups, but this decrease was sustained at 6 months only for the Bulkamid group. This pilot study lacked power to determine if these two treatments for FI differed significantly.

Two trials compared the safety and efficacy of PTQ and Durasphere[303] [304]. In the trial by Tjandra *et al.* the sample size was calculated to detect a 50% reduction in the CCFIS post injection. [285] Thus, 40 patients with FI (mean CCFIS 11.45) were randomised to receive either PTQ or Durasphere. Both groups were similar in

Table 7. Randomised trials of Injectable biomaterials

Author Year	Agent	Patient no.	Injection technique	No. sites	Volume	Outcome	P value < 0.05
Siproudhis[299] 2007	Polydimethylsilozane elastomer silicone biomaterial (PTQ)	22	Intrasphincteric	3	2.5ml	No difference in CCF-FIS: 13.8 to 11.7 PMDS, 14.6 to 11.4 placebo	No
	Saline (placebo)	22	Intrasphincteric	3	2.5ml		
Graf[300] 2011	NASHA/Dx (Solesta)	136	Transanal SM	4	1ml	52% vs. 31% had >50% reduction incont episodes complications in Solesta	Yes
	Saline (placebo)	70	Transanal SM	4	1ml	No difference in CCF-FIS: 14 to 2.5 Solesta, 13 to 1.7 placebo	No
Delhi[271] 2013	Biofeedback	62	NA	NA	NA	StMIS 12.6 to 7.9	No
	Solesta	64	Transanal	4	1ml	StMIS 12.9 to 8.3	
Rydningen [224] 2017	SNM	30	NA	NA	NA	StMIS reduced by 11.2	Yes
	Permacol	28	Transanal	3	2.5ml	StMIS reduced by 2.3	
Altman[261] 2016	Polyacrylamide gel (Bulkamid)	10	Transanal SM	4	4ml	CCF-FIS reduced by 1.8	No
		10	Transanal SM	3	4ml	CCF-FIS reduced by 2.4	
		10	Transanal SM	3	6ml	CCF-FIS reduced by 3.1	
Maeda[302] 2008	Permacol	5	Transsphincteric	3	9ml	StMIS 15 to 12.5	No
	Polyacrylamide hydrogel (Bulkamid)	5	Transsphincteric	3	15ml	StMIS 15 to 12.5	
Tjandra[303] 2008	Polydimethylsiloxane particles (PTQ)	20	Intrasphincteric	4	2.5ml	CCF-FIS 11.5 to 3.8, FIQL and SF-12	Yes
	Pyrolytic carbon coated beads (Durasphere)	20	SM	4	2.5ml	complications, CCF-FIS 11.5 to 7.0 FIQL, SF-12 not improved	
Morris[304] 2013	Polydimethylsiloxane particles (PTQ)	17	Intersphincteric	3-4	2.5ml	Wexner score compared to baseline was reduced by 4.3 (P<0.001), 4.2 (P<0.001), and 1.1 (P=0.24) 6 weeks, 6 and 12 months.	No difference between groups
	Pyrolytic carbon coated beads (Durasphere)	18	SM	4	2.5ml	Improvements in the Durasphere arm for the same time periods were 5.3 (P=0.003), 4.1 (P=0.002), and 1.8 (P=0.19).	

Key: StMIS St Marks Score; SNM Sacral neuromodulation; CCF-FIS Cleveland Clinic Florida Faecal Incontinence Score; SM submucosal; FIQL Faecal incontinence Quality-of-Life score; SF-12 Short Form Health Survey Quali-ty of Life score; NA Not applicable.

terms of age, medical history, FI severity and quality of life scores as well as anorectal manometry results. Although the Durasphere group had a greater reduction in CCFIS at 2 weeks (11.45 to 8.25 vs. 11.45 to 10.9), the PTQ group had a greater reduction in CCF-FIS at 6 weeks, 6 months and 12 months (4.6,2.95 and 3.8 vs. 7.65, 6.2 and 7) and had no complications. The Durasphere group had several complications including anal pain (5%), mucosal erosion (10%), arthritis and skin rashes (5%). Furthermore, the PTQ group demonstrated significant improvements in general and faecal-incontinence-specific quality-of-life scores that were not seen in the Durasphere group. Thus, the conclusion was that PTQ was safer and more effective than Durasphere for the treatment of FI. [285] The second trial, by Morris *et al.*, was of a similar size but and demonstrated an improvement in both groups at 6 weeks and 6 and 12 months. This trial did not identify any difference between the two techniques. [304]

Altman *et al.* randomly employed different injection strategies for Bulkamid in three groups of 10 patients with CCF-FIS >10 using 3 or 4 sites of injection and either 4 or 6 mls of Bulkamid[268]. At 12 months follow-up there was a significant but modest improvement of mean CCF-FIS from 14.7 to 12.4 but no difference between the different injection groups was detected. This study was clearly underpowered to allow any statistical inference.

These trials indicated that PTQ performed better than Durasphere in terms of both safety and efficacy,[303] Solesta, was not superior to biofeedback training[301], SNM was superior to Permacol[228] and in an RCT the dose of polyacrylamide gel did not alter its efficacy[268]

1.4.5. Conclusion

In summary, randomised controlled trials have failed to show any appreciable benefit to the use of injectable biomaterials for faecal incontinence. Furthermore, uncontrolled studies are mostly small, poor quality case series that in general show short-term efficacy. As of November 2020, only one bulking agent, NASHA DX (Solesta), had been approved by the FDA for treating faecal incontinence.

Two systematic reviews[305, 306] and a recently updated Cochrane review[307] have published the data for all injectable agents for faecal incontinence. Due to the poor methodology and small sample sizes of most of these studies, none of these reviews could establish adequate evidence to support the efficacy of any of these agents Randomised controlled trials have not demonstrated clear efficacy in any of these agents against non-operative treatment or placebo. The evidence base for managing FI with injectable biomaterials is of poor quality and their use cannot be recommended at this time. **LEVEL OF EVIDENCE: 2.**

Summary:
The role of injectable biomaterials in treatment of faecal incontinence is not established. The optimum bulking agent and site of injection remain uncertain. Use is not recommended **Grade of Recommendation: C.**

1.5. Puborectal sling

The puborectal sling operation was first reported by O'Rourke in 1974 [308]. In this procedure, an artificial sling is routed behind the anorectal junction and its two ends are fixed to the pubic bone, pulling the anorectal junction up forward with some tension. Similar to the postanal repair, the rationale of this operation is the restoration of the anorectal angle normally maintained by puborectal muscle.

No systematic reviews, randomised controlled trials, non-randomised cohort studies or case control studies have been reported regarding puborectal sling operation for faecal incontinence, while one prospective comparative study (level 2) [309], three prospective case series of good quality (level 3) [265, 310, 311] and three retrospective case series of low quality (level 4)[308, 309, 312] were identified.

O'Rourke[308] reported using Dacron® mesh for the treatment of 3 patients with full rectal prolapse as well as 4 patients with mucosal partial rectal prolapse and faecal incontinence. Of the 4 patients with faecal incontinence and partial prolapse, 3 were reported to have "benefited considerably" from the procedure although a formal evaluation was not performed, and the follow-up period was not documented. O'Rourke and Egerton [312] also reviewed 24 patients in whom the sling operation was performed using a strip of rolled Mersilene® mesh. This procedure, however, was performed mainly for the treatment of rectal prolapse, while it was conducted because of faecal incontinence alone only in two out of the 24 patients, and the outcomes regarding the continence were not formally evaluated.

Shafik [309] reported another sling operation called puborectoplasty utilising a Teflon™ sling for faecal incontinence. Of 31 patients who had been incontinent to solid stool and underwent this procedure, "good results" were achieved in 26 patients (84%) after a follow-up period of between 2 - 4 years: 20 became continent to solid and liquid stool as well as flatus; 6 to solid and liquid stool but not to flatus; 4 to solid stool only; and only one remained incontinent to solid stool.

Shafik and Shafik[309] conducted a prospective comparative study comparing two fascia lata slings (double loop) in 22 patients and one fascia lata sling (single loop) in 22 patients for the treatment of faecal incontinence. After 12 months follow-up, "good results" were achieved in 14 (64%) and 8 (36%) by the double loop and the single loop, respectively

Yamana et al.[310] performed the perineal puborectalis sling operation in 8 patients with passive faecal incontinence using a polyester mesh sling. A rectal ulcer developed in one patient, requiring sling removal. In the 6-month evaluation of the remaining 7 patients, all reported some extent of improvement of their faecal incontinence. Both the Fecal Incontinence Severity Index and the Cleveland Clinic Florida Fecal Incontinence Score (CCIS) significantly improved from 27 to 9 and from 13 to 5, respectively. Moreover, all parameters in the Fecal Incontinence Quality of Life Scale (FIQL) significantly improved: lifestyle from 2.1 to 3.6; coping/behaviour from 1.5 to 3.4; depression/self-perception from 2.3 to 3.7; and embarrassment from 2 to 3.6.

The transobturator posterior anal sling (TOPAS™) is the first puborectal sling, aimed to be commercially available for the treatment of faecal incontinence in women. It is comprised of a knitted, Type 1 polypropylene monofilament mesh, which is covered by removable insertion sheaths, and two insertion needles. It is implanted through a transobturator approach via two small incisions in both thighs and buttocks. The implanted mesh is self-fixating and permanent with tissue in-growth providing additional support to the anorectum.

In a preliminary prospective multicentre study, 29 women were implanted with the TOPAS™ system[311]. Fifteen patients (52%) achieved treatment success, which was defined as a reduction of 50% or more in the number of faecal incontinence episodes compared with baseline, and 33% reported complete continence. The mean faecal incontinence episodes per 14 days significantly decreased from 6.9 at baseline to 3.5 at 24 months of follow-up. The CCIS and FIQL for all 4 domains were significantly improved during the overall follow-up period compared with baseline. A total of 12 patients (41%) experienced 19 procedure- and/or device-related adverse events, but there were no device-related erosions, extrusions or revisions.

In a larger multicentre FDA controlled study, 152 women were implanted with the TOPAS™ system [26493933] At 12 months of follow-up, 69% of the patients achieved treatment success, which was defined as a reduction of 50% or more in the number of faecal incontinence episodes compared with baseline, and 19% reported complete continence. The median number of faecal incontinence episodes per week significantly decreased from 9 at baseline to 2.5 at 12 months. The CCIS and FIQL for all 4 domains were significantly improved from baseline to 12 months. A total of 66 patients (43%) experienced 104 procedure- and/or device-related adverse events, but most of them were short in duration and 97% were managed without therapy or with nonsurgical interventions. There were no treatment-related deaths, erosions, extrusions, or device revisions. **LEVEL OF EVIDENCE: 3**

The puborectal sling operation, particularly with TOPAS™ system, appears promising because it is a simple procedure and yielded reasonably good results with a low rate of serious complications so far. More prospective studies of longer follow-up are warranted; these must closely evaluate complications such as sling infection, erosion and rectal ulcer requiring sling removal. Furthermore, owing to legitimate concens regarding the use of pelvic mesh, it is essential that any patient considered for this procedure should be discussed at a multidisciplinary team meeting (MDM), should be subject to enhanced informed conset processes and be part of a

registry.

Summary:
The efficacy of the puborectal sling remains unproven. It may be of value in selected patients but this must be balanced against potential risk of mesh-related complications. **Grade of Recommendation: C**

1.6. Radiofrequency energy treatment

The administration of radiofrequency energy for the treatment of FI was first used in Mexico in 1997 [313]T. It is commercialized as the SECCA® procedure and received clearance from the Food and Drug Administration (FDA) of the USA in 2002. Suggested mechanisms of action include tissue-tightening effects with collagen contraction, focal wound healing, remodelling, and tissue compliance reduction.

The procedure is generally performed using local anaesthesia and conscious sedation in an outpatient setting. The SECCA® System is made up of a sterile, single-use hand-piece and a reusable RF generator. The hand-piece consists of a clear plastic anoscope with 4 retractable needle electrodes, which are deployed into the internal anal sphincter. The generator delivers low power (465 kHz, 2–5 W), temperature controlled (65°C and 85°C) energy at each needle electrode for 60 seconds. During the treatment, the mucosa is constantly irrigated by chilled water at the base of each needle to avoid burning.

RF energy is delivered at five different insertion levels each at 0.5 cm beginning at the dentate line upwards. When all 5 levels have been treated within a quadrant, the handpiece is rotated through 90° and treatment starts in the next quadrant[314]. This results in a total of 20 radiofrequency deliveries with 80 separate treatment sites. The whole procedure takes approximately 45-60 minutes.

Published studies include only one randomised controlled trial [315] 11 prospective uncontrolled studies and 1 retrospective review of medical records. Results are summarized in **Table 8**.

All studies reported radiofrequency to be an easy, safe, and well-tolerated procedure. Reported complications were mild and rare, including pain, delayed bleeding and mucosal ulceration.

The very favourable results reported by the pioneers of this technique[313, 317] have not been confirmed by later studies. Even though reports were generally positive (significant reduction of fecal incontinence score), most series did not demonstrate a 50% improvement in scores and FI often persisted at levels that were clinically

Table 8. Studies investigating the efficacy of the SECCA procedure

Study	N	FU	Outcome measures	Definition clinical response	FI score	FIQL score	Clinical response
Takahashi et al (2002) [313]	10	12	CCF-FI	>50% red in CCF-FI	13.5–5 (p < 0,001)	Impr 4 categories	80%
Takahashi et al (2003) [316]	10	24	CCF-FI	>50% red in CCF-FI	13.8–7.3 (p=0,002)	Impr 4 categories	70%
Takahashi et al (2008)317	19	60	CCF-FI	>50% red in CCF-FI	14.4–8.3 (p < 0,00025)	Impr 4 categories	84%
Efron et al (2003) [318]	50	6	CCF-FI, VAS	>10% impr at VAS	14.5 –11.1 (p < 0,0001)	Impr 4 categories	60%
Felt-Bersma et al (2007) [319]	11	12	Vaizey score	Subjective improvement	18.8–15 (p=0,03)	-	55%
Lefebure et al (2008) [320]	15	12	CCF-FI, VAS	>50% red in CCF-FI	14.1–12.3 (p=0,02)	Impr 1 category (Depression)	13%
Walega et al (2009) [321]	20	6	CCF-FI FISI	-	12.1–9.3 (p < 0,05) 36,9 – 35,2 (NS)	-	-
Kim et al (2009) [322]	8	6	CCF-FI FISI	Subjective improvement	13,6-9,9 (NS) 35,1-25,6 (p=0,885)	Impr 1 category (Embarrassment)	38%
Ruiz et al (2010) [323]	24	12	CCF-FI	>50% red in CCF-FI	15.6–12.9 (p=0,035)	Impr 3 categories (Embarrassment, Lifestyle, Coping)	12.50%
Abbas et al (2012) [324]	27	24	CCF-FI	Subjective improvement	16–10.9	-	22%
Lam et al (2014) [325]	31	36	Vaizey score	≥50% red of Vaizey score	18–14 (p < 0,001)	Impr 1 category at 6 months (Coping)	6%
Visscher et al (2017) [315]	20	6	Vaizey score	≥50% red of Vaizey score	15,6-13 ,2 (p=0,02)	-	10%
Vergara-Fernandez et al (2020) [326]	10		CCF-FI	>50% red in CCF-FI	13, 8-12,4 (p=0.24)	worsening in the depression category	-

KEY: n = number of patients; FU = Follow- up (months); FI = faecal incontinence; FIQL = Faecal Incon-tinence-related Quality of Life Score; CCF-FI = Cleveland Clinic Florida Faecal Incontinence . Scale; VAS = Visual Analogue Scale; FISI = Faecal Incontinence Severity; red = reduction; impr= improvement; –, not done

unsatisfactory. Morever, Takahashi *et al.* recently published their results of a 15-year follow-up[326] in which the therapeutic effects were not maintained. No study has been able to demonstrate changes in anorectal structure or function. Finally, the only randomized sham-controlled trial (n = 40)[315] showed only a minimal improvement in FI score compared with sham, with a negligible clinical impact, leading the authors to conclude that SECCA should not be recommended for patients with FI.

Summary:
Temperature controlled radiofrequency energy may transiently improve continence in patients with mild to moderate symptoms, but long-term results are disappointing. A single controlled trial showed no benefit. **Grade of Recommendation: C**

1.7. Autologous Cell Therapies

Despite the development of various devices to augment or replace the anal sphincter, there is an inherent feeling that the most ideal solution would be a biocompatible regeneration of tissue and restoration of its function.

Cell therapy appears to be a potential solution for restoring cells, tissues and even organs whose function is impaired following events as trauma, degenerative disease, or aging. Many skeletal muscle diseases are now receiving attention and the anal sphincter is no exception. FI is now the subject of several preclinical and clinical studies. 'Cell therapy' in this context usually corresponds to the use of freshly isolated or culture-expanded cells for local or systemic injection. In contrast, 'tissue engineering' usually corresponds to the use of scaffolds alone, or in combination with cells and/or trophics factors. To date, only cell therapy has been used in clinical studies, however, the successful creation and implantation of intrinsically innervated anal sphincter constructs have been reported in rats and rabbits[327, 328].

To date, data are available for 118 patients with FI receiving cells in 7 studies **[Table 9].** These comprised four observational studies (two with the same patient cohort), one case-control study and three randomised controlled trials. The majority of published cell therapy clinical studies have used autologous myoblasts (usually termed *autologous muscle-derived cells*: AMDC) injected into the EAS under ultrasound guidance. The first study of AMDC in humans was published in 2010 by Frudinger *et al.* [329]. This observational study included ten women with FI from obstetric trauma with non-operated anterior lesions that were refractory to conservative treatment. The authors took a striated muscle biopsy (approximately 1 cm^3) from the pectoralis muscle. In the laboratory, the muscle was digested and myogenic cells were isolated and cultured. After a mean cultivation time of 39 days, cells were harvested and pelleted in a concentration of ~20 million cells/ml medium with 10% autologous serum. Twelve to fourteen AMDC injections of 0.5 ml were performed under ultrasonic guidance in a semi-circular array, including EAS divided ends and the intervening scar. In order to optimise cell integration, patients received electrical stimulation via

Table 9. Studies of autologous cells for faecal incontinence

Study	Study type	N	FU (m)	Cell type	Adjuncts	Main outcomes
Frudinger et al 2010[329]	O	10	12	AMDC	NMS	↓ FIE ↓ Wexner score ↑FIQL
Frudinger et al 2015[330]	O		60	AMDC		↓ FIE ↓ Wexner score ↑FIQL ↑Anal resting pressure ↑ Squeeze pressures
Frudinger et al 2018[331]	O	39	12	AMDC	NMS	↓ FIE ↓ Wexner score ↑FIQL ↑High-pressure zone length
Romaniszyn et al 2015[332]	O	10	12	AMDC	-	18 weeks: subjective impr : 6/9 (66.7 %) ↓ Wexner score ↓FISI 12 months: subjective impr : 4/9 (44,4%) ↓ Wexner score ↓FISI ↑Squeeze anal pressures ↑High-pressure zone length increased ↑Resting pressure ↑ EMG Signal amplitude
Khafagy et al 201[786]	CCS	20 vs. 20	28	BMAC	OASR	↓ Wexner
Sarveazad et al 2017[333]	RCT	9 vs. 9	2	A-D MSC	Post-SR	↑ muscle area and EMG signal amplitude
Boyer et al 2018[334]	RCT	12 vs. 12	12	AMDC	BF	6 months None 12 months - ↓ Wexner score in the cell group - Higher response rate at 12 months in the treated than the placebo arm (58% vs 8%, P = 0.03)
de la Portilla et al 2020[335]	RCT	8 vs.8	11	A-D MSCs	-	None

KEY: n = number of patients; FU = Follow- up (months); FI = faecal incontinence; FIQL = Faecal Incon-tinence-related Quality of Life Score; CCF-FI = Cleveland Clinic Florida Faecal Incontinence . Scale; VAS = Visual Analogue Scale; FISI = Faecal Incontinence Severity; red = reduction; impr= improvement; –, not done

an anal plug 15 min per day for 10 weeks prior to injection and for 28 days post-surgery. At one-year follow-up, there were marked reductions in Cleveland Clinic Incontinence score (mean 14 points) and incontinence episodes per week (mean 8 episodes). Overall quality of life was also significantly increased. However, there were no important changes in ultrasonography and anal pressures were unchanged. No adverse events appeared during follow-up. The authors concluded that the treatment is feasible, safe, well-tolerated, and improved symptoms of anal incontinence due to obstetric anal sphincter trauma.

Five-year follow-up of all ten patients was published in 2015[330] with maintenance of all outcomes and no later adverse events. Moreover, there was a rise in resting and squeeze pressures with the 5-year value significantly higher than at baseline, suggesting an increase of muscle strength with time.

The same year, Romaniszyn *et al*. [332] published a further prospective study of ten patients undergoing AMDC therapy. Muscular biopsy was obtained from the quadriceps. After an average of 5.5 ± 0.8 weeks of *in vitro* culture, a total of $3x10^8$ cells were injected around the entire circumference of the EAS. In patients with an EAS defect, the volume of the suspension was divided into three 1-ml portions: 1 ml was injected on both sides of the muscle scar, one was applied on the remaining circumference of external sphincter muscle ring, and the last portion was injected directly into the scar. Follow-up was available for nine patients. At 18 weeks, six patients (66.7 %) reported subjective improvement with significant increase of squeeze anal pressures and high-pressure zone length on manometry (five very significantly (55.6%)). Electromyographic (EMG) examination showed a significant increase in signal amplitude in all patients. At 12 months, two of the six patients with good results at 18 weeks reported deterioration of continence, with deterioration of manometric and EMG parameters. Nevertheless, mean values were still significantly improved compared to pre-implantation. The remaining four patients (44.4%) persisted with satisfactory results.

A phase II, randomised, double-blind, placebo-controlled trial of AMDC was published in 2018 [334]. Twelve patients received intrasphincteric injections of cells and 12 received placebo. At 6 months, median Cleveland Clinic Incontinence score significantly decreased from baseline in both the therapeutic (9 vs. 15, P = 0.02) and placebo (10 vs. 15, P = 0.01) groups with differences failing to meet the primary endpoint. However, at 12 months, median score continued to reduce in the AMDC group (6.5 vs. 15, P = 0.006), while this effect was lost in the sham injection arm (14 vs. 15, P = 0.35), with a higher response rate observed in the treated group (58% vs 8%, P = 0.03). After delayed frozen AMDC in the placebo group, the response rate was 60% (6/10) at 12 months. Despite these good clinical results, no physiological changes (sonography, MRI or electrophysiological tests) were observed.

More recently, Frudinger *et al*. [331] reported data for 39 patients who received cryo-preserved AMDC for FI due to EAS damage and/or atrophy, including 5 males. Twelve injections (79.4 ± 22.5 × 10^6 AMDC) were extended in a circular array directly into the EAS and all patients performed anal canal electrical stimulation for 4 weeks post-implantation. After 12 months, frequency of weekly incontinence episodes (primary outcome) and FI QoL improved significantly. In 80.6% of males and 78.4% of females, the FI frequency decreased by at least 50%; Cleveland Clinic Incontinence Scores and severity of FI complaints also decreased significantly, independent of sex and aetiology of FI. Anorectal manometry showed a significant change in the functional length of the anal canal (high-pressure zone length), with an increase of 11 mm (95% CI 7-15mm) while the other structural and functional variables remained unchanged. **LEVEL OF EVIDENCE 3**.

Other types of adult stem cell used clinically as a treatment for FI are mesenchymal (bone-marrow- or adipose-derived) stem cells. Three studies have reported their application to reinforce anal sphincter repair. In 2017, a case-control study from Khafagy *et al.* [86] reported results from 20 patients with EAS defect who underwent overlapping anal sphincter repair and autologous Bone Marrow Aspirate Concentrate (BMAC) injection. These were compared to a historical control group of patients managed with sphincter repair alone. At the end of follow-up, group with BMAC injection had significantly lower mean postoperative Cleveland Clinic Incontinence Scores (5.4 ±7.6 Vs 10.6 ± 7.4; p= 0.03). Both groups demonstrated a significant decrease in the size of the residual EAS defect; however, there was no significant difference between groups regarding the extent of the postoperative EAS defect except in patients with smaller preoperative defect (equal to or less than one-third of the anal circumference). The same year, Sarveazad *et al.* published a double-blind randomised trial using allogenic adipose tissue-derived stem cells (ASCs) injected after sphincteroplasty[333]. Nine patients received ASCs injected into each end of the muscle and 9 received placebo in the same manner. After two months, both groups improved equally in symptom scores. However, EMG activity and muscle area (the ratio of the area occupied by the muscle to the total lesion area in echography) were significantly higher in the ASC group (P = 0.002). The authors concluded that injection of ASC during sphincter repair may cause replacement of fibrous tissue with muscle. However, the exact mechanism of action remains unclear. **LEVEL OF EVIDENCE 3**

Most recently, a Spanish randomized, multicentre, triple-blinded, placebo-controlled pilot study[335] reported the use of autologous ASC obtained from surgically excised adipose tissue. Sixteen patients with a sphincter defect not exceeding 100 degrees were included. ASC or placebo (4 ml Ringer's lactate excipient) were injected into the muscular ends of the sphincter defect under endoanal echography guidance. Infusion procedures were successful in all the patients, but 48 weeks after surgery, there were no significant differences in any of the assessed clinical, manometric or ultrasonographic parameters. Other major studies are ongoing e.g. EU-funded AMELIE RCT of microsphere anchored AMDC and others are scheduled to report soon (Cook Myosite study of AMDC).

Currently, the place of cell therapy in the treatment algorithm of faecal incontinence remains to be determined. Safety seems to be assured and encouraging results have been published. However, it is difficult to draw any firm conclusions from the published data because of heterogeneity concerning the type of cells used, the method and the assessment used. Further studies in both animal models and clinical settings are needed before CS therapy for FI can be ready for ordinary clinical use.

Summary:
Current experience of cell therapy is limited and varies in outcome. Given the complexity of the therapy, it remains experimental and should only be offered as part of a well-designed research study. **Grade of Recommendation: C**

1.8. Colostomy

A permanent colostomy is usually formed as a last resort for severe FI when all other interventions have failed. Because colostomy is generally regarded as a failure of treatment, its effectiveness, perioperative complications, and impact on the quality of life have never been properly evaluated except for patients with functional bowel

disorder after spinal cord injury[336, 337]. Colostomy can be a successful management strategy for the population with severe faecal incontinence that restores dignity and allows patients to regain social function. No randomised controlled trials or high quality cohort studies have been reported for colostomy for faecal incontinence; only one systematic review with high levels of heterogeneity (level 4)[338], one poor-quality case-control study (level 4)[339] and two case series (level 4)[340, 341] were identified.

Colquhoun *et al.* [339] conducted a cross-sectional postal survey, comparing quality of life between 71 patients with FI and 39 with a colostomy created for rectal cancer, complicated colonic diverticular disease or FI. Analysis of the Short Form 36 General Quality of Life Assessment revealed significantly higher social function score in the colostomy group than in the FI group (0 vs. -0.6, p=0.022). Age- and sex-adjusted regression analysis of the Faecal Incontinence Quality of Life score revealed significantly higher scores in the coping (2.7 vs. 2.0, p=0.005), embarrassment (2.7 vs. 2.2, p=0.014), and lifestyle scales (3.2 vs. 2.7, p=0.14) in the colostomy group compared to the faecal incontinence group. The authors concluded that a colostomy was a viable option for patients suffering from severe faecal incontinence and offered a definitive cure with improved quality of life.

Tan *et al.* [338] performed a systematic review, using prior published data to compare the cost-effectiveness between end stoma (ES), artificial anal sphincter (AAS) and dynamic graciloplasty (DG). Quality-adjusted life years (QALYs) and incremental cost-effectiveness ratio (ICER) were compared between the three interventions by obtaining probability estimates for patients with FI from the reviewed study data (these being supplemented by expert opinion). The end stoma was the most cost-effective therapy at 5 years, with a QALY gain of 3.45 for GB£16,280 and an ICER of GB£4,719 / QALY, compared to AAS (4.38 for GB£23,569; GB£5,387 /QALY) and DG (4.00 for GB£25,035; GB£6,257/QALY). After 10 years, AAS became the most cost-effective surgical intervention, with a QALY gain of 8.384 for GB£32,397 and an ICER of GB£3,864/ QALY, compared to ES (6.9 for GB£27,910; GB£4,046 /QALY) and DG (7.678 for GB£35,165; GB£4,580 /QALY). Any inference from the results of this study is limited by uncertainty around modelled probability estimates (these themselves being derived from poor quality studies).

Norton *et al.* [340] examined patients' view of a colostomy by conducting a questionnaire study of patients who had a colostomy created to manage their FI. Sixty-nine people (58 women) responded. When patients were asked to rate their "ability to live with their stoma now" on a scale of 0-10, the median score was 8 (range 0 – 10). The majority (83%) felt that the stoma, within the past month, restricted their life "a little" or "not at all". Eighty-four percent answered that they would "probably" or "definitely" choose to have the stoma again. When they were asked the question "compared to when you were incontinent, how much change has having a stoma made to your overall quality of life?" on the scale of -5 (much worse) to +5 (much better), the median rating was +4.5 (range -5 to +5). The authors concluded that health care professionals should discuss the option of a stoma with incontinent patients because of the overwhelmingly positive outcomes.

An end sigmoid colostomy without proctectomy is usually recommended as the procedure of choice for patients who elect colostomy for the management of their refractory FI. Creating such a colostomy, however, does not always solve all the problems of patients. Catena *et al.* [341] reported a retrospective chart review of 44 patients (35 women) who underwent elective end sigmoid colostomy for FI of various etiologies. After colostomy formation, 19 patients (43%) were asymptomatic, while the other 25 experienced such problems with their rectal stump as diversion colitis and mucus leakage. Of the 25 patients, 12 (27% of the total) who underwent a secondary proctectomy due to the rectal stump problems sufficient to warrant the operation, histological examination revealed diversion colitis in 6. Age was the main factor associated with progression to proctectomy with younger patients being more likely to require rectal excision.

Summary:
Formation of an end colostomy should be considered as a reasonable treatment option for patients with refractory faecal incontinence who are unsuitable for or have failed other treatment modalities and who able to accept the associated alteration in body image. **Grade of Recommendation: C**

2. HISTORIC PROCEDURES

2.1. Postanal Repair

Postanal repair was first reported by Sir Alan Parks in 1975 [342]. This procedure was designed to increase the length of the anal canal, restore the anorectal angle, and re-create the flap valve mechanism, which at the time was thought essential for maintaining faecal continence. Success rates rates dropped with follow up to 15% from the initial reports of 83%, further affected by the definition of the success, the length of follow-up, and possibly the cause of incontinence. Published studies regarding postanal repair include four systematic reviews of randomised controlled trials[343-346], two randomised controlled trials[347, 348], two non-randomised cohort studies[349, 350], 8 case series of good quality[89, 351-357] and 11 case series of poor quality (not referenced). Subsequent observational studies with a median follow-up of more than 5 years revealed that continence deteriorated with time. Despite 60-80% of patients reporting persisting symptomatic improvement, only one-third were actually continent to liquid or solid stool [353, 355-358]. Even in the most recent study reporting the long-term outcome of postanal repair [359], only 26% reported none to minimal incontinence with the Cleveland Clinic Florida Fecal Incontinence score being between 0 and 5, while 79% improved symptomatically with a mean follow-up of 9.1 years.

These reports of increasingly poor outcomes have significantly diminished the popularity of this procedure. Since 2012, no new studies regarding the role of postanal repair for the treatment of faecal incontinence, other than one systematic review have been reported [346], with surgeons focusing on newer surgical options.

Summary:
Postanal repair should no longer be offered routinely to patients with faecal incontinence (due to the advent of newer treatments). **Grade of Recommendation: D.**

2.2. Non-Stimulated Muscle Transposition

Several muscle transposition procedures have been described for the treatment of faecal incontinence since the early 20th century when gluteus maximus muscles, transposed in a variety of configurations, were first used to create a neosphincter[360]. Small case series have subsequently described variable success rates [361-365]. A single randomised comparison to total pelvic floor repair in women with post-obstetric incontinence showed similar, variable results[366].

In 1952, Pickrell *et al.* [367] described the use of transposed gracilis muscle to create a neosphincter for incontinent children with neurological and congenital anomalies. Several subsequent series in

children and adults showed variable results that generally deteriorated over time[368-370]. While still used as treatment for recto- and ano-vaginal fistula[371], both gracilis and gluteus transpositions are no longer used to treat incontinence due to early complications such as wound breakdown followed by poor muscle function (see below) and problems of constipation.

Summary:
Unstimulated muscle transpositions should no longer be routinely offered for patients with faecal incontinence. **Grade of Recommendation: D**

2.3. Stimulated Muscle Transposition

Even after successful gracilis muscle transposition, functional outcomes are limited by two physiological factors. First, patients are unable to consciously maintain tonic contraction of their neosphincters over long periods of time. Furthermore, even if patient volition were not a problem, the gracilis muscle is poorly suited to tonic contraction. While the external anal sphincter comprises predominantly slow-twitch, fatigue-resistant type I fibres, the gracilis muscle comprises predominantly type II, fast-twitch fibres that are rapidly fatiguable [372]. Graded electrical stimulation transforms type II into type I muscle fibres, and the use of an implantable electrical pulse generator has been shown to convert transposed gracilis to a muscle with predominantly type I fibres[366]. The gracilis muscle is well suited to electrical stimulation due to the relatively constant proximal location of its neurovascular bundle, which is easily identified at surgery[373].

Successful electrical stimulation of a transposed gracilis muscle [popularly termed either *dynamic graciloplasty* or *electrically stimulation gracilis neoshincter*] was first reported in 1988 [365], and thence in 1990 in a case series of 6 patients of whom 5 had closure of a defunctioning stoma with improvement in continence [374]. Subsequent larger case series (with up to 200 patients) are shown in table 10. No randomised trial has ever been conducted and most case series come from a small group of enthusiastic centres (with some overlap of patients at different publication time points).

However, some multicentre data are available. Madoff *et al*. [375] studied 139 patients from 12 US centres, 128 of whom had gracilis wraps and 11 gluteus wraps. Of the cohort, 104 were treated for faecal incontinence, and 35 underwent total anorectal reconstruction following abdominoperineal resection for cancer. Success rates for graciloplasty were 71% for patients with acquired incontinence and 50% for those with incontinence due to a congenital abnormality. There was a total of 138 complications for the entire group. Wound complications (41 major and 35 minor) were both the most prevalent and the most consequential. Other complications included pain in 28 patients (22%), hardware problems in 14 (11%) and tendon detachment in 4 patients (3%). Centres with significant prior experience of the procedure had substantially fewer major wound complications (17.4 vs. 33.1%) and significantly higher success rates (80% vs. 47%).

Mander *et al*. [376] reported the results of dynamic graciloplasty in 64 patients with refractory faecal incontinence treated at 7 UK centres. There were 24 infective complications, 5 of which involved perineal wound breakdown and 3 of which required re-operation. Forty-four (69%) patients became continent to solid stool 1 month following stoma closure. Evacuation problems developed in 16 patients (25%), and this led to failure in 14. At a median of 10 months follow-up, 29 patients had a good functional result.

Baeten *et al.* [377] reported the results of dynamic graciloplasty in 123 patients treated at 20 centres as part of the Belgium Dynamic Graciloplasty Therapy Study Group (DGTSG). The aims of this study were to assess both the safety and efficacy of this treatment; 189 adverse events occurred in 91 patients, including one death due to pulmonary embolism. There were 18 major and 31 minor infectious complications. There were 42 instances of therapy-associated pain, occurring variably in the donor leg, at the anal canal, or at the device site. There were 11 lead dislodgements but no problems with lead breakage or pulse generator malfunction.

Longer-term data are available on a smaller number of patients [Table 10]. Thornton *et al*. [378] reported on the 5-year follow up of 38 patients who had undergone dynamic graciloplasty. Of the 33 patients available for follow-up by telephone interview, obstructive defaecation was a problem for 11% of the cohort and 16% had been converted to a permanent colostomy. Of those with a functioning graciloplasty (22 patients) who reported a faecal incontinence score of less than 12 (range 0-24), 50% reported problems with obstructive defaecation and 64% felt their bowel habits had negatively affected their quality of life. Long-term complications were primarily related to stimulator problems; ten patients required 15 operations to replace stimulator components. However, 72% of patients reported pain, swelling or paresthesia of the donor leg and 27% reported sexual dysfunction. These results typify other long-term experience with high rates of therapy attrition due to poor function or accumulating adverse events / technical failure. **LEVEL OF EVIDENCE 3**

Two systematic reviews have reached similar conclusions regarding the effectiveness of dynamic graciloplasty. Chapman *et al.* [379] on behalf of the Australian Safety and Efficacy Register of New Interventional Procedures-Surgical (ASERNIP-S) reviewed 37 original articles published between 1991 and October 2000. All papers were judged to be of poor evidential quality (all case series except one case-control study using historic controls). Mortality excluding cancer deaths was 1% (95% confidence interval 1-3%) and morbidity 1.12 events per patient (95% CI 0.14 - 2.08). Success was variably defined between studies but was reported as ranging from 42-58%. The ASERNIP-S Review Group determined that “the safety of the procedure cannot be determined at the present time due to an incomplete and/or poor-quality evidence base” and that “efficacy is established.” Tan *et al.* [338] examined three treatments for faecal incontinence including dynamic graciloplasty, artificial bowel sphincter and end stoma. They concluded that the most cost-effective intervention was an end stoma, the artificial bowel sphincter was most cost-effective after 10 years and that dynamic graciloplasty should only be considered as an alternative in highly specialized centres. **LEVEL OF EVIDENCE 3**

Summary:
Stimulated graciloplasty may still be offered to highly selected patients who have failed or are unsuitable for other modalities of treatment (particularly where there has been gross loss of native sphincter tissue) and who are willing to accept the high risk of harm associated with this procedure. Otherwise, it has largely been superseded by sacral neuromodulation. **Grade of Recommendation: B** [NB: this recommendation is based on availability of suitable implantable devices: the original Medtronic device is no longer available].

2.4. Artificial Anal Sphincter

Various types of artificial sphincter devices have been designed and proposed to treat severely incontinent patients. These had some common characteristics. They frequently derived from innovations and experiments from sister specialties, urology for instance, but also upper GI surgery and their development was supported by

significant investments from companies to establish them in the market. Due to concerns about risks, effectiveness in mid/long-term and reproducibility they have all now been abandoned.

2.4.1. Artificial bowel sphincter (ABS) - Acticon™ Neosphincter

This procedure for anal sphincter replacement was developed in the 1990s. During the surgical procedure, a silicone-made pressure-regulated inflatable cuff was placed around the upper anal canal and tubing from the cuff was directed along the perineum and connected to a pump placed in the scrotum or labia. Tubing was used to connect the pump to a pressure regulating balloon implanted in the pre-vesical space. The balloon gave approximately 100cm H_2O pressure into the perianal cuff. The control pump allowed a fluid transfer from the cuff to the balloon when the patient squeezed the pump to empty the cuff and allow for the anal canal to open and defaecation to occur. The fluid then slowly returned to the cuff which resulted in the closing of the anal canal and restoration of continence.

In a systematic review [1] the primary concerns with ABS implantation were infection, with rates ranging from 20 to 45% and mechanical failure, with a revision rate proportional to the length of follow-up. A further systematic review found that need for surgical revision increased, while continence decreased, with time[389]. The authors concluded that both device refinements by the manufacturer and meticulous aseptic procedures at implantation were keys to help improve these outcomes.

In the previous edition [5] the long-term outcomes of ABS from two specialist institutions were reported. From the Cleveland Clinic, Florida, USA among others[390] the risk of explantation at 5 years after ABS implantation was 57%. In a series of 52 patients from Nantes, France[391] 35 patients (67.3%) still had an activated device *in situ* at last review (mean follow-up: 64.3±46.5 months) but 14 (26.9%) required definitive explantation, the majority due to infection. Very recently a further experienced institution (Maastricht, Netherlands) reported their long-term results with ABS. These concurred with previous data: at a mean 5-year follow-up, 50% patients had the device explanted, 80% suffered from complications and only 29% had faecal continence restored[392]. **LEVEL OF EVIDENCE 3.**

With this background, even specialist centres with a dedicated interest and experience in ABS reduced frequency of implantations and in 2018 the ABS Acticon Neosphincter™ became no longer commercially available after the acquisition of AMS by Boston Scientific. To the authors' knowledge the only similar device is currently the Anal Soft Band [AMI, Feldkirch, Austria] but no recent reports on its use and results were found by systematic review. It is perhaps a pity that an effective and well-performing device is no longer available for patients with end-stage faecal incontinence whose options are very limited.

Horizon scanning, several reports on an artificial anal sphincter mimicking the effect of the puborectalis muscle have come from Chinese centres but to the authors' knowledge it has not been applied to humans to date [393].

Summary:
The artificial bowel sphincter (ABS) was a treatment for patients who failed other modalities of treatment. Obstructed defaecation, device infection/erosion or failure were problematic. ABS is no longer commercially available. **Grade of Recommendation. NOT APPLICABLE**

2.5. Magnetic Anal Reinforcement – Fenix™

The magnetic anal reinforcement device (or magnetic anal sphincter – MAS (FENIX™; Torax Medical, Inc, Shoreview, MN – USA) was a device made of a series of titanium beads with magnetic cores (not MRI-compatible) and designed to augment the native anal sphincter. It formed a flexible ring around the external anal sphincter [394]. The procedure used for MAS device implantation included a single anterior incision. A perianal tunnel was created and a sizing tool allowed for measurement of the correct device size.

Table 10. Dynamic Graciloplasty: General measures of continence

Authors (ref)	Year	Number patients	Follow-up (months)	Percentage continent*
Baeten et al 380	1995	52	25.2 (mean)	73
Geerdes et al 381l	1996	67	32.4 (mean)	78
Cavina et al 382	1998	31	37.8 (mean)	85
Madoff et al 375	1999	131	24 (median)	66
Mander et al 376	1999	64	16 (median)	69
Baeten et al 377	2000	123	23 (mean)	74
Wexner et al 383	2002	83	24	53
Rongen et al 384	2003	200	16.3 (median)	72
Pennickx et al 385	2004	60	48 (median)	55
Thornton et al 378	2004	38	60 (mean)	16 †
Tillin et al 386	2006	49	43 (median)	70
Hassan et al 387	2010	31	67 (median)	71
Mege et al 388	2021	40	100 (mean)	55

*KEY: *variable definitions; does not necessarily denote perfect continence. Issues of divergence in technique arose from these studies, each of which has seen increasing consensus in the literature despite a lack of randomised trial data. Thus, intramuscular (vs. epineural) electrodes are now universally employed and divert-ing stomas and 'vascular delay' prior to muscle transposition are no longer utilized; † as defined by FI score < 12.*

The MAS was then placed with sutures to secure the device around the upper anal canal. Unlike the ABS, the MAS worked immediately once implanted, without the need for further manipulation by either the patient or surgeon.

Interestingly while developing a model of physical simulation of the human defecatory system, bench phantom testing demonstrated a positive action of the MAS to increase resistance to faecal leakage and reduce anorectal angles required to maintain continence [395].

Data concerning safety and efficacy of MAS were limited until recently to several small case series. These showed good restoration of continence with a limited number of complications, mainly infection and/or erosion, at short-[396], medium-[397, 398] and 5 year [399] follow up.

Two recent controlled studies in France (MOS STIC –Clinicaltrials.gov NCT01920607) and in the UK (SAFARI: ISRCTN:16077538 http://ukctg.nihr.ac.uk) [400] sought to compare MAS to SNM in terms of effectiveness and cost-effectiveness. Both were suspended before recruitment was complete due to withdrawal of the Fenix™ device after the acquisition of Torax Medical Co. by Johnson & Jonhson. SAFARI recently reported the outcomes of 99 participants from 18 UK sites (of a prior sample size of 350)[401]. 50 participants were randomised to FENIX vs. 49 participants to SNM. A total of 45 out of 50 participants underwent FENIX implantation and 29 out of 49 participants continued to permanent SNM. Overall, success (defined as 50% reduction in Cleveland Clinic Incontinence Score) was achieved for only 10 out of 80 (12.5%) participants, with no statistically significant difference between the two groups [FENIX 6/41 (14.6%) participants vs. SNM 4/39 (10.3%) participants]. At least one postoperative complication was experienced by 33 out of 45 (73.3%) participants in the FENIX group and 9 out of 40 (22.5%) participants in the SNM group. A total of 15 out of 50 (30%) participants in the FENIX group ultimately had to have their device explanted.

Summary:
The magnetic anal sphincter was a novel treatment for patients who had failed other modalities of FI treatment. Early results were promising, however the device is not available due to commercial decisions. **Grade of Recommendation: NOT APPLICABLE.**

2.6. Pudendal nerve stimulation

Pudendal nerve stimulation has been applied in the field of urology since the 1990s with several publications demonstrating benefit for patients with urge incontinence (mainly OAB) and bladder retention syndromes.

There have been only four observational studies of patients with faecal incontinence including a total of 32 patients who had either failed SNM or who had been deemed unsuitable due to neurogenic indications (mainly cauda equine syndrome) [402-405]. Results were promising with 60-100% success rates accepting the significant caveat of small, uncontrolled, single centre results (noting that three of the four studies came from the same centre).

It is unclear why the procedure fell from favour other than the decision of the manufacturer (Medtronic) not to pursue its license for faecal incontinence further. Reasons may include the relative difficulty (compared to SNM) of accurately placing and securing an electrode lead close to the pudendal nerve, although several methods have now been described to achieve this [406, 407], including now under direct vision [408].

Summary:
Pudendal nerve stimulation has scientific rationale and some clinical data to support its use in patients who have failed or who are unsuitable for SNM. Current use would however be off license. Grade of Recommendation: NOT APPLICABLE

III. SURGERY FOR PAEDIATRIC FAECAL INCONTINENCE

1. ANORECTAL MALFORMATIONS

Anorectal malformations (ARM) occur once in every 3000- 5000 live births. ARMs range from the minor defects that are easily treated and have excellent functional outcome, to complex malformations involving the urinary and genital tracts that are difficult to manage and invariably associated with defaecatory problems including incontinence. Infants with complex ARM may also have associated congenital abnormalities grouped as VACTERL Syndrome **V**ertebral, **A**nal, **C**ardiac**, T**racheooesophageal fistula, **R**enal, **L**imb [409]. Certain syndromes such as Currarino, Townes-Broack and Pallister-Hall syndromes are inherited in an autosomal dominant manner [410 411]. Infants with trisomy 21 also have a higher incidence of ARM.

ARMs have traditionally been classified into high, intermediate, and low malformations depending on the relationship with the levator ani muscle and fistula type [412]. ARM should be suspected at birth and a careful examination of the perineum may reveal a pit or dimple with absence of an anal opening or anterior displacement of the anus indicating a fistula. In a female, careful examination of the vestibule may reveal urogenital malformation. Multidisciplinary assessment is required with appropriate radiological investigation including 3-D image reconstruction.

Surgical treatment depends on the complexity of the ARM and associated abnormalities. A low, simple ARM may require primary anoplasty, whereas more complex ARM require a diverting colostomy with later definitive reconstruction [413]. In a male infant with a urinary fistula, the colostomy should be divided with a mucus fistula to fully disconnect the bowel from the urinary tract. A later distal colonogram is helpful in planning reconstruction [414].

Posterior sagittal anorectoplasty (PSARP) allows the abnormal anatomy to be assessed under direct vision and facilitates precise corrective surgery [415]. In brief, a mid-sagittal incision is performed, and the sphincter mechanism is completely divided in the midline. The rectum is separated from the genitourinary tract and moved down to the perineum. The most challenging aspect of the operation is separation of the rectum from the vaginal or urinary tract, which effectively requires creating two walls out of one septum without damaging each structure. This approach can also be used for reoperation in anorectal malformations [416] and can be applied for reconstruction of severe perineal trauma [417].

In both male and female infants, urethral-perineal fistula is the simplest to correct. This requires the so-called “minimal posterior sagittal approach” which enlarges the stenotic orifice and relocates the rectal orifice posteriorly within the limits of the sphincter complex. For males with recto-urethral-bulbar fistula or recto-urethral-prostatic fistula and females with recto-vestibular fistula or cloaca with a short (less than 3cm) common channel, the posterior sagittal approach is the main operation performed. For males with higher fistulae such as a recto-bladder neck fistula and other complex and

unusual defects and females with cloacae with a long (greater than 3cm) common channel and complex defects, the posterior sagittal approach needs to be coupled with abdominal access.

Laparoscopic assisted anorectal pull-through procedure (LAARP) [418], is associated with shorter hospital stays and fewer wound complications [419 420]. Robotic assisted LAARP has also been described[421] and may offer short term benefits [422]. In brief, a sharp dissection and cautery is used laparoscopically to expose the rectal pouch down to the urethral or vaginal fistula, which is clipped distally and divided. The pelvic floor musculature and the puborectal sling are identified and electrostimulation is used externally to define the centre of the anal dimple. A skin incision is made, centred at the strongest cephalad contraction. Guided by laparoscopic visualization, a trocar, consisting of a radially expandable sheath over a Veress needle, is passed through the defined plane in the external sphincter muscle complex and advanced into the pelvis between the two limbs of the pubococcygeus muscle, forming a passage through the centre of the striated muscle complex and levators. The rectal fistula, which has been dissected out laparoscopically, is grasped using the perineal trocar and exteriorized to the perineum. Anorectal anastomosis is then performed [418] .

A recent study of long term functional outcome comparing PSARP (n=34) to LAARP (n=32) ARM children with recto-bladder neck and recto-prostatic fistula found that LAARP is a less invasive procedure (shorter operative time and post-operative hospital stay) and both short term- and long term outcomes after LAARP were equivalent if not better than those of PSARP in children with high ARM [420, 423] **LEVEL OF EVIDENCE: 3.**

The most complex malformations are cloaca and cloacal exstrophy. In females with cloaca, the rectum, vagina, and urethra fail to develop separately and instead drain via a common channel that opens into the perineum as a single orifice. The repair of cloacal malformations is most often performed using a posterior sagittal anorecto-vagino-urethroplasty (PSARVUP) or total urogenital mobilization (TUM) with or without laparotomy [424]. The PSARVUP extends the anorectoplasty with a meticulous dissection of the combined vaginal–urethral walls, followed by the reconstruction of distal parts of both structures. In 1997, total urogenital mobilization (TUM) was presented by Peña as a new, faster, surgical approach for certain cases of cloacal repair with better cosmetic results[425], however a recent systematic review found that complications rates after PSARVUP and TUM were similar [424].

TUM separates the rectum from the vagina and both vagina and urethra are then mobilised together. The advantage of this technique is to avoid separating rectum, vagina, and urethra completely which is not always feasible and risks damaging these structures. This technique avoids the risk of urethrovaginal fistula and vaginal stricture previously reported as complications in 10% of the cloacal repair and also gives enough mobilisation to allow more than 50% of all cloacal repairs without opening the abdomen [426 427] . Functional outcomes depend on the severity of the malformations.

A review of more than 1000 anorectal malformation cases showed 100% of infants who had perineal fistula repair achieved continence. Approximately 55% of patients who had been operated for recto-vestibular fistula had bowel control. Any malformations more complicated resulted in only up to 30% achieving continence. All patients who had recto-bladder neck fistula repair were incontinent. The defects were categorised by the length of the common channel that can be measured endoscopically. The length of the common channel can vary from 1 to 10 cm. The longer the common channel (>3 cm), the higher the chance for poor bowel control, neurogenic bladder, and reproductive abnormalities[426]. Overall, it is estimated that nearly 40% will have voluntary bowel movement and no soiling but some of them may still lose bowel control in case of severe diarrhoea and 25% of all repairs will result in total incontinence[427].

For the group of patients with persistent incontinence following the corrective surgery, the next aim will be to keep the colon clean to avoid incontinence and improve quality of life. A good option is implementation of a bowel management program whereby the patient and family are instructed in the use of a daily enema, manipulation of diet and medication to remain clean[428]. This is also a good treatment for constipation, which is the most common difficulty after corrective surgery.

The Pediatric Colorectal and Pelvic Learning Consortium found that bowel management programmes need to be individualized and to change as children age [429]. Although most young children accept their parents administering enemata, when they get older, they want privacy and rectal enemata on daily basis become an unpleasant routine. In such cases, continent appendicostomy is a feasible option, whereby a conduit for the administration of an antegrade continence enema (ACE) is created. First described by Malone [430] , it has become an important option in paediatric surgery for functional bowel disorder [431]. According to the initial description, appendicostomy was created by dividing the appendix at its base and reimplanting by a reverse manner into the cecum, which was then exteriorized through the right lower quadrant. Malone later revised the technique and reimplantation of appendix is no longer considered necessary [432] . Levitt introduced utilising the appendix in situ and added caecal plication to prevent reflux of stool and exteriorizing through umbilicus fold rendering it less noticeable [433]. This appears to yield good long-term results though other studies have shown that caecal fixation and wrap may be unnecessary for appendicostomy [434]. The construction of appendicostomy with burial of the appendiceal tip appears to help avoid problems of exposed mucosa such as bleeding and mucus discharge. From this perspective, a few techniques have been suggested such as V-Y flap [432] and Y-appendicoplasty [435] .

For patients without an appendix, a neoappendix could be formed from ileum or caecum [436-438]. A laparoscopic antegrade continence enema procedure has been reported to yield as good result as the open procedure [439-442]. This procedure is not a cure to the problem but a more acceptable method for many children to engage in a bowel management programme without the need for rectal enemata. The success rate is variable, between 61-96%[438, 441, 443-446] with older children benefiting more[447]. Hoekstra *et al.* reported that almost 85% of patients were satisfied with their ACE stoma [448] **LEVEL OF EVIDENCE 3.**

As with any operation, there are complications associated with antegrade continence enema. Preteen patients (<12 years old) experience more stomal leakage than teenage patients[449]. These complications cause 10-33% of patients to undergo revision of the appendicostomy[427, 450]. Stoma prolapse, pressure sore, wound infection, anastomotic leak, stomal granulation, caecal-flap necrosis and caecal volvulus are less common complications reported after ACE [451, 452]. **LEVEL OF EVIDENCE: 3**

Summary:

Anorectal malformation is amenable to surgical reconstruction. Laparoscopically assisted anorectal pull-through procedure is offered as the preferred technique. Outcomes primarily relate to the height and complexity of the abnormality. Evacuation disorders and incontinence often require daily enemas. The Malone antegrade continence enema may provide a more acceptable means of managing continence. **Grade of Recommendation: C**

IV. SURGERY FOR EVACUATION DISORDERS AND INCONTINENCE

Significant rectal retention of faeces results in faecal incontinence in children and older people, indeed, constipation with or without faecal impaction may be the commonest cause of incontinence in these age groups[453, 454]. Similarly, if the rectum is completely empty then incontinence (at least of faeces) cannot occur. On this basis, health technologies that address rectal emptying are often recommended on a regular basis or for specific occasions e.g. enemata, trans-anal irrigation. There is however increasing recognition that a very significant proportion (approximately 40% in a recent study of over 4,000 patients)[455] of adults presenting for specialist management have coexistent symptoms and many have radio-physiological evidence of a significant rectal evacuation disorder. Such patients may describe classic symptoms of post-defaecatory leakage but as commonly have a mixed pattern of incontinence (e.g. urge / passive) that may not immediately indicate rectal evacuation disorder, not least because they may also have a functional or structurally defective sphincter concomitant on a shared pelvic pathophysiology[456]. **LEVEL OF EVIDENCE: 3.**

This observation has important implications to specialist management. First, it supports the use of tailored biofeedback therapy given that this has potential to improve both sphincter function, sensation of rectal filling and coordinated anorectal relaxation[457, 458]. Secondly, it promotes caution when using sphincter augmenting procedures. Worsened or new symptoms of obstructed defaecation have been reported in approximately one third of patients after overlapping anterior anal sphincter repair [116] and up to 50% patients after gracilis transposition[459]. There are also data suggesting that a pre-existent evacuation disorder prejudices the outcomes of neurostimulation[153]. This raises the question of whether proven structural causes of rectal evacuation disorder e.g. rectocele and internal prolapse should be surgically targeted before other procedures are offered. The latter is supported by some studies of rectocele repair that show significant improvement in faecal incontinence after surgery [460] but also by an evolving body of literature on use of rectal suspension procedures, notably laparoscopic ventral rectopexy (LVR) [461, 462]. Significant improvements in incontinence symptoms and prospectively studied summative incontinence scores[462-465] have been documented for several studies of LVR in patients treated primarily for obstructed defaecation syndrome with internal prolapse. Further, LVR has been specifically targeted to patients with faecal incontinence in two studies [466, 467]. The first of these studies evaluated the faecal incontinence severity index (FISI) in 72 patients with high-grade internal prolapse [Oxford grade III or IV] [465] with incontinence not responding to maximal medical treatment and demonstrated a reduction in median score from 31 to 15 points, [P <0.01]. These authors went on to suggest and a sequence of care where SNM is reserved for patients with persistent faecal incontinence after LVR [468]. Despite concern that nearly all studies supporting this line of reasoning have arisen from one institution (Oxford), it seems reasonable that patients presenting with faecal incontinence should be directly questioned regarding symptoms of obstructed defaecation and undergo appropriate clinical examination and radio-physiological investigations e.g. proctography as part of the decision-making process. **LEVEL OF EVIDENCE 4**.

Patients with high grade internal rectal prolapse should be considered for rectopexy to address the internal prolapse before consideration of other advanced interventions. This is especially true for patients with transanal rectal intussusception [Oxford grade IV or V] where the prolapse itself will compromise anal closure. A repair should be undertaken for clinically significant rectoceles in which trapping of contrast can be demonstrated post simulated defaecation. **LEVEL OF EVIDENCE 4.**

Stapled transanal resection of rectum (STARR), a technique developed by Antonio Longo from the PPH (procedure for prolapse and haemorrhoids, also known as stapled haemorrhoidopexy) may also have a role in managing patients with rectal intussusception and rectocele resulting in obstructed defaecation and associated incontinence. A detailed review is beyond the remit of this monograph, however the European STARR registry reporting outcomes in 2,838 patients, found significant improvements in the CCF-IS at both 6- and 12-months following surgery in addition to improvements in the symptoms of obstructive defaecation [469]. There is an increase in urgency of defaecation in 20% of patients and new onset incontinence in 1.8%. More recently a survey among colorectal specialists from European centres with experience of STARR reported up to 10% new onset incontinence following the procedure. The particular role for STARR in managing patients with incontinence associated with obstructed defaecation remains to be established [470] and the general poularity of this procedure is declining in any case due to concerns about other long-term complications e.g. chronic pain. **LEVEL OF EVIDENCE 4.**

Summary:
Obstructed defaecation is common and may contribute to incontinence. Comprehensive assessment is required. Rectocele repair or ventral rectopexy may improve continence in carefully selected patients. Randomized studies are lacking. Grade of Recommendation: C

V. OUTCOME MEASURES IN FAECAL INCONTINENCE

There is no doubt that this is another area of challenge for FI researchers. The current literature is beset with an over-reliance on choosing a single metric as a primary outcome for studies. The commonest choice by far has been some measure of FI episodes per unit time (usually per week). This continuous variable is then commonly converted to a binary category that takes a notional percentage change as indicative of treatment 'success'. On this basis, the proportion of patients with a 50% reduction in symptoms is compared between intervention and comparator.

There is general agreement that patient-based outcome measures (PROMs) are most appropriate for studies of faecal incontinence. However, standardisation of the optimal instrument or combination of instruments remains a challenge in clinical incontinence research. While many incontinence-related quality of life measures have been proposed and claim to have been "validated,", adequate psychometric validation is lacking for many [471]. Whether the main outcome measure following incontinence treatment ought to be incontinence severity, incontinence-related quality of life, or a combination of these factors is unknown.

FI is a complex symptom relating not only to the continence mechanism itself, but also to the general bowel function in terms of motility, sensory and/or motor disturbances on spinal and supra-spinal levels. Thus, FI as a symptom can present differently depending on the underlying disease and lifestyle.

Hallbook and Sjodahl developed a bowel questionnaire for assessment of functional outcome following restorative rectal resection that took account of how the function affected the individual's daily life[472]. Bakx *et al.* [473] developed this concept with a colorectal functional outcome (COREFO) questionnaire which they validated in 179 patients. When compared with that of Hallbook, more patients found that the psychometric questions in the COREFO questionnaire reflected their concerns. ICI has extended the focus on psychometric outcomes in the recently developed[474, 475] and validated[476] ICIQ-B questionnaire suitable for use in patients with incontinence of varying cause, however the large number of items (forty-two) thus far limit the application of ICIQ-B. A short version of this questionnaire (8 questions) has been used in two recent clinical trials[190, 477] where it proved highly acceptable to patients. Full validation of this shortened version is now underway.

However, how patients and physicians rank the severity of faecal incontinence differs. Clinicians put greatest importance on actual episodes and frequency of incontinence to solid stool, whereas patients are generally more concerned about leakage, hygiene, smell and social embarrassment [478]. A study examining colorectal specialists' perception of symptom severity using the LAR score revealed that specialists did not have a very thorough understanding of which bowel symptoms truly mattered to the patient after sphincter-preserving treatment, nor how these symptoms affected the patient's QoL. Although the specialists performed better than chance , there was considerable discrepancy between the specialist's perspective and patient experience [479]. The same was also true for specialists' perception of symptoms bothering patients after restorative proctocolectomy[480].

Disease specific incontinence scores have been developed for neurogenic bowel dysfunction[481], Low Anterior Resection Syndrome[482, 483] and pouch dysfunction after ileo-anal anastomosis[484]. Included items were selected from a pool extracted from existing bowel function assessment instruments and the current literature. By applying binomial regression on the response to these items obtained from disease specific cohorts of Danish patients, those showing the highest prevalence and impact on QOL were identified and included in the score creating a patient-based outcome score. This has provided a platform for a common understanding and evaluation of functional outcomes for these patient categories. However, as these scores have been developed specifically in collaboration with these patient categories, they are not necessarily applicable in others, regardless of similar symptoms. Recently, the ICIQ-B questionnaire has been revised and validated for use in patients with inflammatory bowel disease as the ICIQ-IBD[485]. For other non-specific diseases with a FI component both the CCF-FIS[67] and St Mark's scales[486] are available. Whereas the CCF-FIS does not score the urgency component, the St Mark's scale scores it as ability to defer defaecation for more or less than 15 minutes. Though both scores include elements of severity, preventive measures, and impact on quality of life, the individual elements are not weighted in the total score according to patient perception. Other newer scores include the faecal incontinence severity index[487].

Bowel movement diaries are considered to be the gold standard measurement, but these are highly influenced by the patient's willingness to stray from the toilet and the validity of the data has never been evaluated. A study on the effect of SNM for FI showed that 46% of the patients with more incontinence episodes at follow-up than at baseline were satisfied with the treatment result. These patients explained that they had obtained a more active social life after the SNM therapy, an aspect of social behaviour that is not addressed in the bowel habit diary, and traditional evaluation would consider these patients as failures[195]. For both the bowel movement diaries and the FI scores additional validation work is needed to assess the potential effect of recall bias

The FIQL[70] is a well-validated quality outcome measure but it yields separate scores on 4 individual scales. It is desirable that a single score outcome be developed. Furthermore, quantitative changes in FIQL have not been anchored to the corresponding impact on patient quality of life and thus remain speculative.

In the future, evaluation of surgical interventions for FI should focus on patient satisfaction and QOL, in combination with bowel scores and diaries to obtain a more accurate measure of therapy efficacy. Striving to develop and implement a standardized tool the approach should be based on appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility.

Summary:
PROMs should be developed and validated according to the impact of symptoms from a patient perspective. It remains to be established if PROMs should be general / disease / treatment specific. Currently available technologies allow real time data capture that may be more relevant in assessing continence outcomes. **Grade of Recommendation: C**

VI. RESEARCH PRIORITIES IN FAECAL INCONTINENCE

1. BASIC SCIENCE AND PATHOPHYSIOLOGY

A quick review of this chapter shows that the focus, past and present, remains on trying to augment the barrier to treat faecal incontinence. However, a summary of techniques that are still in common use must lead the reader to speculate on the logic of this approach. In fact, many procedures are no longer in use. The current gold standard in surgery – sacral neuromodulation does not appear to modify sphincter structure or gross motor function. The problem is that far too much emphasis has been placed on the position of the sphincter in anal incontinence and too little on more important supra-sphincteric mechanisms, especially the rectum. In contrast, urology focuses much more on bladder function even though, arguably, with a fluid like urine, the sphincter should have a much greater role than it does for faeces that must be pushed out of its storage organ by coordinated contraction or compression of the rectum – this is why stress incontinence represents 50% of urinary leakage and only about 5% anal (and then mostly flatus). A relevant research question is what is wrong with the rectum and how can it be fixed? This has been addressed superficially with studies of rectal mucosa[488] but a real understanding will require knowledge of the initiation and control of defaecation[489]. Such an approach is now supported by some SNM literature which points to modulation of afferent activity, including spinal and probably spinobulbar reflexes as the mechanism of action for both UI and FI. It may also help to explain the failure of misguided attempts to constrict the sphincter

that disturb important local and pudendal reflexes from the anus to the rectum – this accounting for the very common problems of rectal evacuation following sphincter augmentation. Such studies can build on the human electrophysiological studies of Swash and Parks [490] and Read and Sun [491] or maybe in animals where there is more written on reflex functions of the rectum in primary studies of bladder physiology than there has been in dedicated colorectal studies.

Tied in with the understanding of the pathophysiology is a need to advance diagnostics. Currently, dependence on manometry leads to measurement of two main variables: resting pressure, which does not distinguish health from incontinence, and maximal squeeze pressure, which measures a non-physiological task – continence is not maintained by volitional squeeze. Newer techniques that evaluate both sphincter contractile function and anal closure are under evaluation[492] and may in time come to complement current techniques.

FI is an important quality of life issue amongst patients who have survived pelvic cancer[482, 493]. The mechanism of FI related to pelvic surgery/radiotherapy are not fully understood. Volumetric changes of the neorectum compared to the original rectum or neuronal damage due to surgery/radiation are postulated, however, there are a limited number of histological or manometric studies in this field and more work is needed to elucidate the mechanism of FI relating to pelvic surgery and/or chemoradiotherapy[494]. Any research into mechanisms underlying FI that may lead to new approach of diagnosis and treatment is strongly encouraged.

2. IMPROVING EVALUATION OF SURGICAL TECHNIQUES

There are almost no adequately powered, high quality randomised trials in the field of FI surgical treatment with an overdependence on quantity rather than quality when it comes to evidence. For some therapies, like SNM, there are multiple observational studies of varying quality but no single high quality trial. While there are data concerning immediate repair of the anal sphincter after OASIS, there are no level 1 data concerning sphincteroplasty and evidence is derived from observational data, much of which comes from low-quality observational series.

Some high quality RCTs like SAFARI (SNM vs Magnetic anal sphincter) [401] failed to recruit before the Fenix device was withdrawn; others like SUBSONiC (SNM vs Sham) [495] are underway but have been delayed by COVID. Some are funded and due to start e.g. AMELIE (anchored autologous muscle cells) [https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/news/2020/oct/amelie-trial]. These offer encouragement, however, there has been little progress since the last ICI. Thus, there remain unanswered questions on colostomy, choice between SNM and sphincteroplasty and the role of bulking agents.

A study to randomise patients with sphincter injury for SNM versus sphincteroplasty was strongly recommended by the both the 2007 and 2016 Committees. Attempts were made but these collapsed due to a combination of reduced enthusiasm from industry, lack of funding and evolution of a pragmatic treatment algorithm in Europe [496]. This emphasizes a requirement for coordinated efforts to collaborate between multiple centres with a large institutional or governmental funding for swift delivery of large trials.

Recognition of the impact of obstructed defaecation on incontinence symptoms[455] is a major area of uncertainty that requires investigation. Laparoscopic ventral rectopexy may improve some elements of FI symptoms such as those related to transanal rectal intussusception. At the same time, such mechanical phenomena may be part of global weakness of the pelvic floor and rectopexy may correct only a part of pelvic floor dynamics. How does the outcome of rectopexy compare with posterior repair of the vagina for large rectoceles? In the absence of expertise-based trial designs, large mulitcentre (multinational) prospective studies backed by radio-physiological tests are strongly recommended.

3. OUTCOME MEASURES

The lack of an agreed core outcome set for patients undergoing therapies for FI continues to cause uncertainty when evaluating existing and new surgical interventions. Various outcome measures and scoring systems exist but most of them have been devised by clinicians with little formal input from patients or attention to psychometric performance. The only scoring system to be designed with rigorous qualitative interview of patients is International Consultation on Incontinence Modular Questionnaire-Bowel Symptoms (ICIQ-B) [474]. However, it is lengthy and contains items that are not scored. A form short version of the ICIQ-B performed well in a recent high quality trial [477] but has not undergone rigorous validation. Comparison of outcomes of different surgical interventions thus remains hampered by use of different scoring systems and various definitions of 'successful treatment'. Patient-facing studies of symptom impact and quality of life [487, 497] are providing further data but formal Delphi intiatives and international consensus to define a core outcome set for faecal incontinence are still eagerly awaited.

4. HORIZON SCANNING: NEW TECHNOLOGIES

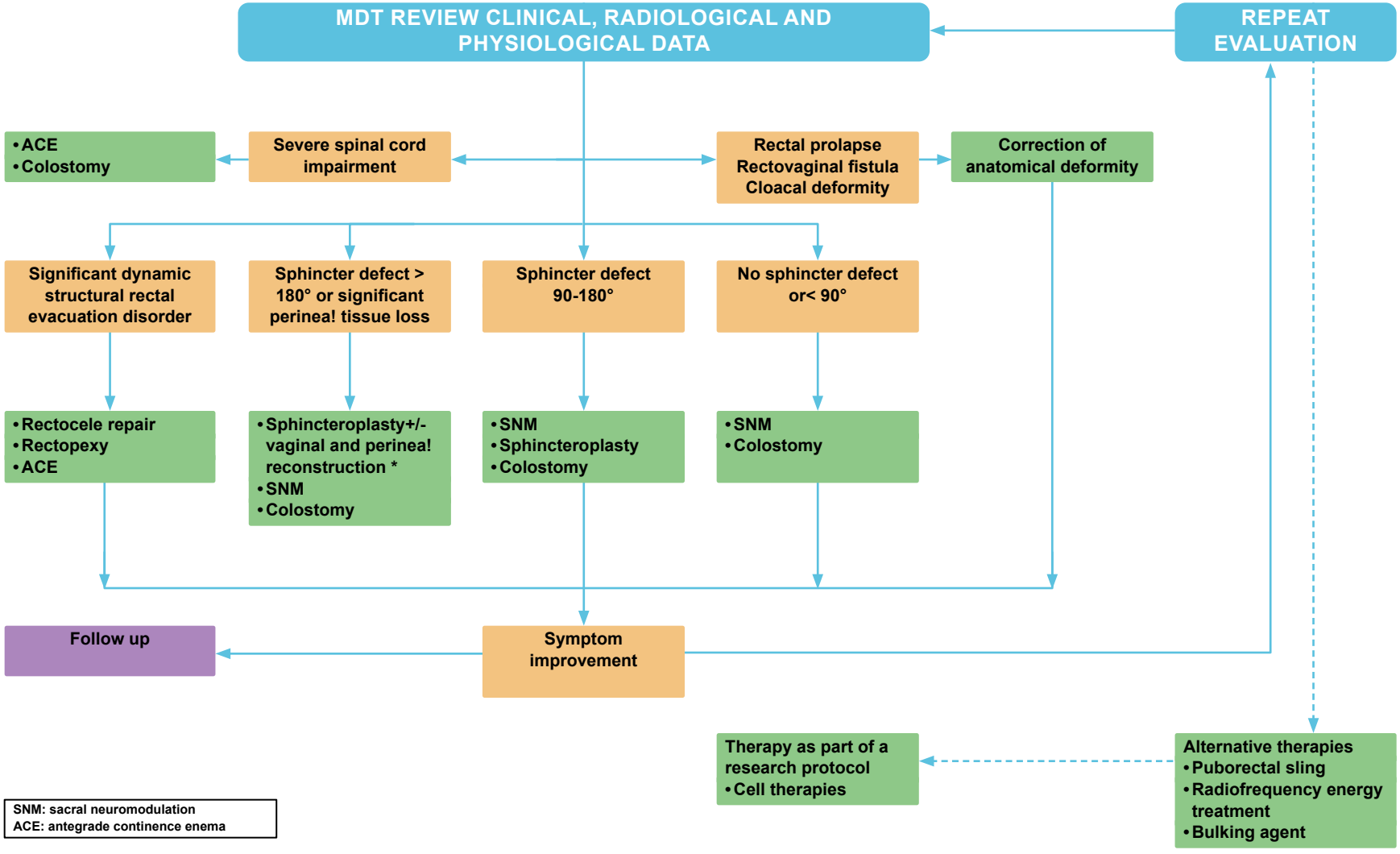
Where does the future lie in surgical treatments for FI? One thing is certain - approaches that use surgical methods to fix, tighten or reinforce the sphincter mechanism regularly fail. The future lies in the restoration of function. Sacral neuromodulation is far from perfect with modest long-term functional outcomes. Evolving regenerative medical approaches with autologous muscle cells will prove costly and are likely to be subject to regulatory constraints. Nevertheless, these are heading in the right direction and further innovation is certainly possible. In neuromodulation, targeting nerves other than the S3 root may be more appropriate in certain individuals. Stimulation parameters might might vary with closed loop feedback and real-time therapy modulation in response to physiological sensing. Integrated therapies with a combination of locally injected growth factors and neurostimulation may give enhanced results. All is possible with an open mind, investment and attention (methodologically) to delivering better evidence than in the past.

ALGORITHM: SURGERY FOR FAECAL INCONTINENCE

Figure 1 presents a summary of the chapter in relation to decision-making for adult patients with FI. In keeping with the 2016 iteration there are 4 main groupings based on clinical and diagnostic findings. These each lead to several possible surgical choices of procedure with little evidence to inform choice beyond patient pref-

erence after the benefits and potential harms of each are adequately explained.

SURGICAL MANAGEMENT OF FAECAL INCONTINENCE



* Consider dynamic graciloplasty: if local expertise and device hardware available
Consider appropriate use of CONTINENCE PRODUCTS

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Chair
Maher, Christopher (Australia)

Members
Antosh, Danielle (United States)
Baessler, Kaven (Germany)
Cheon, Cecilia (Hong Kong)
de Tayrac, Renaud (France)
Deffieux, Xavier (France)
Gutman, Robert (United States)
Lee, Joseph (Australia)
Nager, Charles (United States)
Schizas, Alexis (United Kingdom)
Sung, Vivian (United States)

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LIST OF ABBREVIATIONS

AC Anterior Colporrhaphy
ACOG American College Obstetrics and Gynaecology
ASCP Abdominal Sacrocolpopexy
ASH Abdominal Sacral Hysteropexy
AUGS American Urogynecologic Society
BMI Body Mass Index
BSO Bilateral Salpingo-Oopherectomy
CCCS Cleveland Clinic Continence Score
CCIS Cleveland Clinic Incontinence Score
DVT Deep Venous Thrombosis
ERP External Rectal Prolapse
FDA Food and Drug Administration
FISI Fecal Incontinence Severity Index
FSFI Female Sexual Function Index
HRQOL Health-related quality of life
HVS High Volume Surgeon
ICS International Continence Society
IIQ Incontinence Impact Questionnaire
IRP Internal Rectal Prolapse
ITT Intention to Treat
IUGA International Urogynaecology Association
IVS Intravaginal Slingplasty
LAM Levator ani Muscle
LSCP Laparoscopic Sacrocolpopexy
LSH Laparoscopic Sacral Hysteropexy
LUSHP Laparoscopic Uterosacral Hysteropexy
LVMR Laparoscopic Ventral Mesh Rectopexy
LVS Low Volume Surgeon
MUS Mid-Urethral Sling
OAB Overactive Bladder
ODS Obstructed Defaecation Syndrome
PE Polyester
PFDI Pelvic Floor Distress Inventory
PFMT Pelvic Floor Muscle Training
PGI-I Patients global Impression of Improvement
PISQ Pelvic Organ Prolapse/Incontinence Sexual Questionnaire
POP Pelvic Organ Prolapse
POPQ Pelvic Organ Prolapse Quantification
PP Polypropylene
RCT Randomised Controlled Trial
RSCP Robotic Sacrocolpopexy
RVMR Robotic Ventral Mesh Rectopexy
SBO Small Bowel Obstruction
SCP Sacrocolpopexy
SCerP Sacrocervicopexy
SIS Small Intestine Submucosa
SSLF Sacrospinous ligament Fixation
SSPH Sacrospinous Hysteropexy
SUI Stress Urinary Incontinence
TAH Total Abdominal Hysterectomy
TFS Tissue Fixation System
TLH Total Laparoscopic Hysterectomy
TVH Total Vaginal Hysterectomy
TVL Total Vaginal Length
TVT Tension free Vaginal Tape
TVM Trans-vaginal mesh
UDI Urinary Distress Inventory
USHP Uterosacral hysteropexy
USLS Uterosacral ligament suspension
VMH Vaginal Mesh Hysteropexy
VR Ventral Rectopexy
VRS Vaginal Reconstructive Surgery

I. EPIDEMIOLOGY

Pelvic organ prolapse (POP) is a common problem affecting up to 50% of parous women and between 620% of women will have undergone a surgical correction for pelvic organ prolapse by the age of 80.(1-3) Prolapse surgery is an increasingly important aspect of gynaecological practice due to our ageing population, and already prolapse surgery is performed at least as frequently as continence surgery and, the operating and admission times are at least three times greater than for continence surgery. Given the increasing time and resources that will be required for POP surgery in the future it is paramount that we perform effective, durable, cost-effective interventions with minimal morbidity. This chapter serves to outline and summarise the information relating to POP surgery reported in the English-language scientific literature after searching PubMed, Medline, Cochrane library and Cochrane database of systematic reviews, published up to Apr 2021.

1. INCIDENCE AND PREVALENCE OF PELVIC ORGAN PROLAPSE (POP)

There is a lack of robust epidemiological studies of the natural history, incidence and prevalence of POP.

It is widely accepted that 50% of women will develop prolapse with an increasing prevalence with age, but only 10-20% of those seek evaluation for their condition.(4) In the current literature, the overall prevalence of POP varies significantly depending upon the definition utilised, ranging from 3-60% (Table 1). A recent systematic review also found a wide range of POP prevalence rates from 1.1% to 14.6% across four racial/ethnic groups in USA.(5) Where POP is defined, and graded on symptoms, the prevalence is 3-6% as compared to 41-50% when based on examination, as mild prolapse on examination is common and frequently asymptomatic.(4,6-8) On examination anterior compartment prolapse is the most frequently reported site of prolapse and is detected twice as often as posterior compartment defects and three times more commonly than apical prolapse.(9,10) Following hysterectomy 6-12% of women will develop vaginal vault prolapse(11,12) and in two-thirds of these cases multi-compartment prolapse is present.(13)

There is little knowledge about the natural history of POP. The reported incidence for cystocele is around 9 per 100 women-years, 6 per 100 women-years for rectocele and 1.5 per 100 women-years for uterine prolapse.(9) Some data shows that there is a 1-year incidence of POP of 26% and a 3-year incidence of 40% with regression rates of 21% and 19%,(14) respectively consistent with another community cohort from Australia,(15) showing an incidence of 45% in 5 years, progression rate of 29%, regression rate of 17%. In general, older parous women are more likely to develop new or progressive POP than to show regression. Over a three year period 11% of the women aged over 65 had prolapse progression of more than 2 cm whilst only 2.7% had a regression by the same amount.(16) A similar study of women who declined treatment, a progression rate of 19% was reported,(17) whereas another study showed a progression rate of 15% (18) in women who waited over 9months for their surgery. Overall rate of prolapse increased from 40.9% to 43.8% over 5 years, in a large cohort of post-menopausal women, who gained on average 4.4kg during that time suggesting that being overweight or obese is associated with progression of prolapse.(19) In a study of patients who underwent mid-urethral sling surgery, patients with asymptomatic stage 2 prolapse are un-

likely to progress over 5 – 7 years and even more unlikely to require surgery(20).

Luber has shown in a large demographic study that the peak incidence of symptoms attributed to prolapse is between ages of 70 to 79 whilst POP symptoms are still relatively common in women of younger age.

Demographic changes including an ageing population have significant implications for the future planning of women's health services. Wu et al (22) have predicted that by 2050 the number of women suffering from symptomatic POP in the United States will increase at minimum by 46% (from 3.3 up to 4.9 million women and in a "worst-case scenario" up to 200% or 9.2 million women with POP. These figures were based upon population growth statistics in the United States however models that evaluate the impact of decreasing parity and increasing elective caesarean section rates are required to more accurately predict future rates of POP.

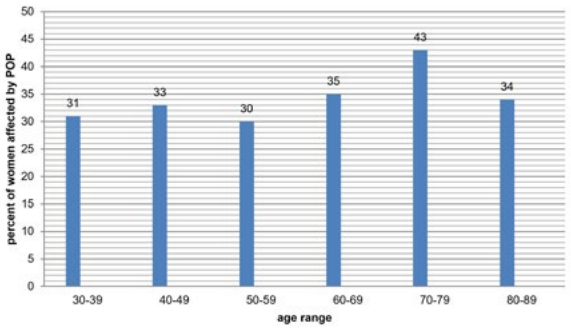

Figure 1. Shows the distribution of POP among women seeking care, US 2000 (Modified Luber 2001(21))

Table 1. Prevalence and Incidence of Pelvic Organ Prolapse

Study	Definition	Prevalence	Incidence	Country
Rorveit, 2007	Symptom	5.7%		USA
Nygaard, 2008	Symptom	2.9%		USA
Hendrix, 2002	WHI-Study, Examination	Any prolapse: 41.1% Cystocele: 34.3% Rectocele: 18.6% Uterine: 14.2%		USA
Handa, 2004	WHI-Study, Examination	Any prolapse 31.8% Cystocele: 24.6% Rectocele: 12.9% Uterine: 3.8%	Cystocele 9.3 Rectocele 5.7 Uterine 1.5	USA
Nygaard, 2004	Examination	2.3% stage 0 33% stage 1 63% stage 2 1.9% stage 3	/ 100 women yrs	USA
Bradley, 2007	Examination	23.5 - 49.9%	26%/1 year 40%/3 year	USA
Maccharoni, 1999	Examination	Vault-prolapse: 12%		Italy
Aigmueller, 2009	Examination	Vault-prolapse: 6-8%		Austria
Mou 2021	4 studies Qs 1 study Examination	White 10.8% Hispanic 6.6% Black 3.8% Asian 3.4%		USA
Cooper, 2015(23)	Symptoms Qs	Vaginal bulge 8.4% Lump outside vagina 4.9%		UK
Li, 2019(24)	Examination + Qs	Rural Women 9.1% Age >70 26.1%		PRC
Seo, 2006(25)	Examination	Prevalence 31.7%		South Korea
Masenga, 2018(26)	Examination	Rural women 64.6%		Tanzania

Adapted: Sung and Hampton 2009(27)

2. INCIDENCE AND PREVALENCE OF PELVIC ORGAN PROLAPSE SURGERY

Both incidence and prevalence for prolapse surgery increase with age. Women older than 80 years are currently the fastest growing segment of the population. The estimated lifetime risk of an American woman undergoing at least one surgical intervention by the age of 80 was frequently reported as 6.3%.(1) More recently the estimated lifetime risk of prolapse has been reported at 13.7% in the USA(3), 18.7% in Denmark (28) and 19% in Western Australia. (2) Also the reoperation rate reported by Olsen et al was 29.2% rate however, a more recent, prospective study showed a significantly lower reoperation rate of only 13% at 5 years, which may be explained by improved surgical procedures.(29)

Not only is there significant variation in the reported lifetime risk of prolapse surgery there is also wide variation in the rate at which surgical interventions for pelvic organ prolapse are performed. Haya et al (30) demonstrated significant variation in the rates and types of surgical interventions for prolapse in 2012 in various countries in the Organisation for Economic Co-operation and Development (OECD). The rate of prolapse procedures were five times higher in the USA (2.6/1000 women) as compared to Switzerland (0.5/1000 women). There was also very significant variation in the type of interventions undertaken. Transvaginal mesh for anterior compartment prolapse was used eight times more frequently in Germany (26%) than in England (3.3%). Sacral colpopexy was employed 13 times more frequently in France (66%) than in Sweden (5%) for apical vaginal prolapse. Such large variation in rate and types of surgery performed for pelvic organ prolapse maybe explained by a variety of factors including women's preferences, cultural and demographic variables, access to healthcare professionals, health professional training and a lack of clear consensus guidelines on the surgical management of prolapse. The lack of consistency in the rates and types of surgical intervention for pelvic organ prolapse needs further evaluation and ensures difficulty in the allocation of health care resources for future planning for pelvic organ prolapse.

The annual incidence for POP surgery is stated to be between 1.5 and 1.8 cases per 1000 women-years with the incidence peaking in women between 60-69 years,(31,32) although annual rates were lower in Germany (0.87), France (1.14) and England (1.13). Shah et al (32) also demonstrated a peak incidence in 70 year old women however surprisingly high numbers of younger women were also undergoing surgical treatments reflecting a similarity in the prolapse symptoms reported in younger women by Luber 2001 (Figure 2).(21) Wu et al found the annual incidence of prolapse surgery increased linearly with age and peaked at 72 years of age at 4.3 cases per 1000 women.(3)

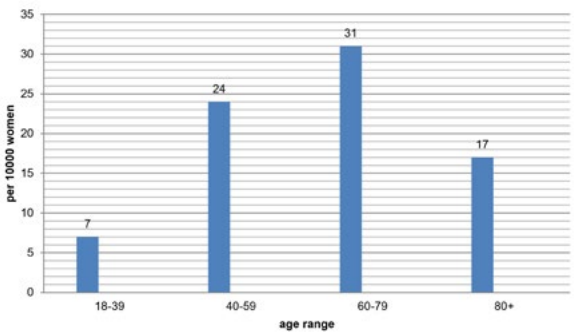

Figure 2. Shows the surgical treatment for POP/ rate per 10000 women (2003)

In the US, POP is thought to be the leading cause for more than 200,000 surgical procedures per year (22.7 per 10,000 women) with 25% undergoing reoperations at a total annual cost of more than 1 billion dollars.(31-34) Also of note during a nine-year period (1996 – 2005) the ambulatory costs related to pelvic floor disorder increased by 40% and if these figures are extrapolated to POP surgery the total annual cost would be over 1.4 billion dollars. While it has been predicted that due to our aging populations the rate and cost of surgery for prolapse will rise by as much as 40%, counter-intuitively some studies are demonstrating decreasing rates of surgical interventions for prolapse. In Denmark, the lifetime risk of prolapse surgery by age of 80 decreased from 26.9% in 1978 to 18.7% in 2008.(28) Over a similar time period in Washington state USA, the rate of surgery for pelvic organ prolapse decreased from 2.1 in 1987 to 1.4 per 1000 women aged 20-84 years in 2009.(35) The authors eloquently linked the decrease in the rate of in-patient prolapse surgery to higher rates of caesarean section and lower rates of instrumental delivery during the same time period. Further detailed modelling of factors that will impact on future rates of POP in the community are required so that services can be provided to match the future demands of POP surgical interventions.

II. OUTCOME ASSESSMENT

Pelvic organ prolapse, like all pelvic floor disorders, is a multidimensional phenomenon and "success" of treatment is often difficult to define. Historically, most studies evaluating the treatment of pelvic organ prolapse have focused exclusively on anatomic success without considering other important areas such as symptoms, vaginal compliance, quality of life, or socioeconomic outcomes. For an individual patient, the most important outcome of a surgical procedure is the relief of her symptoms and improvement in her quality of life,(36) yet until recently these areas have largely been ignored. Fortunately, over the last 15 years, measures to evaluate POP have improved; there is now an internationally-accepted and reliable assessment of the anatomic support of the uterus and vagina (POPQ) and a number of valid, reliable and responsive symptom questionnaires and condition-specific HRQOL instruments. (37-42) A recent joint report from the International Continence Society (ICS) and International Urogynaecology Association (IUGA) recommended that the following outcomes be reported in studies of POP surgery: Objective (e.g. POPQ), Patient reported outcomes (particularly the presence or absence of vaginal bulge symptoms), Satisfaction, Quality of Life, and Perioperative data (e.g. operative time, hospital stay, etc.).(43) A careful report of short- and long-term complications are also essential to assess the risk-benefit ratio of each procedure.

1. OUTCOME ASSESSMENT: ANATOMY

The Pelvic Organ Prolapse Quantification system (POPQ), introduced in 1996, is the international standard for describing female pelvic organ support.(39) The POPQ allows a reproducible and reliable description of the support of the anterior, posterior and apical vaginal segments using precise measurements to a fixed reference point, the hymen, and established criteria for "staging" the various levels of pelvic organ support from good support (POPQ Stage

0 or I) to almost complete lack of support (POPQ Stage IV).(39) The POPQ system has proved a valuable measurement tool that over the last 15 years has improved our understanding of POP and allowed a reliable assessment of the anatomical success of POP surgeries. However, there remain several critical challenges in the anatomical assessment of POP surgery.

First, it is difficult to establish dichotomous anatomical outcome criteria for success and failure, especially in the absence of symptoms. Traditionally researchers have defined surgical success using the NIH satisfactory anatomic outcome (POP-Q Stage 0-1) and defined surgical failure as POPQ stage 2 or greater. More recently it is suggested that these anatomic definitions are too strict as over 75% of women presenting for annual gynaecological examinations without symptoms of pelvic organ prolapse would not meet the definition of “optimal anatomic outcome” and almost 40% would not meet the definition of “satisfactory anatomic outcome”.(7,44) Thus, a substantial number of women considered “surgical failures” by these definitions would be within the normal distribution of vaginal support for parous women. The hymen maybe a more clinically relevant anatomic threshold for surgical success and some researchers have begun defining anatomic failure after surgery as POP that extends beyond the hymen.(36,45-48)

Second, the five-level staging system of the current POP-Q (Stages 0-IV) may be insufficient to discriminate among clinically important groups of women with POP, placing virtually all such women into Stage II or III. While the staging may facilitate comparisons, it may not describe sufficient detail as the individual POP-Q measurements provide. A third area of uncertainty is whether or not apical prolapse should be considered by the same anatomic standards as prolapse of the anterior or posterior vaginal wall. Some researchers have chosen descent more than one-third or one-half of total vaginal length as anatomical failure for the apex.(49,50)

The recent joint committee of IUGA/ICS on the terminology of female pelvic organ prolapse evaluated these points and elected to leave the POP-Q staging unchanged.(51) The decision was based on the principle that POP-Q was developed to address uniform anatomical reporting which it has undoubtedly achieved. POP-Q classification was never designed to replicate subjective outcome and anatomical outcome remains vitally important to surgeons when evaluating, undertaking surgical interventions and reporting these interventions. The division of Stage II prolapse into Stage IIa (-1cm to hymen) and Stage IIb (hymen to +1cm) was also considered. The committee felt the subdivision of Stage II prolapse in POP-Q classification would be open to significant observer and inter-observer error as each subgroup has a range of only 1cm, and would further complicate a grading system already criticised for being too complicated. An alternative proposal to classify Stage II as extending to the hymen and Stage Ш beyond the hymen was also rejected. The committee remained open to further evaluation of all aspects of terminology relating to female pelvic organ prolapse.

Controversy also surrounds the impact that the observer recording the anatomical outcomes has upon reported success rates. Traditionally in the retrospective assessment of anterior compartment trials the reported success rates ranged from 80-100%.(52-55) However, prospective assessment of similar surgical interventions utilising similar definitions of success under the auspices of randomised controlled trials report significantly lower success rate ranging from 37-64%.(56,57) Further variation is also reported in prospective evaluations of prolapse staging depending upon whether the assessor is blinded to the surgical intervention. Antosh et al (58) demonstrated that the recurrence rate in a RCT comparing native tissue and transvaginal mesh repairs was significantly higher when performed by a blinded versus unblinded assessor at 3 months (68 versus 53%) and at 1 year (57 versus 43%). Finally, it is not uncommon for authors with financial conflict of interest related to the commercial products being evaluated reporting the outcomes of surgical interventions, which further increases the risk of reporting bias.

2. OUTCOME ASSESSMENT: SYMPTOMS

Women seeking care for POP often have concurrent pelvic symptoms. Ellkermann et al found that in 237 women evaluated for POP 73% reported urinary incontinence, 86% reported urinary urgency and/or frequency, 34-62% reported voiding dysfunction and 31% complained of faecal incontinence.(59) The evaluation of a patient with vaginal prolapse requires a comprehensive review of the full spectrum of pelvic floor symptoms and an assessment of how these symptoms affect their quality of life. The most valid way of measuring the presence, severity, and impact of pelvic floor symptoms on a patient’s activities and well-being is through the use of psychometrically robust self-administered questionnaires.(37-42)

We have gained an improved understanding of the relationship between pelvic organ support and the development of symptoms. Most symptoms often attributed to POP have at best weak to moderate correlations with worsening pelvic organ support, however, the one symptom that is almost consistently acknowledged by patients with advanced POP is the presence of a vaginal bulge that can be seen or felt.(8,59-62) The absence of vaginal bulge symptoms post-operatively has a significant relationship with a patient’s assessment of overall improvement and improvement in quality of life after surgery, while anatomic success alone does not and ensures that symptom of vaginal bulge remains an important outcome assessment of POP surgery.(36)

3. OUTCOME EVALUATION: PATIENT REPORT OUTCOMES & QUALITY OF LIFE

The United States Food and Health Administration (FDA) introduced the term patient reported outcomes (PRO).(63) In the United Kingdom, it is sometimes known as patient reported outcome measures PROM. A PRO tool could measure any aspect of a patient’s health status that comes directly from the patient (ie without the interpretation of the patients responses by a physician or anyone else). A PRO could be used to measure the impact of an intervention on one or more aspects of patients’ health status ranging from symptoms to more complex concepts like ability to carry out activities of daily living, to extremely complex concepts such as quality of life, which is widely understood to be a multidomain concept with physical, psychological, emotional and social components. Health-related quality of life (HRQOL) is a type of PRO. Measures of PRO can be classified into two types: generic and condition-specific. Generic PRO instruments are used to assess health status in a broad range of illness or populations while condition-specific measures are designed to measure the impact of a specific disease. Women with advanced POP (Stage IIIIV) have decreased generic and condition-specific HRQOL compared to women with normal vaginal support.(64) It is recommended that investigators describe the impact of POP surgical treatment using psychometrically robust

PRO tools. Validated PRO tools are reliable, valid and responsive. Robust validation require reliability over time (test/retest), across items (internally consistent), across different researchers (interrater reliability), demonstrate face, content, criterion & discriminant validity as well responsiveness to change, or minimally important difference (MID,) in a clinically meaningful way. One or two questions within a validated PRO (65) (eg Q3 of PFDI20, Q16 UDI, Q28 APFQ) has often been used to define subjective success in prolapse intervention trials.

Most studies that have assessed condition-specific PRO after POP surgery have demonstrated a significant improvement post-operatively. Improvements in generic PRO after POP surgery have been seen in some studies but not others. Maher et al reported significant improvements in condition-specific and generic PRO after SSLF, similar to that after abdominal sacrocolpopexy.(66) The CARE trial reported significant improvements in condition-specific quality of life following sacrocolpopexy at three months and two years.(67,68) Barber et al demonstrated significant improvements in generic and condition-specific HRQOL in a prospective cohort of elderly women receiving vaginal surgery for POP and demonstrated similar improvements in women undergoing reconstructive surgery and those receiving colpocleisis.(69) While some of these condition-specific HRQOL incorporate assessment of sexual function (42) (APFQ) specific validated questionnaires on sexual function are available and provide a discreet and reproducible method for evaluating sexual health. The Pelvic Organ Prolapse/Incontinence Sexual Questionnaire (PISQ)(70) or PISQ-IR(71) and the Female Sexual Function Index (FSFI)(72) are two validated frequently used questionnaires. FSFI could dichotomise women into those with or without sexual dysfunction, helping clinician understand if pelvic floor interventions contribute to sexual dysfunction. In contrast, PISQ-IR is suitable for women with pelvic floor dysfunction, including those who are not sexually active. The joint ICS/IUGA paper on reporting outcomes after prolapse surgery has also recommended authors report the sexual function status of all individual participants pre and post intervention as seen in Figure 3.(43)

Patient satisfaction is the subjective, individual evaluation of treatment effectiveness, achieved when results of therapeutic intervention are aligned with patient's expectations, therefore allowing clinicians to ascertain appropriateness of treatment. Many factors could potentially influence a patients determination of their satisfaction, including treatment's efficacy, side effects, cost, availability of information on condition, general information giving, availability of resources, continuity of care, accessibility/convenience as well as pleasantness of surroundings or facilities. Patient satisfaction is commonly used as an anchor to determine MIDs for PRO tools. Patient global impression (of severity or improvement PGI-S or PGI-I(73)) is often used as the validated PRO to measure improvement and satisfaction following prolapse treatment. PGI-I gives a more overall global overview of treatment, more likely to encompass the range of benefits and harms of treatment, as it covers other aspects of treatment such as de novo incontinence or persistent pain.

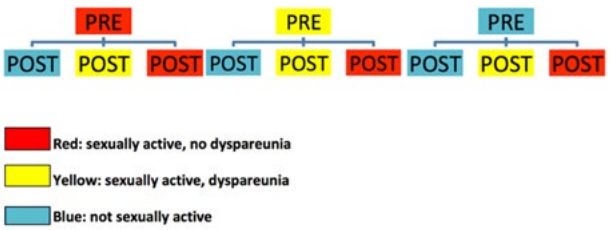

Figure 3. Describes colour coordinated approach to systematically recording pre-and post-intervention sexual function outcomes from Toozs-Hobson 2012(43)

4. OUTCOME ASSESSMENT: REOPERATION

Reoperation after POP surgery for recurrence is an important measure of procedure efficacy. It is important to realise that reoperation rates are likely to represent the "tip of the iceberg" in terms of unsuccessful surgical outcomes as many women with recurrence of symptomatic prolapse may not elect to undergo another operation, nonetheless the repeat surgery for recurrent POP is an undesirable outcome that should, in most cases, be considered a surgical failure. The rates of reoperation after POP surgery vary widely in the literature, in large part because of varying definitions and timeframes. Olsen et al using administrative data from a large U.S. healthcare system reported a lifetime reoperation rate of 29.2%.(1) Importantly, this study included both POP and stress incontinence surgery and did not distinguish between reoperation for incontinence or POP in their report. Moreover, the authors did not distinguish between reoperation for POP in the same compartments originally operated versus the development of new POP in a new segment of the vagina ("de novo POP"). More recently several investigators have looked specifically at the issue of site-specific recurrence with reoperation rates ranging from 3.4%-9.7%.(74,75) In a meta-analysis of 258 studies evaluating reoperation rates after apical prolapse repairs, Diwadkar et al, reported a reoperation rate of 3.9% (95% CI 3.5-4.4%) for traditional vaginal vault suspensions (sacrospinous ligament suspension and uterosacral vault suspensions) after a mean of 32 months, 2.3% (95% CI 1.9-2.7%) for sacrocolpopexy with a mean follow-up of 26 months and 1.3% (95% CI 1.0-1.7%) after transvaginal mesh procedures at a mean follow-up of 17 months.(76) Notably, the total reoperation rate if one includes reoperations for recurrent POP and for complications was highest in the transvaginal mesh group (8.5%).(76)

In order to provide some clarity for future studies reporting reoperation rates after POP surgery, the joint ICS/IUGA report on reporting outcomes after prolapse surgery has proposed the following standardised terminology for POP surgery studies(43):

4.1 Primary surgery for POP is the first procedure required for the treatment of POP in any compartment.

4.2 Further surgery gives a global figure for the number of subsequent procedures the patient undergoes directly or indirectly relating to the primary surgery. This is subdivided into:

4.2.1 Primary prolapse surgery/different site: A prolapse procedure in a new site/compartment following previous surgery in a different compartment (e.g. anterior repair following previous posterior repair).

4.2.2 Repeat surgery: is a repeat operation for prolapse arising from the same site. Where combinations of procedures arise, e.g. new anterior repair plus further posterior repair these should be reported separately i.e. repeat posterior repair and primary anterior repair.

4.2.3 Surgery for complications: e.g. mesh exposure or extrusion or pain or patient compromise e.g. haemorrhage (see complications section).

4.2.4 Surgery for non-prolapse related conditions: e.g. subsequent surgery for stress urinary incontinence or faecal incontinence.

4.3 Defining Treatment Success

The definition of success substantially affects treatment success rates following POP surgery.(36) Since the publication of the NIH Workshop recommendations, considerable variability in defining treatment success still persists in studies evaluating surgery for prolapse. A number of trials define success as POP-Q stage 0 or I consistent with the Workshop's "satisfactory anatomic outcome" definition with one reporting success rates as low as 30% using standard surgical techniques.(57,77) Some have used the Baden-Walker prolapse grading system rather than the POP-Q system.(66) Other studies have used a combination of anatomic criteria and the presence or absence of symptoms to define treatment success.(77-79) A recent analysis of RCTs evaluating interventions for anterior vaginal prolapse, showed significant heterogeneity in reported outcomes. Such variability makes it difficult to compare study results, let alone patient counselling. Moreover, there are many unknowns, including clinical relevance of these definitions or how different outcome definitions might affect the comparison between treatment arms within a study.

Despite avoiding the definition of success or failure, the joint ICS/IUGA paper on reporting outcomes after prolapse surgery(43) has recommended reporting subjective outcome (presence or absence of vaginal bulge), objective outcomes (POP-Q), validated reliable and responsive symptom questionnaires (bladder, bowel, prolapse, sexual function), condition-specific HRQOL instruments, satisfaction, and clearly defined reoperation rates as well as perioperative data including complications. Complications relating to mesh and native tissue repairs should be reported using tools such as IUGA/ICS classification system for prosthesis/graft complication (80) or the Clavien-Dindo classification.(81) The reporting of these single outcome measures individually rather than as composite measures, allows more ready and reliable comparison in meta-analysis.

CONCLUSION

The committee made the following points:

- Significant variation is reported in the rates and types of interventions performed for pelvic organ prolapse. Such variation requires further analysis and standardisation of guidelines for the surgical management of prolapse maybe helpful. (GoR C) should be reported as levels of evidence 1-4 and based on that.
- Early evidence of decreasing rates of surgical intervention for prolapse over the last 30 years are unexpected and require further evaluation.
- (GoR C) Anatomical outcomes reported should include all POP-Q points and staging utilising traditional definition of success. Assessment should be prospective and assessors blinded as to the surgical intervention performed if possible and without any conflict of interest related to the assessment undertaken. (GoR C)
- Subjective success post-operatively should be defined as absence of vaginal bulge. (GoR C)
- Functional outcomes are best reported using valid, reliable and responsive symptom questionnaires and condition-specific HRQOL instruments. (GoR C)
- Sexual function is best reported utilising validated condition specific HRQOL that assess sexual function or validated sexual function questionnaires such as the Pelvic Organ Prolapse/Incontinence Sexual Questionnaire (PISQ) or the Female Sexual Function Index(FSFI). The sexual activity status of all study participants should be reported pre-and post-operatively under the following categories: sexually active without pain, sexually active with pain or not sexually active. (GoR C)
- Prolapse surgery should be defined as primary surgery, and repeat surgery sub-classified as primary surgery different site, repeat surgery, complications related to surgery and surgery for non-prolapse related conditions. (GoR C)

III. ANTERIOR COMPARTMENT SURGERY

Ahlfelt stated in 1909 that the only remaining problem in plastic gynaecology was the permanent cure of cystocele and now more than a century later unfortunately this problem persists.(82) Following high reported objective failure rates and reoperation rates after native tissue repairs and the success of mesh tapes in continence surgery and mesh utilised abdominally at sacral colpopexy, the last decade has seen both a rapid uptake and subsequent decline of transvaginal permanent meshes utilisation in the management of anterior compartment prolapse.

1. NATIVE TISSUE REPAIRS

Historically anterior colporrhaphy was the standard procedure in the management of anterior compartment prolapse with objective success rates ranging from 80-100% in retrospective series.(52-55) White (83) as early as 1912 demonstrated the importance of paravaginal defects in anterior compartment prolapse. Richardson (84) in 1976 described a series of defects in the pubocervical fascia explaining why no single repair should be applied indiscriminately to all with anterior compartment defects. He also advocated the abdominal paravaginal repair which has a 75-97% success rate for cystoceles reported in case series (Table 2).(84-88) The surgical technique of the laparoscopic paravaginal repair is well described however little information is available on the efficacy of this approach. Shull (89) also reported on the safety and efficacy of the vaginal paravaginal repair in 1994. Although the success rates of the vaginal paravaginal repair for cystoceles in case series vary from 67–100% (83,89-93) significant complications have been reported recently. Mallipeddi (92) reported on complications in a series of 45 including: 1 bilateral ureteric obstruction, 1 retropubic hematoma requiring surgery, 2 vaginal abscesses; 2 transfusions. In a series of 100 women Young (93) reported a 21 major complications and a 16% transfusion rate.

No randomised control studies have evaluated the abdominal or vaginal paravaginal repair in isolation. Benson et al (94) and Maher et al (95) have reported RCT's on upper vaginal prolapse comparing abdominal sacral colpopexy and vaginal sacrospinous

colpopexy. Abdominal paravaginal repair was performed in the abdominal group if required and an anterior colporrhaphy with or without vaginal paravaginal laterally. Both authors reported the abdominal group to have a statistically lower rate of postoperative anterior vaginal prolapse than the vaginal group.

Raz et al (96) popularised the needle suspension type procedure for cystoceles and reported success rates in case series may vary from 90-98%.(97-99) The addition of polyglactin mesh to the repair appears to have little impact on the success(100,160). Dmochowski et al (101)reported a lower success rate using a stricter outcome definition of success.

Goldberg et al (102) reported results from a case control study of women with cystocele and stress urinary incontinence. He suggested that the addition of the pubovaginal sling to the anterior colporrhaphy significantly reduced the recurrence rate of cystocele from 42% in the control group to 19% in the anterior colporrhaphy and sling group (P<0.05).

The role of adequate apical support has long been thought to be important in reducing the recurrence rate of AC used for Delancey Level 11 defects. Recently, Eiber et al (103) demonstrated that 10 years after an AC, the reoperation rate for prolapse could be reduced by nearly half, from 20.2% to 11.3% by performing an apical suspending procedure at the time of AC. Unfortunately, this message is not reflected in clinical practice. In a sample of just over 1500 hysterectomies performed for vaginal prolapse in Michigan in the 17months from January 2013 only 25% underwent some form of colpopexy at the time of surgery.(104)

Table 2.Anterior vaginal wall prolapse procedures.

Author	Year	No.	Follow-up	Success Rate
Anterior Colporrhaphy				
Stanton(54)	1982	54	up to 2 yrs	85%
Macer(52)	1978	109	5-20yrs	80%
Walter (55)	1982	76	1.2yrs	100%
Porges (53)	1994	388	2.6yrs	97%
Colombo (105)	2000	33 AC 35 colposuspension	8-17yrs 8-17 yrs	97% 66%
Sand (56)	2001	70 AC 73 AC& vicryl mesh	1yr 1yr	57% 75% No mesh complications
Weber (57)	2001	57 AC 26 AC+ vicryl mesh	23month 23 month	37% 42% No mesh complications
Vaginal Paravaginal Repair				
White (83)	1912	19	up to 3 yrs	100%
Shull (89)	1994	62	.6 yrs	67%
Grody (90)	1995	72	0.5-3yrs	99%
Elkins (91)	2000	25	0.5-3yrs	92%
Mallipeddi (92)	2001	45	.6yrs	97%
Young (93)	2001	100	11 months	78%
Morse (106)	2007	27 VPVR 86 AC	13 24	54% 45%
Abdominal Paravaginal Repair				
Richardson (84)	1976	60	1.7yrs	97%
Richardson (85)	1981	213	0.5-6yrs	95%
Shull (86)	1989	149	0.5-4yrs	95%
Bruce (87)	1999	27 APR& sling 25 APR	17 months 17 months	93% 76%
Scotti (88)	1998	40	39 months	97%
Sling type support				
Raz (96)	1989	107 AC & needle	2yrs	98%
Raz(97)	1991	50	2.8yrs	90%
Gardy (98)	1991	58 AC & needle	2yrs	95%
Benirzi (99)	1996	36 AC & vaginal wall sling	17months	95%
Dmochowski (101)	1997	47 Raz type	47months	43%

Author	Year	No.	Follow-up	Success Rate
Cross (107)	1997	36 AC & sling	20months	92%
Safir (100)	1999	112 Raz + polyglactin mesh	21months	92%
Goldberg (102)	2001	53 AC& sling 90 AC	1 yr 1yr	81% 58%

APR Abdominal paravaginal repair
AC Anterior colporrhaphy Definition varies between authors

In line with our surgical colleagues from early 2000's there has been a move towards the use of prosthesis to augment native tissue repair in reconstructive Gynaecology. This movement took much of its impetus from two early papers. Firstly, Olsen et al (1) reported a reoperation of 29% following prolapse and or continence surgery and Weber (57) reported a 70% failure rate of native tissue anterior compartment repair. Recent re-evaluation of the Olsen's same demographic 10 years later revealed a significantly lower re-operation rate of 17% (108) and the reader should be cautious in making conclusions even from this data as the surgical interventions performed in 1995 are not representative of interventions performed today. More importantly, Weber et al (57) and Sand et al (56) in randomised control trials reported the anterior colporrhaphy to be successful in the management of cystocele in only 30% and 57% respectively. Recent re-analysis of data from Weber's paper using the hymen as the threshold for objective success reported considerably better outcomes with only 10% of subjects developing anatomic recurrence beyond the hymen, 5% of subjects developing symptomatic recurrence and re-operations less than 1% at 23 months follow-up.(109)

During the decade between these initial and subsequent publications surgeons introduced a plethora of biological and mesh grafts to improve the outcomes of anterior compartment prolapse surgery.

Table 3. Anterior vaginal wall prolapse procedures.

Author	Year	Type	No	Review Months	Success Rate	Complication
Julian(110)	1996	Marlex	12	24	100	25% mesh erosion, infection
		Control	12		66	
Nicita (111)	1998	Prolene	44	14	100	3 uterine prolapse
Flood (112)	1998	Marlex	142	38	100	3 mesh erosions
Migliari (113)	1999	Mixed fiber	15	23	93	
Natale (115)	2000	Polypropylene	138	19	97	13 mesh erosions,9 dyspareunia, 1 haematoma
Sand(56)	2001	Polyglactin	73	12	75	no mesh complications
		AC	70		57	
Weber(57)	2001	Polyglactin mesh	26	23	42	no mesh complications
		AC	57	23	37	
Salvatore(116)	2002	Prolene	32	17	87	13% mesh erosions
de Tayrac(117)	2006	Polypropylene	55	37	89	9.1% mesh erosion, 5.5% mesh shrinkage 16.7% dyspareunia
de Tayrac (117)	2007	low weight coated polypropylene	32	13	93	6.3% erosion,12.8% de novo dyspareunia
Sivaslioglu (118)	2007	RCT:low weight, self styled	43	12	91	6.9% mesh erosions
		Polypropylene				4.6% de novo dyspareunia
		Site specific vicryl AC 4	42	12	72	
Nguyen (119)	2008	RCT	38	12	89%	5% Erosion
		Armed Polypropylene				9% dyspareunia
		Perigee				16% dyspareunia
		AC	38	12	55%	5% reoperations 1 tape , 1 POP
Carey (120)	2009	RCT repair with polypropylene gynemesh augmentation	69	12	81%	6.5% mesh erosion O reoperation prolapse

Author	Year	Type	No	Review Months	Success Rate	Complication
		Ant &post colporrhaphy	70	12	66%	Denovo dyspareunia equal both groups
Nieminen (121)	2010	RCT low weight self styled armed Polypropylene	104	36	87	19% erosions 24% reoperations 6 POP, 5tapes, 14 mesh exposure
		AC	97	36	59	19% reoperation 10 POP 9 tapes
Vollebregt (122)	2011	RCT polypropylene Avulta Bard	56	12	91%	4% mesh exposure 0 reoperations POP Baseline dyspareunia resolved 20% Denovo dyspareunia 15% rectocele 10%
		Vicryl AC	58		41%	Denovo dyspareunia 9% 5% reoperations POP, denovo rectocele 10% Baseline dyspareunia resolved 80%
El-Nazier(123)	2012	AC	20	12	70%	No difference between groups operating time, blood loss, in-patient time
		Self-styled polypropylene Gynecare Ethicon	21		95%	5% mesh erosion
Menefee(124)	2011	AC	32	24	87%	No re-operation prolapse either group
		Self-styled Polypropylene mesh	36		96%	14% mesh erosion
Turgal(125)	2013	AC	20	12	75%	denovoSUI 5% each group
		Polypropylene mesh kit	20		95%	
		Parieten Sofradim				Mesh erosion 15%
Delroy(126)	2013	AC	39	12	56%	
		Polypropylene mesh kit Nazca Promedon	40		82%	5% mesh exposure
De Tayrac(127)	2013	AC	82	12	64%	2.8% re-operation prolapse
		Polypropylene mesh kit	80		89%	
		Ugtex, Sofradim				9.5% mesh erosion, 1 patient re-operated dysparreunia
Allegre(128)	2019	AC	39	7 years	69%	9% reoperation
		Polypropylene mesh kit	36		68%	13% mesh exposure
		Ugtex, Sofradim				Extended results from trial above
Tamanini(129)	2014	AC	55	24	64%	No re-operation prolapse either group
		Polypropylene mesh kit	45		76%	16.2% reoperation rate in mesh group
		Nazca Promedon				
Gupta(130)	2014	AC	54	12	100%	Optimal or satisfactory outcome 100% in both groups.
		Self styled polypropylene mesh (vypro JnJ)	52		100%	Operating time and blood loss greater in the mesh group
						High rate of blood transfusion in both groups
Lamblin(131)	2014	AC	35	24	84%	
		Polypropylne armed mesh	33		100%	6% mesh erosion
		Perigee AMS				
Rudnicki(132)	2014	AC	79	36	41%	
		Polypropylene mesh kit	82		91%	Mesh erosion 14.7%
		Avulta Bard				

2. SYNTHETIC GRAFTS IN ANTERIOR COMPARTMENT SURGERY

As seen in Table 3 as early as 1996 Julian et al (110) demonstrated in a prospective case control study that in women who had undergone at least 2 previous vaginal repairs, the overlaying of a Marlex (Bard) mesh to the anterior colporrhaphy reduced the recurrence rate of cystocele from 33% to 0%. The Marlex mesh was associated with a mesh erosion rate of 25%. Flood et al (112) in a retrospective review of 142 women with Marlex mesh augmentation of anterior colporrhaphy demonstrated a 100% success rate for cystoceles at 3.2 years and a mesh erosion rate of only 2%.

Absorbable meshes are an attractive option as an augmenting material as they offered the increased strength during the early healing phase without the long-term complications of permanent mesh and have been evaluated in 2 randomised controlled trials. Weber et al (57) in a randomised control trial compared the anterior colporrhaphy (33), ultra-wide anterior colporrhaphy (24) or anterior colporrhaphy with absorbable polyglactin (Vicryl) 910 mesh (26) in the management of cystocele. The study size was too small to detect small differences in efficacy or adverse events. However, at a mean follow-up of nearly 2 years the groups had similar proportions of women experiencing satisfactory or optimal anatomic results, 30%, 46% and 42% respectively.

Sand et al (56) in a larger RCT allocated cystoceles to anterior colporrhaphy alone (n=70) and to anterior colporrhaphy plus polyglactin mesh underlay (n=73). At I year the success rate in the mesh group was 75% and significantly greater than the 57% success rate in the anterior repair group alone (P=0.02). Concurrent paravaginal defects were present in 11 women and concomitant paravaginal repair was significantly associated with a lower recurrence of cystocele overall (P=0.02).

The 2016 Cochrane review on anterior compartment prolapse reported on three trials that evaluated the effects of using absorbable polyglactin (Vicryl) mesh inlay to augment prolapse repair. (56,57,133) There was insufficient data for analysis on awareness of prolapse and reoperation for prolapse. There was no difference in rate of recurrent anterior wall prolapse between the groups (RR 0.82, 95% CI 0.57 to 1.18). The authors concluded there was little advantage to utilising an absorbable mesh as opposed to anterior colporrhaphy for anterior compartment prolapse.

The 2016 Cochrane review also reported on 16 trials evaluating nearly 2000 women comparing anterior colporrhaphy with permanent polypropylene mesh for anterior compartment prolapse. The meta-analysis demonstrated some advantages and disadvantages to the utilisation of polypropylene mesh and the summary of findings is reproduced in Table 4. Moderate quality evidence demonstrated that awareness of prolapse (RR 0.56, 95% CI 0.43 to 0.73), recurrent anterior wall prolapse (RR 0.34, 95% CI 0.25 to 0.46) and reoperation for prolapse RR 0.44, 95% CI 0.24 to 0.46) were significantly less common following mesh repair as compared to AC

There were no differences between the groups in terms of quality-of-life outcomes or rates of dyspareunia. However, the transvaginal polypropylene mesh group had higher rates of reoperation rate for mesh exposure, stress urinary incontinence or prolapse (RR 1.62, 95% CI 1.15 to 2.28), prolapse in the apical or posterior compartment (RR 1.85, 95% CI 1.01 to 3.37) and at POP-Q point Bp (MD 0.53, 95% CI 0.10 to 0.95,) as compared to AC. The operating time (MD 17.9 mins, 95% CI 10.0 to 25.8), rate of transfusion (RR 2.37, 95% CI 1.32 to 4.24), cystotomy (RR 4.65, 95% CI 1.22 to 17.77;) and de novo stress urinary incontinence (RR 1.55, 95% CI 1.02 to 2.35) were higher after transvaginal polypropylene mesh as compared to AC. The mesh erosion rate after polypropylene mesh was 11.5% and 7% underwent surgical correction for the mesh exposure.

More recently the majority of the polypropylene mesh products evaluated in this meta-analysis have been voluntarily withdrawn by the manufacturers in the face of ongoing litigation. The products with tradename Ugtex and Paritiene (Sofradem, France) and Nazca (Promedon, Argentinia) remain available in some countries.

Newer light-weight transvaginal polypropylene mesh products that have been introduced to decrease the complication rate, specifically mesh erosion, Uphold (Boston Scientific, USA) and Restorelle (Colpoplast, USA) remain available in some countries. Altman et al (134) reported a multi-centre prospective case series evaluating 207 women with apical prolapse undergoing Uphold pelvic floor system and reported a subjective success rate of 90% at one year. However, the complication profile was similar to other transvaginal mesh kits at one year with a mesh exposure rate of 6.3%. Contrarily, De Tayrac et al found at 3-years, in 79 women with grade 3-4 cystocele, an anatomic success rate of 95%, a satisfaction rate of 98% and a mesh exposure rate of 1.3% using a lightweight (28 g/m^2) polypropylene mesh (Surgimesh® Prolapse Xlight, Aspide Medical, France).(135)

Recently Nager et al reported a large multicenter RCT comparing hysteropexy with Uphold Lite mesh in the anterior and apical compartment compared to vaginal hysterectomy with uterosacral support and native tissue anterior colporrhaphy and demonstrated no significant difference between the groups with three-year review on a wide variety of outcomes. The mesh exposure rate was not insignificant at 8% following the lightweight mesh.(136)

Two RCTs have compared permanent anterior vaginal mesh at vaginal surgery with sacral colpopexy for the management of cystoceles. Lucot et al in a large multicenter French RCT compared laparoscopic SC (n=130, hysteropexy and subtotal hysterectomy) with 4-armed monofilament polypropylene anterior mesh with hysteropexy or hysterectomy (n=132) at one year.(137) They reported a significantly lower rate of grade three Clavein-Dindo complications in LSC as compared to vaginal mesh (0.8% versus 9.4%) without a difference in quality of life or subjective outcomes. The vaginal length was significantly shorter and dyspareunia higher in the vaginal mesh group as compared to LSC.

De Castro et al reported a single centre trial that evaluated polyvinylidene fluoride (PVDF) mesh (Dynamesh, Aachen, Germany) as a newer non polypropylene permanent mesh in the anterior compartment at time of vaginal hysterectomy and sacrospinous colpopexy (n=35) compared to open sacral colpopexy (OSC n=36) in those with grade 3-4 uterine prolapse.(138) The study failed to achieve required recruitment and at 12 months demonstrated no difference in subjective and objective outcomes between the groups however the surgical reintervention rate was significantly higher for compilations in the vaginal group (11%) as compared to OSC (0%). Furthermore, the mesh exposure rate for the PVDF mesh at 11% was similar to that reported with polypropylene mesh.

One anomaly remains challenging from the Cochrane 2016 meta-analysis of anterior compartment prolapse. Only one case of

reoperation for dyspareunia or pain were reported in the nearly 1000 cases of transvaginal mesh evaluated. However, pain and dyspareunia were leading causes of adverse events that triggered the 2011 FDA warnings on the safety of transvaginal mesh.(139) In series reporting on re-intervention after transvaginal mesh pain and dyspareunia are the leading indicator for re-operation and at a rate equal to higher than mesh exposure.(140-142) These findings raise the possibility that pain and dyspareunia following transvaginal mesh reviewed in the Cochrane review maybe under-reported and possibly only identified in trials with longer-term evaluation.

Table 4. Summary of Findings tables comparing anterior colporrhaphy and polypropylene mesh for anterior compartment prolapse. Reproduced from the 2016 Cochrane review on anterior compartment prolapse.

Outcomes	Anterior repair (col-porrhaphy)	Polypropylene Mesh	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Awareness of prolapse	256 per 1000	143 per 1000 (110 to 187)	RR 0.56 (0.43 to 0.73)	974 (7 studies)	⊕⊕⊕⊠ moderate1
Repeat surgery - Prolapse	16 per 1000	7 per 1000 (4 to 13)	RR 0.44 (0.24 to 0.81)	1619 (12 studies)	⊕⊕⊕⊠ moderate1
Repeat surgery - Surgery for prolapse, SUI or mesh exposure	56 per 1000	91 per 1000 (64 to 128)	RR 1.62 (1.15 to 2.28)	1518 (12 studies)	⊕⊕⊠⊠ low2,3
Recurrent anterior compartment prolapse	406 per 1000	138 per 1000 (101 to 187)	RR 0.34 (0.25 to 0.46)	1481 (11 studies)	⊕⊕⊕⊠ moderate1
Apical or posterior compartment prolapse	93 per 1000	172 per 1000 (94 to 313)	RR 1.85 (1.01 to 3.37)	300 (2 studies)	⊕⊕⊠⊠ low4,5
Stress urinary incontinence (de novo)	86 per 1000	133 per 1000 (88 to 202)	RR 1.55 (1.02 to 2.35)	939 (6 studies)	⊕⊕⊠⊠ low5,6
De novo dyspareunia	36 per 1000	67 per 1000 (34 to 132)	RR 1.86 (0.94 to 3.66)	583 (8 studies)	⊕⊕⊕⊠ moderate7

[1] Poor reporting: many studies failed to report method of allocation concealment and or rates of attrition bias
[2] poor reporting: adequate methods of allocation concealment or randomisation were not reported in 6 trials
[3] If random effects model utilised difference not significant
[4] one trial moderate data attrition and both participants and reviewers unblinded
[5] Confidence interval compatible with benefit in teh native tissue group or no effect
[6] blinding of participants or reviewers were not performed or not reported in most trials
[7] poor reporting: allocation concealment not reported in 3/8 and blinding of reviewers not performed or reported in 5/8

Table 5. Biological Grafts in anterior compartment prolapse

Author	Year	Graft	N	Months	Success rate	Complications
Allografts						
Cosson(143)	2001	Autologous Vaginal patch	47	16	93%	None
Groutz (144)	2001	cadaveric & pubovaginal sling	19	20	100%	None
Kobashi (145)	2002	cadaveric fascia lata & sling	132	12	87%	1 osteitis pubis
Chung (146)	2002	cadaveric dermis	19	24	84%	1 infection removal
Clemons (147)	2003	cadaveric dermis	33	18	59%	1 incision breakdown
Powell (148)	2004	cadaveric fascia lata	58	24	81%	10% graft erosion 2 transfusions, 1 cystotomy 3 ureteral kinking
Frederick (149)	2005	cadaveric fascia lata & sling	251	6	93%	1 osteitis pubis
Gandhi (150)	2005	RCT AC & fascia lata (Tutoplasta) AC no graft	76 78	13 13	82% 71%	no graft complications

Author	Year	Graft	N	Months	Success rate	Complications
Ward (151)	2007	cadaveric dermis	39	24	42%	1 de novo dyspareunia No graft erosions
Xenographs						
Lebouf (152)	2004	FDR & Pelvicol PDR	9 24	15 15	84% 100%	None None
Salomon (153)	2004	porcine dermis transobturator	27	14	81%	1 graft r/o vaginal pain
Gomelsky (154)	2004	porcine dermis	70	24	87%	None
Wheeler (155)	2006	porcine dermis Uterosacral repair	28	18	50%	2% granulation tissue
Meschia (156)	2007	Porcine AC	98 103	12 12	93% 81%	1% vaginal extrusion
Handel (157)	2007	Porcine dermis Polypropylene AC	56 25 18	13 13 13	64% 96% 94%	21% vaginal extrusions 4% mesh erosion
Simsiman(158)	2006	Porcine graft	89	24	78%	17% erosions
Robles (159)	2007	Porcine dermis Polypropylene arm	90	8	85%	no complications
Guerrette(160)	2009	AC Bovine pericardium collagen	27 17	24	63% 77%	17% erosions no complications
Hviid (161)	2010	AC Porcine dermis graft	26 28	12	85% 93%	Recurrent POP Sur 8% 10%
Feldner(162)	2010	AC Porcine small intestine Submuosa	27 29	12	67% 86%	Dyspareunia 15% 25%
Natale (163)	2009	porcine graft self-styled polypropylene mesh	94 96	24	58% 72%	Mesh erosion 0 6.3%
Menefee (124)	2011	AC Vag paravaginal porcine dermis Vag paravaginal polypropylene	32 31 36	24	55% 52% 86%	Mesh erosion 0 4% 14%
Dahlgren(164)	2011	AC Porcine dermis graft	66 65	36	43% 38%	2% perineoplasty 4.4% graft erosion
Robert(165)	2014	AC Porcine small intestine submucosa	29 28	12	61% 57%	11% pelvic pain 13% pelvic pain
Iyer(166)	2019	AC AC +acellular dermal graft	70 44	84	56% 68%	None attributed to graft

Variable definitions of success used.

3. BIOLOGIC GRAFTS IN ANTERIOR COMPARTMENT SURGERY

Alternatively to synthetic prosthetic grafts autologous material may have a lower risk of host rejection or infection. Cosson (143) described an autologous 6-8cm long and 4cm wide vaginal patch suspended from the tendinous arches of the pelvic fascia and tucked under the anterior repair. The success rate (<grade 1 POP) was 93% at a mean follow-up of 16 months.

Allografts from post-mortem tissue banks have been used for many years in orthopaedic surgery and decrease the risk associated with harvesting autologous rectus sheath or fascia lata. Cadaveric fascia lata with or without pubovaginal sling has been utilised to correct anterior compartment prolapse with a success rate varying from 81-100% with acceptable complication rates. (144, 145, 148, 149) Gandhi et al have reported preliminary results of a randomised control trial comparing anterior colporrhaphy alone and augmented with fascia lata graft for cystoceles. (150) At 1 year they were not able to demonstrate that the addition of the fascial lata graft improved outcomes with the success rate

after anterior colporrhaphy alone being 71% as compared to 82% in those augmented with the fascia lata graft (P=0.07). No complications were reported. Cadaveric dermis has been employed as a graft material in the anterior compartment with success rates varying from 42-84% at 2 years (146,147,151,167). Concerns regarding prion transmission causing infectious diseases (168) or residual antigenicity (169) that may cause host graft reactions have encouraged the use of porcine or bovine xenografts as detailed in Table 4.

Leboeuf et al retrospectively reviewed 24 women with native tissue four corner defect repair (FDR) and 19 FDR with porcine dermis.(170) At 15 months the success rate was 100% in the FDR group and reduced to 84% if porcine dermis overlay was utilised. Wheeler et al reported on 36 women who all underwent high uterosacral vault suspension with anterior repair augmented with porcine dermis and at 17 months found a 50% recurrence rate. (155) The authors highlighted that despite the high objective failure rate greater that 90% of the women were satisfied or somewhat satisfied with the repair and 83% would undergo the surgery again. Handel et al retrospectively compared anterior colporrhaphy (n=18), porcine dermis (n=56) and polypropylene graft (n=24) in those with cystocele.(157) The success rate at 13 months was 94%, 64% and 96% respectively with a 21% rate of vaginal extrusion of the porcine dermis graft. Alternatively to these relatively disappointing results, a number of groups have reported satisfactory objective results utilising porcine dermis.(154) (158)

Meschia et al in a multicentre randomised clinical trial compared the anterior colporrhaphy (n=103) and anterior colporrhaphy-augmented with 4x7cm piece of porcine dermis.(171) The success rate at 1 year was 93% in the anterior colporrhaphy with porcine graft overlay group as compared to 81% in anterior colporrhaphy alone group (P<0.001) with a 1% rate of graft erosion.

Hviid et al reported a smaller randomised controlled trial comparing polyglactin plication anterior colporrhaphy and porcine dermis 4x7cm graft at one year.(161) The objective failure rate (defined as point Ba ≥-1) was 2/28 in the porcine dermis group as compared to 4/26 in the anterior colporrhaphy and was not significant. Guerette et al compared the anterior colporrhaphy group (n=17) and anterior colporrhaphy with bovine pericardium collagen (n=27) matrix graft reinforcement and reported no difference on objective examination with success rate of 63% after the AC and 77% in the bovine pericardium collagen repair at 2 years.(160) The reoperation rate for prolapse was 37% in AC group and 23% in the bovine pericardium group. De novo dyspareunia occurred in 5% following AC only. There was no difference in quality-of-life outcomes between the groups utilising Urinary Distress Inventory and Pelvic organ prolapse and Incontinence sexual questionnaire.

Feldner et al compared anterior colporrhaphy with 7x10cm small intestine submucosa (SIS) graft in a randomised control trial and demonstrated reduced operating time in AC group (30 min versus 46) as compared to SIS (p=0.02).(162) The objective failure rate of 33% (9/27) was significantly higher after the AC versus 14% (4/29) in the SIS group. The dyspareunia rate was similar in both groups (AC 4/27 versus 5/20 SIS) and no reoperations were reported. Prolapse quality of life assessment (P-QOL) improved postoperatively in both groups with no significant difference between the groups. In another RCT, Natale_ et al compared polypropylene mesh (Gynemesh) with porcine dermis (Pelvicol). At two years, significantly fewer women had anterior vaginal wall recurrence in the mesh group 28% (27/96) versus to 44% (41/94) of the porcine graft group (RR 0.64, 95% CI 0.43 to 0.96). Mesh erosion was seen in 6.3% following mesh surgery. Although similar numbers of women reported dyspareunia (10 versus 12), the authors reported superior sexuality outcomes in the porcine graft group as compared to polypropylene mesh (p = 0.03).(163)

Finally, Menefee et al in a randomised control trial compared three operations, anterior colporrhaphy, vaginal paravaginal repair using porcine dermis graft and vaginal paravaginal with self-styled polypropylene mesh and also reported a higher objective success rate after the polypropylene mesh 86% (25/29) as compared to 52% (12/23) in the porcine dermis arm (124) and 53% (10/19) in the AC arm. The subjective failure rate was not significantly different and was 3.4%, 12% and 13% respectively. The graft erosion rate was 1/23 (4.3%) in the porcine dermis group and 4/29 (13.8%) in the mesh group.

In 2016 Cochrane review on the surgical management of anterior compartment prolapse eight trials (124,150,156,160-162,164,165) compare AC (n=413) with various biological grafts (n=450). Porcine dermis (Pelvicol) was utilised in four trials (Dahlgren 2011; Hviid 2010; Menefee 2011, Meschia 2007), small intestine submucosa in two trials (Feldner 2010, Robert 2014), cadaveric fascia lata patch in Gandhi 2005 and bovine pericardium collagen in Guerette 2009. Meschia 2007 evaluated only primary anterior compartment prolapse and Dahlgren 2011 only included those who had at least one failed prior surgical intervention in the treated compartment. Hviid 2010 included those only with anterior compartment prolapse and concomitant surgery was excluded.

There were no differences detected between porcine dermis graft or small intestine submucosa and AC for the primary outcomes of awareness of prolapse, prolapse on examination and re-operation for prolapse. When all biological grafts were analysed together biological grafts had similar outcomes to AC in awareness of prolapse and reoperation for prolapse, however the recurrent anterior prolapse rate on examination was less after biological graft repair as compared to anterior colporrhaphy (RR 0.74, 95% CI 0.55 to 0.99 n= 646, I^2=29%, low quality evidence). The AC operating time was less than the biological graft procedure (MD -10.35, 95% CI -14.45 to -6.24).

4. RECURRENT ANTERIOR PROLAPSE

Many clinicians believe the primary role of polypropylene mesh may be in complex or high risk prolapse such as recurrent prolapse. Fayyad et al prospectively evaluated 36 women with recurrent anterior compartment prolapse and reported an objective success rate (less than stage 2 anterior compartment prolapse) of 47% with a mesh exposure rate of 19%.(172) In a prospective multicentre Dutch RCT trial in women with recurrent anterior or posterior compartment prolapse were randomised between native tissue repairs and tension-free vaginal polypropylene mesh.(173) The authors reported little advantage to mesh augmentation at 7 years. The composite success was 53% (95% CI 41, 66) for mesh and 54% (95% CI 42, 65) for native tissue. Repeat surgery for POP was 25% for mesh and 16% for native tissue (difference 9%; 95% CI -5, 23) and occurred in untreated compartments in the mesh group and treated compartments in the native tissue group. Mesh exposure rate was 42% and the rates of vaginal pain (mesh 39% NT 50% and dyspareunia (mesh 20%, NT 17%) similar in both groups.(174)

More recently Ow et al, reported on a retrospective comparison of 237 women undergoing 185 native tissue repair and 161 transvaginal mesh repairs (self-styled and mesh kits) for recurrent prolapse. The transvaginal mesh group had significantly lower rates of symptomatic prolapse, prolapse on examination and reoperation for prolapse than the native tissue repairs. However, the mesh exposure rate (15% anterior, 21% posterior mesh) and reoperation for mesh exposure (anterior 9%, posterior 15%) were significant. There was no difference in the total reoperation rate between the groups (mesh 24%, NT 19%).

In 2020 the Prospect group reported a RCT that compared native tissue versus polypropylene mesh in those with recurrent anterior or posterior vaginal wall prolapse. Using the unvalidated primary outcome measure of Pelvic Organ Prolapse Symptom score no difference was detected in the two interventions. However the validated and blinded assessors demonstrated anatomical improvement in the mesh group for Point Ba, total vaginal length and stage of POP and the validated QOL scale EQ-5D-3L also reported a more favourable outcome in the mesh group. The mesh exposure rate in the mesh kit group was 9% at 2 years.(175)

The data from these three trials suggest that in women with recurrent anterior prolapse transvaginal mesh has advantages and dis-advantages to native tissue repairs. The risk profile is similar to that described for primary repairs except the mesh exposure rates appear to be higher in recurrent prolapse surgery.

Clinical practice worldwide.
In a 2017 survey of members of British Urogynaecology Society to which about 50% responded over 90% performed anterior colporrhaphy for primary anterior compartment prolapse.(176) For recurrent anterior wall prolapse only 11% would utilise a permanent synthetic mesh as compared to 56% in a similar survey conducted 5 years previously. Clinical practice in the BSUG responders closely reflects the data presented above. There remains significant variation in clinical practice worldwide with transvaginal mesh for vaginal prolapse prohibited in many countries including USA, United Kingdom and Ireland, Canada, France, Australia and New Zealand(177) in response to concerns outlined above including high rates of mesh exposure and vaginal pain/ dyspareunia that are challenging to treat. In many European and Asian countries transvaginal mesh remain a viable option for women with vaginal prolapse.

CONCLUSION
The following conclusion can be made regarding surgical interventions for anterior vaginal compartment repairs:

- Absorbable mesh augmentation of native tissue repair improves the anatomical outcome as compared to native tissue repair alone with no increased complication rate in meta-analysis of 2 RCTS (GoR B).

- Biological grafts have improved anatomical outcomes with no change in subjective outcomes as compared to native tissue repairs (GoR B). Conflicting level one evidence supports porcine dermis graft (Meschia, Hviid, Menefee) and single RCT supports small intestine submucosa as graft material in anterior compartment prolapse surgery (Feldner) (GoR B).

- Polypropylene mesh has a superior anatomical outcome as compared to biological graft (Pelvicol) in the anterior compartment (Feldner, Menefee). Mesh exposure rate was significantly higher in the polypropylene mesh group (GoR A).

- Polypropylene mesh demonstrates improved anatomical and subjective outcomes as compared to AC with no difference in functional outcomes using validated questionnaires or a lower reoperation rate for prolapse. The mesh group was also associated with longer operating time, greater blood loss and a non-significant tendency towards higher cystotomy, de novo dyspareunia and de novo stress urinary incontinence rate as compared to AC. Apical or posterior compartment prolapse was significantly more common following polypropylene mesh and mesh extrusion rate was 10.4% with 6.3% undergoing surgical correction (GoR B).

- Data for recurrent anterior vaginal wall prolapse is conflicting regarding the advantages for polypropylene mesh compared to AC with relatively high rates of mesh complication reported in the longterm (GoR C).

IV. SURGICAL TREATMENT OF UTEROVAGINAL PROLAPSE

It has been shown that defects in Level 1 support, the uterosacral cardinal ligament complex, lead to uterine descent.(178) Despite the fact that most gynaecologists and pelvic reconstructive surgeons consider the uterus to be a passive structure in prolapse development, it is frequently removed during uterovaginal prolapse surgery. In fact, prolapse is one of the most commonly listed indications for hysterectomy.(179) As interest in uterine preservation increases, it is important to critically evaluate the safety and efficacy of hysteropexy to determine if similar results can be achieved with uterine conservation compared to hysterectomy.

Queries of United States (US) women presenting for prolapse care suggest that 36-60% would choose uterine preservation assuming equal surgical efficacy.(180,181) Similar results were observed during queries of women from the Netherlands, Austria/Germany and Russia with 43%, 40% and 54% respectively that preferred uterine preservation assuming equal outcomes.(182,183) However, 66% of female gynaecologists in the Czech Republic, Slovenia and Slovakia preferred concomitant hysterectomy at the time of hypothetical prolapse repair assuming equal outcomes. (Urdzik 2020) Women elect uterine preservation for a variety of reasons including the desire to preserve future fertility, that the uterus contributes to their sense of feminine identity and wish to avoid hysterectomy perceived as a major surgery associated with significant risks. However, surveys have shown that many of the reasons for desiring uterine conservation have more to do with ovarian conservation. These include beliefs that removal of the uterus will worsen mood, relationships, quality-of-life, sex drive and result in weight gain.(180) Patient demographics have been associated with hysteropexy preferences. For example, college educated women were almost three times more likely to choose uterine conservation, and women living in the southern US were less likely to request uterine preservation (OR 0.17 95% CI 0.050.7)).(181) Whether it is cause or effect, a greater number of hysterectomies are performed in the US south compared to other geographic regions.(179) Each patient's interest in uterine conservation should be assessed during surgical planning. This can easily be accomplished by listing the patient's goals and preferences early on during the informed consent process.

Conservative management with a pessary is recommended for women with uterovaginal prolapse that are interested in future childbearing or uncertain about their reproductive plans. Due to limited data regarding risks associated with subsequent pregnancy

and delivery, surgery should be reserved for those that cannot be managed with a pessary. We do not know which type of hysteropexy is the safest with respect to fertility, pregnancy and delivery. We also do not know the impact of pregnancy and vaginal or cesarean delivery on postpartum pelvic support with hysteropexy. Assuming pregnancy and delivery decreases the long-term success of the prolapse repair, native tissue vaginal or laparoscopic hysteropexy may be preferable as a temporising solution. This is based on the belief that future surgical management will likely be required for recurrent prolapse. This review focuses on women who have completed childbearing and are postmenopausal or practicing reliable contraception.

1. PATIENT SELECTION

Candidates for uterine conservation should be carefully considered and strict selection criteria applied to decrease the likelihood of subsequent hysterectomy, which may be more technically challenging. Most contraindications to hysteropexy are relative since the majority of cases (except LeFort colpocleisis) maintain access to the cervix and endometrial cavity for screening and sampling. Women at increased risk for endometrial, cervical or ovarian cancer and those with a personal history of oestrogen receptor positive breast cancer, especially those taking Tamoxifen should have their uterus, cervix and possibly ovaries removed at the time of prolapse repair. Hysteropexy should also be avoided in cases of uterine abnormalities listed in Table 1. Patients with recent postmenopausal bleeding even with a negative workup should probably undergo hysterectomy based on a 13% risk of unanticipated endometrial cancer or hyperplasia.(184) Premenopausal women and those without postmenopausal bleeding had low rates of endometrial pathology. The overall rate of endometrial cancer was 0.3% in this study (184) and 0.8% in another large study.(185) During the consent process for post-menopausal women considering uterine preservation or hysterectomy, women should be informed of the lifetime risk of cervical (0.6%), uterine (2.7%), and ovarian cancer (1.4%).(186,187) While ovarian cancer is uncommon, the general late presentation of disease is associated with poor outcomes. Routine bilateral oophorectomy demonstrated a 10-fold decrease in the small risk of ovarian cancer without increased morbidity when results were stratified by age.(188,189) Furthermore, all women who have completed their family and are considering prolapse surgery should be informed that bilateral salpingectomy may decrease the risk of ovarian cancer by 42-56%, is cost effective at hysterectomy and is not associated with increased morbidity.(190,191)

The 2019 updated ACOG Committee Opinion recommends counseling all women planning hysterectomy or other pelvic surgery (ie prolapse surgery) about the benefits of opportunistic salpingectomy. Performance of opportunistic salpingectomy is not feasible during vaginal hysteropexy repairs and as such is a relative contraindication. When considering vaginal hysterectomy for the treatment of uterine prolapse, salpingectomy can be successfully performed 74 to 88% of the time.(192-194) However, route of hysterectomy may impact ability to successfully complete salpingo-oophorectomy for women that are at higher risk of ovarian disease or desire removal. A retrospective comparison of women undergoing vaginal hysterectomy (n=163) and laparoscopic assisted vaginal hysterectomy (n=144) for prolapse found that rates of salpingectomy (1% vs 34%) and salpingo-oophorectomy (45% vs. 66%) were lower in the vaginal hysterectomy group plus planned salpingo-oophorectomy was unable to be completed in 36% of vaginal hysterectomies vs. none of the laparoscopic hysterectomies. Peri-operative complications and inpatient stay were significantly greater in the vaginal hysterectomy group.(195) The ACOG Committee Opinion further recommended not altering the route of surgery based on the decision for opportunistic salpingectomy, but route may need to be altered for those in desiring salpingo-oophorectomy or hysteropexy. Consequently, this should be part of the informed consent process and surgical planning. Higher risk women with hereditary conditions (BRCA mutations, Lynch Syndrome) and obesity should consider hysterectomy with or without oophorectomy during prolapse repair. Table 6 lists possible contraindications to uterine preservation and includes pre-operative cervical elongation. A prospective two-part study showed an almost 11-fold increased risk of failure in patients with cervical elongation undergoing sacrospinous hysteropexy (SSHP). Success rates were 96-100% after excluding patients with severe prolapse and performing partial trachelectomy for cervical elongation.(196) Other studies have shown similar high success rates using partial trachelectomy at the time of hysteropexy.(197,198) The majority of studies exclude women with menstrual disorders and abnormal uterine or cervical pathology. One study performed over 20 concomitant uterine/cervical procedures among 65 laparoscopic sacrohysteropexy (SHP) subjects to correct abnormal pathology.(199) Procedures included 8 trachelectomy for cervical elongation, 5 cervical/endometrial polypectomy, 4 myomectomy/uterine artery occlusion, 2 cervical conisations for CIN2 and 1 mesh excision. The relaxed exclusion criteria may be a factor that led to more symptomatic recurrences that required treatment (9 pessary, 1 surgery) in the hysteropexy group. This example illustrates the need for stringent selection criteria.

Table 6 Relative contraindications to uterine preserving surgery

Uterine abnormalities
Fibroids, adenomyosis, endometrial pathology sampling
Current or recent cervical dysplasia
Abnormal menstrual bleeding
Post-menopausal bleeding
Cervical elongation
Familial cancer BRAC1&2: ↑risk ovarian cancer and theoretical risk fallopian tube and serous endometrial cancer
Hereditary Non-Polyposis Colorectal Cancer (Lynch Syndrome): 60% lifetime risk endo-metrial cancer
Tamoxifen therapy
Obesity: up to 3-fold increased risk endometrial cancer18
Vaginal uterine preserving surgery in those desiring opportunistic salpingectomy
Unable to comply with routine gynaecology surveillance

Hysteropexy Outcomes

A variety of hysteropexy techniques have been described to treat uterovaginal prolapse. Studies show short-term safety and efficacy with decreased blood loss, shorter operating time and more rapid recovery compared to hysterectomy. Although the quantity and quality of hysteropexy studies is growing, most studies lack controls and contain variable techniques and definitions of success. The primary purpose of this analysis is to compare hysteropexy and hysterectomy surgical outcomes for treatment of uterovaginal prolapse. Hysteropexy procedures can be subdivided into native tissue and mesh repairs. While apical or anatomic success is most commonly reported, a few studies used composite outcomes and most

reported reoperation rates for prolapse. Mesh exposures have also been included when applicable. Only studies containing a control or comparison hysterectomy group with an apical support procedure are included. Studies lacking controls, non-English language, containing poorly defined outcomes as well as those that are unable to distinguish between various hysteropexy and hysterectomy outcomes are excluded.

2. NATIVE TISSUE HYSTEROPEXY PROCEDURES

There are ostensibly four different types of native tissue repairs involving uterine conservation. LeFort colpocleisis involves obliteration of the vaginal lumen and is an excellent option for women that are no longer sexually active and are not interested in preserving coital function. The Manchester procedure had fallen out of favor for years but is gaining increased interest with encouraging results (200,201) despite the fact that it is primarily a treatment for cervical elongation. Sacrospinous hysteropexy and uterosacral hysteropexy (USHP) (vaginal, abdominal or laparoscopic) are the most commonly utilised native tissue procedures that maintain coital function.

2.1. Partial Colpocleisis without Hysterectomy

Partial colpocleisis is the ultimate hysteropexy procedure due to high success and low morbidity in an older population with advanced prolapse and multiple medical comorbidities. It is reserved for women who are not sexually active and are not interested in preserving coital function. Shorter operating time, less blood loss and similar anatomic success was reported after partial colpocleisis compared to total colpocleisis.(202) An older, retrospective cohort comparing LeFort colpocleisis (n=21) to vaginal hysterectomy with anterior and posterior repair (n=42) for complete uterovaginal prolapse found shorter operating time with no differences in prolapse symptom resolution or complications.(203) There are no prospective trials and three retrospective cohort studies that compared LeFort colpocleisis to colpocleisis with hysterectomy.(204-206) One single institution study involving LeFort colpocleisis (n=46) and colpocleisis with vaginal hysterectomy (n=65) with median 4 month follow-up showed no difference in overall adverse event rates excluding urinary tract infections (15.2% vs 13.8%, p=0.84) . Concurrent hysterectomy resulted in longer operating time (144 vs 111 minutes, p<0.001), higher estimated blood loss (253 vs 146 mL, p=0.01) and higher transfusion rate (9.3% vs 4.3%, p=0.02)[21] (Hill 2016) Another study utilized the ACS-NSQIP database to compare colpocleisis (n=893) to colpocleisis with vaginal hysterectomy (n-134) and showed shorter operating time with fewer serious medical complications (0.8% vs 3.7%, p=0.03) in the colpocleisis group.(204) The third more recent study compared LeFort colpocleisis (n=70) to vaginal hysterectomy and total colpocleisis (n =172) at a mean follow-up of 44 months. (Lu 2021) The authors found shorter operating time and less blood loss with uterine conservation. Both groups had high satisfaction (98.6% vs 98.8%) and low regret (0 vs 0.6%). In the hysterectomy group, there was one case of bleeding that required reoperation and transfusion, one case of recurrent prolapse and one case of endometrial cancer (0.6%) diagnosed on pathology despite the absence of postmenopausal bleeding and a negative ultrasound preoperatively. The authors concluded hysterectomy should be reserved for uterine abnormalities identified preoperatively or concerns about difficulty evaluating subsequent vaginal bleeding and a decision analysis favored LeFort colpocleisis over colpocleisis with vaginal hysterectomy after balancing risk of delayed endometrial cancer with hysterectomy complications plus the need for possible laparotomy.(207)

2.2. The Manchester Procedure

The Manchester procedure is one of the oldest prolapse repairs that involves amputation of the cervix and reattachment to the cardinal ligaments. Modified Manchester repairs include plication of the uterosacral ligaments posteriorly and cardinal ligaments anteriorly for apical support. Premenopausal women wishing to maintain fertility and older women with medical co-morbidity, originally considered good candidates for a Manchester procedure, have better surgical options since the repair is primarily a treatment for cervical elongation. It is more important than ever to critically evaluate the quality of the literature with respect to this prolapse surgery as interest in uterine conservation increases prompting a relative resurgence of this technique. All of the studies using this technique are retrospective and the majority are case series showing relatively good anatomic and symptomatic improvement with low complication rates. There are no RCT's and four retrospective cohort studies comparing Manchester to vaginal hysterectomy.(208,209) (201,210) Table 7) These retrospective cohort studies generally showed no difference in anatomic or symptomatic outcomes with decreased operating time and blood loss in the Manchester group. Unfortunately, several of the studies contained poorly defined anatomic outcomes, variable lengths of follow-up and limited reporting of anatomic outcomes and reoperation rates especially for the hysterectomy group so meta-analysis was not performed. Two of the four comparative trials appear to lack an apical support procedures at the time of vaginal hysterectomy (201,210) and only one study describes a high midline plication uterosacral suspension (USLS).(208) The latter study showed 100% vs. 96% successful apical support but only 40% overall anatomic success < stage 2 with high rates of anterior wall recurrence (46-48%).(208) The most recent cohort revealed no difference in their primary outcome of no prolapse symptoms (69% vs 74%) using the prolapse domain of Urogenital Distress Inventory.(201) Reoperations for recurrent prolapse ranged from 2-4% in the Manchester group and two studies also commented on retreatment with a pessary being 3-4%. There were several additional procedures required to evaluate and treat abnormal cervical cytology and menstrual disorders. All of the Manchester descriptions include the use of Sturmdorf sutures to close the amputated cervical stump potentially leading to cervical stenosis and future menstrual issues. Due to the quality of the data, a combined analysis of Table 7 is not possible but there appears to be no differences in anatomical success and reoperation between Manchester and hysterectomy. Despite good success rates, Kalogirou concluded, "that the Manchester procedure has a limited place in modern gynecology…".(209)

The data from the Danish database on Manchester repairs is discussed fully below.

Table 7 Manchester versus Hysterectomy

Reference	Study type and surgery	Review (months)	Success N (%) < stage/grade 2		Reoperation prolapse		Complications
			Hysteropexy	Hysterectomy	Hysteropexy	Hysterectomy	
Thys 2011	Retrospective Matched Cohort Manchester vs TVH USS	72	79/98 (81)	80/98 (82)	4/98 (4)	9/98 (9)	Hemorrhage: 4 vs 5 Bowel lesion: 1 vs 0 Urinary retention: 33 vs 11 Dyspareunia: 4 vs 5
de Boer 2009	Retrospective Cohort Manchester vs TVH/ USS	12	20/50 (40)	25/48 (52)	MD	MD	Bleeding: 0 vs 1 Urinary retention: 9 vs 12
Kalogirou 1996	Retrospective Cohort Manchester vs TVH	36	181/190 (95)	MD (?/231)	4/190 (2)	MD (?/231)	Transfusion: 5% vs 11%
Thomas 1995	Retrospective Cohort Manchester vs TVH	30	61/67 (91%)	MD (?/105)	2/67 (3%)	MD	Transfusion: 3% vs 10%

2.3. Sacrospinous Hysteropexy

Sacrospinous hysteropexy (SSHP) is performed by transfixing the cervix or uterosacral ligaments (USL) to the sacrospinous ligament (SSL) using permanent or delayed absorbable sutures. Most studies approach the SSL via a posterior or apical approach with attachment to the posterior cervix. A cohort study suggested that better subjective outcomes may be achieved when approaching the SSL posteriorly and anchoring to both the anterior and posterior cervix compared to posterior cervical attachment.(211) Another case series promoted an anterior approach to the SSL with anterior cervical attachment as a safe and efficacious SSHP technique.(212) These findings were reinforced by a recent retrospective cohort comparing anterior approach SSHP to vaginal hysterectomy and uterosacral or sacrospinous suspension.(213)

An initial RCT, reported more apical recurrences (21% vs. 3%, p=0.03), similarly frequent anterior recurrences (51% vs. 64%) and similar subjective improvement comparing SSHP (n=37) to vaginal hysterectomy with uterosacral suspension (USLS) (n=34).(214) All three hysteropexy women with stage 4 prolapse had apical recurrences within one year. The largest RCT showed SSHP (n=103) to be non-inferior to vaginal hysterectomy with USLS (n=105) at one year.(215) Success rates were 100% vs 96% for the primary composite outcome using the apex less than stage 2 as the threshold. Most of the recurrences occurred anteriorly. This same group published two-year outcomes for sexual function showing no difference between the procedures using the Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire short form (PISQ-12).(216) More recently, the authors reported five-year study outcomes revealing no differences in anatomical failure, reoperation for prolapse (3% vs 7%) or symptomatic outcomes including quality of life and sexual function. Interestingly, the rate of anterior wall recurrent prolapse did not increase over time and anterior prolapse recurrence beyond the hymen was uncommon (6% vs 8%) at 5 years. They did report less anatomic apical failure (1% vs 8%) and more successful treatment (87% vs 76%) in the SSHP group using a similar apical composite outcome for failure as well as a composite outcome for success including no prolapse beyond the hymen.(217) Another RCT comparing SSHP to vaginal hysterectomy only reported sexual function outcomes using the Female Sexual Function Index-7.(218) There were no differences noted between groups and sexual function remained relatively unchanged with infrequent dyspareunia (5%). Transient buttock pain is a common complaint in up to 15% of patients and usually resolves without intervention.(218-220) As mentioned previously, women with cervical elongation should consider partial trachelectomy to improve apical cure.(196) No differences in anatomic success or symptomatic improvement were reported among 6 other prospective (221) and retrospective (219,220, 222,2013) cohort studies except for one retrospective cohort that revealed worse anatomic outcomes in the SSHP group that were no longer significant after adjusting for baseline differences.(223) Combined analysis of data from Table 8 revealed similar high anatomic success (89%) and a low reoperation rate (4.5% vs 3.8%) for SSHP and hysterectomy.

Table 8 Sacrospinous Hysteropexy versus Hysterectomy and Native Tissue Repair

Reference	Study type and surgery	Review (months)	Success N (%) < stage/grade 2		Reoperation prolapse		Complications
			Hysteropexy	Hysterectomy	Hysteropexy	Hysterectomy	
Schulten 2019[33]	RCT SSHP vs TVH/ USLS	60	101/102 (99)*	94/102 (92)*	3/102 (3)	7/102 (7)	No new procedure related complications after 1 year

Reference	Study type and surgery	Review (months)	Success N (%) < stage/grade 2		Reoperation prolapse		Complications
			Hysteropexy	Hysterectomy	Hysteropexy	Hysterectomy	
Detol-lenaere 2015[31 †]	RCT SSHP vs TVH/ USLS	12	102/102 (100)*	96/100 (96)*	1/102 (1)	4/102 (4)	Death: 0 vs 1 (paralytic ileus, aspiration pneumonia) Reop bleeding: 0 vs 1 Buttock pain: 9% vs 0
Dietz 2010[30]	RCT SSHP vs TVH/ USLS	12	27/34 (79)**	30/31 (97)**	4/35 (11)	2/31 (6)	1 ureteral obstruction - TVH
Jeng 2005[34]	RCT SSHP vs TVH	6	MD	MD	MD	MD	Buttock pain 15%
Plair 2021(213)	Retrospective Cohort Ant SSHP vs TVH/ USLS or SSLF	8	46/50 (92)***	89/97 (92%)***	1 (2) surgery 2 (4) pessary	0 3 (3) pessary	Conversion to open: 0 vs1 Bladder injury: 0 vs 2 Ureteral kink/injury: 1 vs 1 Transfusion: 1 vs 4 Sepsis: 1 vs 2 Nerve injury/entrapment: 1 vs 2 Hematoma: 1 vs 1 Suture removal/cuff revision: 1 vs 2 Hospitalization: 2 vs 2
Lo 2015	Retro Cohort SSHP vs TVH/ SSLF	86	13/26 (50)	86/120 (72)	0/26	2/120 (2)	Vault infection, inpatient care: 0 vs 1
Hefni 2003	Pros Cohort SSHP vs TVH/ SSLF	33	57/61 (94)~	46/48 (96)~	3/61 (5)	2/48 (4)	Buttock pain 3% vs 4% Hematoma 0 vs 6% – 1 reop to drain Transfusion 0 vs 4%
Van Brum-men 2003	Retrospective Cohort SSHP vs TVH	19	39/44 (89)	28/30 (93)	3/57 (5)	3/52 (6)	Hemorrhage: 2% vs 7% Nerve injury: 2% vs 0
Maher 2001	Retrospective Cohort SSHP vs TVH/ SSLF	26 vs 33	20/27 (74)	21/29 (72)	2/27 (7)	2/29 (7)	Buttock pain 6% vs 3% Dyspareunia 7% vs 3%
Hefni 2006	Retrospective SSHP vs TVH/ SSLF	57	60/65 (92)~	114/117 (97)~	MD	MD	Buttock pain 7% Dyspareunia: 2 Rectal injury: 2 Transfusion: 1 Vault hematoma: 7 Reop bleeding: 3
Total			**363/409 (88.8)**	**508/574 (88.5)**	**16/358 (4.5)**	**18/382 (3.8)**	
			MD 0.5% (-0.4%,4.9%),p=0.8		**MD 0.6%(-.1%, 2.5%) p=0.9**		

SSHP sacrospinous hysteropexy, TVH total vaginal hysterectomy, USLS uterosacral suspension, SSLF sacrospinous fixation, MD missing data

** composite apex < stage 2, no prolapse symptoms, no apex reoperation*

*** apex < stage 2*

**** composite no prolapse beyond hymen, no apical descent 1/3 TVL, no bulge symptoms, no retreatment pessary or surgery*

~ composite apex < -6 cm, no prolapse symptoms, able insert 2 fingers without discomfort

† data from this trial was not included in summation as same trial as Schulten 2019

2.4. Uterosacral Hysteropexy

Uterosacral hysteropexy (USHP) involves shortening or plicating the uterosacral ligaments ipsilaterally or in the midline with permanent or absorbable sutures placed vaginally, abdominally or laparoscopically. There are no RCTs comparing USHP to hysterectomy. A prospective cohort study comparing laparoscopic USHP (n=28) to total laparoscopic hysterectomy (TLH) with USLS (n=27) found similar anatomic success (79% vs. 78%).(224) A retrospective cohort study comparing laparoscopic USHP (n=25) to age-matched vaginal hysterectomy prolapse repair (n=25) reported better symptomatic (92% vs. 80%) cure with fewer reoperations for recurrent prolapse (0 vs 3) following laparoscopic USHP.(225) Another retrospective cohort found lower anatomic success (47% vs. 63%) and more reoperations for recurrent prolapse (28% vs. 21%) after laparoscopic USHP (n=104) compared to laparoscopic hysterectomy with USLS (n=160).(226) A more recent retrospective cohort reported similar anatomic (94% vs. 85%) and composite cure rates (98% vs. 96%) with no reoperations for recurrent prolapse after laparoscopic USHP (n=48) compared to vaginal hysterectomy with USLS (n-103).(227) (Haj-Yahya 2020) A retrospective cohort comparing vaginal USHP (n=100) to vaginal hysterectomy with USLS (n=100) reported similar outcomes with good apical (96% vs. 97%), anterior (87% vs. 94%) and posterior (98% vs. 100%) support.(198) A more recent retrospective cohort comparing vaginal USHP (n=52) to vaginal hysterectomy and USLS (n=52) age and prolapse severity matched controls found similar anatomic (73% vs. 75%) and symptomatic (81% vs 90%) cure and satisfaction using the patient global impression of improvement (1.7 vs 1.4).(228) However, there were more apical recurrences (21% vs 2%, p=0.002) and reoperations (13% vs 2%, p=0.04) in the USHP group due to cervical elongation despite the fact that 15% had concomitant partial trachelectomy. Complications were rare for all of the studies with only 2 ureteric obstructions identified for over 700 USLS. Combined analysis from Table 9 revealed a non-significant tendency to a lower anatomic success rate -6.1% (-12.7%, 0.2%) p=0.06 and higher reoperation rate 4.7% (-0.8%, 10.2%) p=0.09 for USHP compared to USLS with hysterectomy. Overall success rates and reoperation rates are extremely variable among the six studies.

Table 9 Uterosacral Hysteropexy versus Hysterectomy with Uterosacral Suspension

Reference	Study type and surgery	Review (months)	Success N (%) < stage/grade 2		Reoperation prolapse		Complications
			Hysteropexy	Hysterectomy	Hysteropexy	Hysterectomy	
Milani 2019	Retrospective Cohort VUSHP vs TVH/USLS	35	38/52 (73)	39/52 (75)	7/52 (13)	1/52 (2)	Suture granuloma: 1 vs 0 Ureteral kinking: 0 vs 1
Romanzi 2012	Retrospective Cohort VUSHP vs TVH/USLS	24	59/68 (87)	91/97 (94)	MD	MD	Hemorrhage: 4 vs 3 Cystotomy: 0 vs 3 Ureteral obstruction: 0 vs 2 Rectal injury: 1 vs 1
Haj-Yahya 2020	Retrospective cohort LUSHP vs TVH/USLS	17	45/48 (94)	88/103 (85)	0/48	0/103	Transfusion: 0 vs 1 Cuff bleeding/hematoma: 0 vs 6 Suture exposure/granulation tissue: 4 vs 0
Bedford 2013	Retrospective Cohort LUSHP vs TLHorLAVH/ LUSLS	34 vs 22	49/104 (47)	100/160 (63)	29/104 (28)	33/160 (21)	Cystotomy: 1 Reoperation SBO: 1
Rosen 2008	Prospective Cohort LUSHP vs TLH/ LUSLS	24	22/28 (79)	21/27 (78)	4/28 (14)	3/27 (11)	Dyspareunia: 1 each group
Diwan 2005	Retrospective Cohort LUSHP vs TVH/midline USLS	7	MD	MD	0/25 (0)	3/25 (12)*	*De novo dyspareunia: 2 vs 4*
Total			**213/300 (71)**	**339/439 (77)**	**40/257 (16)**	**40/367 (11)**	
			-6.1% (-12.7%, 0.2%) p=0.06		**4.7% (-0.8%, 10.2%) p=0.09**		

VUSHP vaginal uterosacral hysteropexy, TVH total vaginal hysterectomy, USLS uterosacral suspension, LUSHP laparoscopic uterosacral hysteropexy, TLH total laparoscopic hysterectomy, LAVH laparoscopic assisted vaginal hysterectomy, LUSLS laparoscopic uterosacral suspension, Midline USLS Midline plication uterosacal suspension or McCall culdoplasty, SBO small bowel obstruction, MD missing data

* *reoperation apical prolapse*

3. MESH HYSTEROPEXY PROCEDURES

There are two main types of mesh hysteropexy procedures, SSHP with graft previously referred to as vaginal mesh hysteropexy and sacrohysteropexy (SHP) done abdominally or laparoscopically. Technique, graft type and configuration varies considerably for each of these procedures. The use of vaginal mesh repairs with mesh kits was on the rapid decline following the US Food and Drug Administration (FDA) safety communications in 2008 and 2011 resulting in reclassification from class II, moderate-risk devices, to class III, high-risk devices in 2016. In November and December of 2017, Australia and New Zealand banned the use of transvaginal mesh for prolapse surgery. In July 2018, the United Kingdom halted sales of transvaginal mesh until a registry was developed to track complications when performed by properly trained surgeons. On April 16, 2019, the US FDA banned commercial transvaginal mesh kits for prolapse stating that the risks outweigh the potential benefits. Based on the current situation, the SSHP section with graft contains previous ICI findings and recommendations plus provides an update on the recent results of a large RCT. On the other hand, laparoscopic sacrohysteropexy (SHP) has been gaining popularity as a minimally invasive approach to uterine conservation with the potential for increased durability, though long-term data is lacking for this procedure. While transabdominal mesh use for prolapse has not been banned, the class action lawsuits and advertisements have fuelled patients' fears about mesh use in reconstructive pelvic surgery resulting in a further shift toward native tissue prolapse repairs.

3.1. Sacrospinous Hysteropexy with Graft

SSHP with graft is performed with vaginal placement of mesh into the anterior wall with uterine conservation. In order to be a hysteropexy procedure, a concomitant apical support procedure must be performed such as a SSLF or USLS. Level 1 evidence demonstrates improved anterior wall support with the addition of vaginally mesh.(229) Thus, the addition of anterior mesh has the potential to decrease rates of anterior recurrences seen with other hysteropexy repairs. Early anterior mesh kits did not include apical support unless a concomitant posterior mesh kit with apical support was inserted or a separate apical support procedure was performed. These products were replaced by trocarless anterior mesh kits that are anchored into the sacrospinous ligament via an anterior approach. Notably, all of the first and second generation anterior and posterior mesh kits are no longer commercially available.

The only multicentre RCT conducted by the Pelvic Floor Disorders Network compared SSHP with anterior graft (n=88) using Uphold to vaginal hysterectomy with USLS (n=87) at and at 5 years there were fewer failures for the hysteropexy and permanent mesh group than hysterectomy group (adjusted hazard ratio, 0.58; 0.36-0.94; P 0.03), with failure rates of 37% vs 54%, respectively. With the exception of the Urogenital Distress Inventory, no group differences were demonstrated in patient reported pelvic floor symptoms, prolapse symptoms, bowel function symptoms, general quality of life, body image, or pelvic pain.(230) Mesh exposures occurred in 8% of hysteropexy (all related to prolapse mesh, no sling exposures) and 5% of hysterectomy (all from slings). There was more granulation tissue and suture exposures observed with hysterectomy (1% vs 11% and 3% vs 21% respectively) although none of the mesh exposures, suture exposures or granulation tissue required reoperation.

A single prospective cohort study compared SSHP with mesh (n=66) to vaginal hysterectomy with vaginal mesh repair (n=30) using Uphold and revealed high anatomic success with only 1 mesh exposure at 6 months follow-up.(231) Three retrospective cohort studies compared SSHP with mesh graft to vaginal hysterectomy with vaginal mesh repair using Perigee/Apogee (American Medical Systems, Minnetonka, MN, USA), Total Prolift (Ethicon, Somerville, NJ, USA) and Posterior Intravaginal Slingplasty (Tyco Healthcare, Norwalk, CT, USA).(197,232,233) Combined analysis from Table 10 showed no difference in anatomic support (96% vs. 97%, p = 0.5), but more mesh exposures in the hysterectomy group (5% vs. 11%, p = 0.02). These findings are consistent with an early Prolift study that reported a 5-fold increased odds of mesh exposure with concomitant hysterectomy.(234) Thus, there may be a benefit for uterine conservation at the time of vaginal mesh repair for uterovaginal prolapse to decrease mesh exposure risks. The only study that included reoperations for prolapse found more reoperations (5% vs. 0) in the hysteropexy group when using total Prolift.(233) Currently all of the devices used in Table 10 are no longer commercially available and no comparative data exists for surgeons that fashion their own vaginal mesh implants.

Table 10 Sacrospinous Hysteropexy with Graft versus Vaginal Hysterectomy and Vaginal Mesh Repair

Reference	Study type and surgery	Review (months)	Success N (%) < stage 2		Complications	Mesh exposure N(%)	
			Hysteropexy	Hysterectomy		HP	Hyst
Chu 2011	Retrospective Co-hort (Perigee/Apogee) SSHP/graft vs TVH/VMR	9	50/52 (96)	39/39 (100)	Abnormal sensation: 3 vs 3 Transfusion: 0 vs 1	2/52 (4)	5/39 (13)
Neuman 2007	Retrospective Co-hort (post IVS) SSHP/graft vs TVH/VMR	29	32/35 (91)*	42/44 (95)*	None	4/35 (11)	6/44 (14)
Vu 2012	Retrospective Co-hort (Uphold) SSHP/graft vs TVH/VMR	12	52/53 (98)	22/24 (96)	Left labial numbness: 1	1/53 (2)	2/24 (8)
Huang 2015	Retrospective Co-hort (Total Prolift) SSHP/graft vs TVH/VMR	30	74/78 (95)	23/24 (96)	Dyspareunia: 1 vs 0 Vaginal pain: 2 vs 0 Vaginal infection: 0 vs 2 Reop mesh exposure: 2 vs 3	6/78 (8)	5/24 (21)

Reference	Study type and surgery	Review (months)	Success N (%) < stage 2		Complications	Mesh exposure N(%)	
			Hysteropexy	Hysterectomy		HP	Hyst
Ker 2018	Prospective Cohort (Uphold) SSHP/graft vs TVH/VMR	6	64/66 (97)	30/30 (100)	Dyspareunia: 2 vs 3 Hematoma: 0 vs 2	1/66 (2)	0/30
TOTAL			**272/284 (96)**	**156/161 (97)**		**14/ 284 (5)**	**18/161 (11)**
P value			**-1.1% (-4.6%, 2.9%) p=0.5**			**-6.1%(-12%, -0.8%) p=0.02**	

HP hysteropexy, Hyst hysterectomy, SSHP/graft sacrospinous hysteropexy with mesh gratt, TVH total vaginal hysterectomy, VMR vaginal mesh repair, post IVS posterior intravaginal slingplasty

* *< stage 3*

4. SACROHYSTEROPEXY

Sacrohysteropexy (SHP) typically involves the attachment of at least one graft from the cervix and uterus to the anterior longitudinal ligament near the sacral promontory. This is an abdominal procedure that can be performed via an open, laparoscopic or robotic approach. A variety of graft materials, configurations and operative techniques have been described. The most common technique involves a single polypropylene mesh strap extending posteriorly from the sacrum to the uterus. The graft then bifurcates and the two smaller arms are passed through windows in the broad ligament and secured to the anterior cervix. The length of graft extension down the anterior and posterior vaginal walls as well as the use of a second mesh strap varies and may explain differences in anterior wall recurrences and development of cervical elongation. Some studies use a single anterior graft attached to the proximal anterior vaginal wall similar to sacral colpopexy (SCP). The graft bifurcates and the arms are passed through windows in the broad ligament and anchored into a posterior graft if present or directly into the anterior longitudinal ligament. The majority of studies compare SHP to total hysterectomy with SCP or supracervical hysterectomy with sacrocervicopexy (SCerP) plus a few studies using native tissue controls.

One RCT comparing abdominal SHP (n=41) to vaginal hysterectomy with USLS (n=41) found similar subjective and anatomic outcomes. However, the hysteropexy subjects underwent more planned or performed reoperations (22% vs. 2%).(235) Similarly to this, a pilot RCT comparing laparoscopic SHP (n=40) to vaginal hysterectomy with USLS (n=39) demonstrated that while apical support and total vaginal length were superior in the laparoscopic SHP group, 21% of the hysteropexy group required additional anterior colporrhaphy compared to none in the vaginal hysterectomy group.(236) The laparoscopic approach had a longer operating time however blood loss, admission and recovery time were reduced compared to the vaginal hysterectomy group. A prospective cohort comparing laparoscopic SHP (n=44) to vaginal hysterectomy with midline plication USLS (81) discovered similar subjective outcomes, sexual function and rates of reoperation or pessary use at two years. (237) Similarly, another recent retrospective cohort comparing laparoscopic SHP (n=46) to vaginal hysterectomy with midline plication USLS (n=86) revealed no significant differences in symptomatic prolapse recurrence, satisfaction and reoperation.(238)

A retrospective cohort compared abdominal SHP (n=35) to abdominal hysterectomy with SCP (n=63) or USLS (n=70).(239) In this cohort, SHP had superior anatomic success (100% vs. 74%) over abdominal hysterectomy and USLS. For the combined native tissue comparisons in Table 11, SHP had similar anatomic success (80% vs. 69%, p = 0.09) and reoperation rate (13% vs. 9%).

Table 11 Sacrohysteropexy versus Hysterectomy and Uterosacral Suspension

Reference	Study type and surgery	Review (months)	Success N (%) < stage 2		Reoperation prolapse (includes planned reoperation)		Complications	Mesh exposure N (%)	
			Hysteropexy	Hysterectomy	Hysteropexy	Hysterectomy		HP	Hyst
Roovers 2004	RCT ASHP vs TVH/USLS	12	26/41 (63)	25/41 (61)	9/41 (22)	1/41 (2)	Transfusion: 1 vs 2 Bowel injury: 0 vs 1 Vault abscess: 2 vs 0 Reop: 3 (hernia, 2 infected implants) vs 1 (vaginal stricture)	2/41 (5)	n/a
Jeon 2008	Retrospective Cohort ASHP vs TAH/USLS	36	35/35 (100)	52/70 (74)	MD	MD	Ureteral obstruction: 0 vs 1 SBO: 0 vs 1	0/35	n/a
Rahmanou 2014	RCT LSHP vs TVH/USLS	12	MD	MD	8/40 (20)	7/39 (18)	None	0/40	n/a
Lone 2018	Prospective Cohort LSHP vs TVH/midline USLS	24	MD	MD	2/44 (5)*	3/81 (4)	Bowel injury: 2 vs 0 Bladder injury: 0 vs 2	0/44	n/a
Sukur 2020	Retrospective Cohort LSHP vs TVH/midline USLS	48	MD	MD	3/46 (7)	10/86 (12)	MD	MD	n/a
Total			**61/76 (80)**	**77/111 (69)**	**22/171 (13)**	**21/247 (9)**		**2/160 (1)**	**n/a**
			11% (-2%, 23%) p=0.09		**4.4% (-2%,11%) p=0.2.**				

hysteropexy, Hyst hysterectomy, ASHP abdominal sacrohysteropexy, TVH total vaginal hysterectomy TAH total abdominal hysterectomy, LSHP laparoscopic sacrohysteropexy, USLS uterosacral suspension, SBO small bowel obstruction, MD missing data,
**includes 2 subjects with symptomatic prolapse using pessary*

There are no RCTs comparing SHP to hysterectomy and SCP. Meta-analysis from nine comparative studies evaluating 815 women found a lower anatomic success rate -6.3% (-12, -1%) p=0.01 and higher reoperation rate 5.4%(2%,9%) p=0.001 after SHP as compared to SCP and hysterectomy although the hysterectomy group were associated with significantly greater risk of mesh exposure 7% (3, 11%) p<0.001

Supracervical hysterectomy and sacrocervicopexy (SCerP) was introduced to obtain benefits of SCP and hysterectomy without the risk of mesh exposure.

A recent retrospective cohort study compared one-year outcomes for laparoscopic SHP (n=38) to laparoscopic supracervical hysterectomy (LSH) and SCerP (n=195) or total laparoscopic hysterectomy (TLH) and SCP (n=38).(240) There were no apical failures and more anterior recurrences (stage 2) in the SHP group (21% vs 8%, p = 0.02). Mesh complications were similar between groups (2.6% vs 1.3%, p = 0.46). We contacted the authors to obtain a breakdown of the outcomes for each of the three separate arms (see Table 6) and there were no differences in anatomic success or mesh related complications when comparisons were done among the three groups. Another retrospective cohort study comparing robotic assisted LSH with SCerP (n=43) and TLH with SCP (n=40) found more recurrent anatomic prolapse (≥ stage II) (41.9 % vs 20.0 %, p = 0.03; OR 2.8, 95 % CI, 1.07-7.7) and a tendency to greater prolapse beyond the hymen (18.6% vs. 12.5%, p=0.45) and symptomatic recurrence (18.6 % vs 10.3 %, $p = 0.29$) that did not reach statistical significance in the group that underwent LSH and SCerP. The composite success rate (67.4% vs. 75%, p=0.45) were not significantly different and mesh exposures were more common with total hysterectomy (2.3% vs. 7.5%, p=0.35).(241) The anatomic and symptomatic outcomes between LSH SCerP and TLH SCP need to be further investigated with larger prospective studies. This will help surgical planning and informed consent when considering the balance between anatomic and symptomatic success compared to mesh related complications.

Table 12 Sacrohysteropexy versus Hysterectomy and Sacral Colpopexy

Reference	Study type and surgery	Review (months)	Success N (%) < stage 2		Reoperation prolapse		Complications	Mesh exposure N (%)	
			Hysteropexy	Hysterectomy	Hysteropexy	Hysterectomy		HP	Hyst
Costantini 2005	Prospective Cohort ASHP vs TAH/SCP	51	31/34 (91)*	35/38 (92)*	0/34 (0)	0/38 (0)	Hematoma: 2 vs 4 Transfusion: 2 vs 2	0/34	3/38 (8)
Costantini 2013	Prospective Cohort ASHP vs TAH/SCP	12	32/32 (100)**	36/36 (100)**	0/32 (0)	0/36 (0)	MD	MD	MD
Cvach 2012	Retrospective/Prospective Cohort ASHP vs TAH/SCP	17	15/18 (83)***	8/8 (100)***	1/18 (6)	0/8	Transfusion: 0 vs 2	0/16	3/9 (33)
Jeon 2008	Retrospective Cohort ASH vs TAH/SCP	36	35/35 (100)	60/63 (95)	MD	MD	Abscess: 0 vs 2 Ureteral obstruction: 0 vs 1 SBO: 0 vs 3	0/35	5/63 (8)
Bai 2005	Retrospective Cohort ASHP vs TAH/SCP	12	10/10 (100)^	18/19 (95)^	MD	MD	Transfusion: 3 vs 5 Wound dehiscensce and closure: 0 vs 2	0/10	3/19 (16)
Costantini 1998	Retrospective ASHP vs TAH/SCP	32	7/7 (100)	8/9 (89)	MD	MD	DVT/PE: 2 Femoral neuropathy: 1 Incisional hernia: 2	0/7	0/9
Pan 2015	Retrospective Cohort LSHP vs TLH/LSCP	33	47/65 (72)~	30/34 (88)~	10/66 (15)†	0/34 (0)†	None	0/65	0/34
Iliano 2020	Prospective Cohort LSHP vs TLH/LSCP	65	47/54 (87)	77/82 (94)	0/54	0/82	Transfusions: 2 vs 5 Hernia: 1 vs 1 Hematoma: 0 vs 1 Sigmoid stenosis: 1 vs 0	2/54	6/82
Gagyor 2020	Retrospective Cohort LSHP vs LSH/LSCerP (n=195) and TLH/LSCP (n=38)	12	30/38 (79)	215/233 (92) x/38	MD	MD	Transfusions: 1 vs 1 Bladder injury: 2 vs 8 Dindo grade III: 0 vs 4	1/38	3/233x/38
Total			**254/293 (87%)**	**272/289 (94%)**	**11/204 (5.4%)**	**0/196**		**2/221 (0.9%)**	**20/254 (7.9%)**
			-6.3% (-12, -1%) p=0.01		**5.4%(2%,9%) p=0.001**			**-7% (-11,-3%) p<0.001**	

HP hysteropexy, Hyst hysterectomy, ASHP abdominal sacral hysteropexy, TAH total abdominal hysterectomy, SCP sacral colpopexy, LSHP laparoscopic sacral hysteropexy, TLH total laparoscopic hysterectomy, LSCP laparoscopic sacral colpopexy, LSH laparoscopic supracervical hysterectomy, MD missing data

** < stage 2 plus apex < -6 cm*

*** apex < -6 cm*

**** composite: anatomic cure (no prolapse beyond hymen) plus no bulge symptoms*

^ < stage 1

~ < stage 1 and at least 3 cm above hymen

† reoperation prolapse or pessary use

4.1. Laparoscopic Sacrohysteropexy vs. Sacrospinous Hysteropexy with Graft

A recent prospective multicentre cohort study compared laparoscopic SHP using anterior and posterior mesh straps (n=64) to SSHP with graft using Uphold (n=61).(242) There was no difference at 1 year in composite cure (72% vs. 74%, p=0.27) using validated outcome measurements/POP-Q. Composite cure was defined as no prolapse beyond the hymen, apex above the mid vagina, no symptoms and no reoperation or pessary use. There were only 2 reoperations for recurrent prolapse, both in the vaginal group. Mesh exposure rates were 2.7% for laparoscopic and 6.6% for vaginal hysteropexy. Satisfaction was 95% for both groups and symptoms resolved in 90-95%.

4.2. Laparoscopic vs. Open Sacrohysteropexy

A retrospective cohort compared laparoscopic (n=54) and open (n=57) SHP repairs.(243) Aside from longer operative time and blood loss with open abdominal surgery, there were no differences in satisfaction (94% vs. 91%), anatomic success (POP-Q < stage 3: 96% vs. 98%), reoperation (4% vs. 2%) and mesh exposure (0 vs. 5%).

4.3. Sacrospinous Hysteropexy with Mesh vs. Dermal Graft

An ambidirectional cohort comparing SSHP with mesh (Uphold) (n=247) to human dermal graft (n=45) found improved anatomic support and lower anatomic failure rates at 1 year (hymen – 3% vs. 9%, p=0.007; stage 2 – 18% vs. 29%, p=0.03) with the mesh augmented repairs.(244) Mesh exposures occurred in 6% of mesh augmented repairs with 2% requiring surgical excision and there were no exposures in the dermal group.

4.4. Laparoscopic Uterosacral Hysteropexy vs. Sacrohysteropexy

A retrospective cohort study with cross- sectional survey comparing laparoscopic USHP (n=55) to laparoscopic SHP (n=42) discovered more bulge symptoms and/or retreatment with a pessary or surgery at 6 months after SHP (36% vs 13%, p=0.007).(245) However, after controlling for baseline differences including older age, menopausal status and worse prolapse in the SHP group, the results were no longer statistically significant.

4.5. Laparoscopic Sacrohysteropexy vs. Sacrospinous Hysteropexy

A multicentre non-inferiority RCT (LAVA-trial) is underway in the Netherlands comparing laparoscopic SHP with vaginal SSHP. A methods paper has been published for this trial.(246) They will include women with stage 2 or higher uterine descent. Success is defined as a composite outcome with the cervix above the mid-vagina (C < -TVL/2), no bulge symptoms and no retreatment at 1 and 5 years. They plan to enrol an estimated sample size of 124 subjects.

4.6. Different Hysteropexy Procedures vs. Hysterectomy Using Database/Registry

A recent large retrospective cohort study using the California Office of Statewide Health Planning and Development database for women undergoing reconstructive prolapse repairs or uterovaginal prolapse compared reoperation rates without hysterectomy (n=51,491) and with hysterectomy (n=42,340).(247) There were many baseline differences between the two groups and mesh was more commonly implanted in the no hysterectomy group (17.6% vs. 9.6%). Reoperation rate for prolapse was lower in the hysterectomy group (3% vs. 4.4%, RR 0.67, p<0.001) and this difference persisted after multivariate modelling. Furthermore in those undergoing apical suspensions only (hysterectomy 21,487 and hysteropexy 18,839), hysterectomy was protective for recurrent prolapse in the apical (1.9 versus 3.3% p<0.001), anterior (1.3% versus 2.2% p <0.001) , posterior (1.3% versus 2.2% p<0.001) or more than one compartment (1.1% versus 1.9% p<0.001) when compared to hysteropexy. Perioperative complications were more common with hysterectomy including transfusion (2.5% vs 1.5%), infection or sepsis (0.9% vs. 0.4%), readmission for infection (0.7% vs 0.3%) and urologic injury or fistula (0.9% vs. 0.6%).

Another recently published retrospective population-based cohort study identified a total of 310,938 French patients that underwent surgical procedures for prolapse (primary, recurrent and vault) from 2008 to 2014.(248) Reoperation for recurrent prolapse represented 4.4% of the sample. Procedures performed included anterior and/or posterior repair, SSLF, LeFort colpocleisis, laparoscopic or open SCP (with or without hysterectomy), and laparoscopic or open rectopexy. The authors were unable to differentiate vaginal mesh and non-mesh interventions. The route of POP surgery was vaginal 55%, abdominal 36%, combined 4% and transanal in 4%. Hysterectomy was performed in approximately 50% of vaginal cases but only 12.5% of abdominal interventions. Unfortunately, we are unable to differentiate between the non-hysterectomy group that includes those with post hysterectomy prolapse or uterine preserving interventions. However, despite these limitations and after multiple regression analysis, concomitant hysterectomy (aHR 0.51 [0.49-0.53]) and the abdominal approach (aHR 0.62 [0.59-0.65]) at the first surgery was associated with a significantly lower risk of reoperation for recurrence.

Another recent large cohort study compared Manchester procedure (n=2,786), vaginal hysterectomy (n=4,045) and SSHP (n=416) for apical prolapse using the Danish National Patient Registry from 2010 to 2016.(249) The surgical procedures evaluated and the lower rate of hysteropexy compared to hysterectomy (1/10) in the Danish trial speaks to the uniqueness of the Danish data set compared to the Californian and French database evaluations. There were many baseline differences between the three groups including the vaginal hysterectomy group being older and having greater stage 3 and 4 apical and posterior compartment prolapse pre-intervention compared to Manchester procedure. SSHP had higher risk of reoperation compared to Manchester (aHR 5.0) and vaginal hysterectomy (aHR 3.3) with greater risks of reoperations in the apical compartment (aHR 40.2 and 8.5 respectively). Vaginal hysterectomy had slightly increased risk of reoperation compared to Manchester (aHR 1.5) that was worse in the apical compartment (aHR 4.2). Five-year reoperations rates were highest with SSHP (30%) followed by vaginal hysterectomy (11%) and Manchester (7%). It is unclear what type of apical support procedure was performed at the time of vaginal hysterectomy.

These three large database studies confirm the general tendency to poorer outcomes associated with hysteropexy interventions demonstrated above from level I and II evidence. The Danish data also suggests that Manchester has advantages over vaginal hysterectomy and SSHP but there is the potential for large selection bias with many potential confounders and limitations in this study.

A multicentre non-inferiority RCT (SAM study) is underway in the Netherlands comparing modified Manchester procedure with SSHP for primary uterovaginal prolapse that will address many of these unanswered questions.(217) Women with symptomatic prolapse of any stage are included if the uterine descent and POP-Q point D is less than or equal to minus 1cm. Thus, they are evaluating treatment for milder cases of uterine prolapse due to the belief that the Manchester procedure is not appropriate for more severe prolapse. Success is defined as a composite outcome with no prolapse be-

yond the hymen, no bulge symptoms and no retreatment at 2 years. They plan to enrol an estimated sample size of 424 subjects.

5. HYSTERECTOMY RISKS

Most providers recognise that hysterectomy is a relatively safe procedure with low risks of severe morbidity. The most common injuries that occur during pelvic reconstructive surgery involve the urinary tract system. These injuries are often preventable or recognised with routine cystoscopy and repaired prior to leaving the operating room. Most hysterectomies performed for prolapse involve small uteri, especially in postmenopausal women, leading to short operative times for this portion of the procedure. If we assume similar success with hysteropexy and hysterectomy, risks of hysteropexy and subsequent hysterectomy, which may be more challenging, must be weighed against concomitant hysterectomy risks. This section reviews some of the risks that may be encountered when hysterectomy is performed at the time of uterovaginal prolapse repair.

5.1. Premature ovarian failure

Performance of a hysterectomy alone or at the time of prolapse repair (native tissue or mesh) may have a negative impact on ovarian function among premenopausal women. Two large prospective cohort studies showed an increased risk of earlier onset of menopause in women undergoing hysterectomy compared to nonsurgical controls, even with conservation of both ovaries.(250,251) There was an approximately 2-fold increased risk of undergoing menopausal over a 5-year time period with hysterectomy alone. The risk increased to almost 3-fold with removal of one ovary.(251) While this may not be a major factor in peri- and postmenopausal women, it must be considered during surgical planning for premenopausal women.

5.2. Mesh exposure

Total hysterectomy at the time of SCP has been shown to increase mesh exposure rates when compared to SHP or supracervical hysterectomy with SCerP. In Tables 10 and 11, mesh exposure risks were 6% versus 14% for vaginal mesh repairs and 1% versus 8% for SCP. Even with cessation of vaginal mesh repair and the trend toward primary native tissue prolapse repairs, laparoscopic SCP with or without robotic assistance still may have a role in the primary treatment of uterovaginal prolapse. This is based on the assumption that minimally invasive SCP will provide better anatomic support with more durable outcomes. However, evidence favouring SCP as the best prolapse repair is largely founded on studies involving surgical management of post-hysterectomy vault prolapse. Many providers have extrapolated these results to primary uterovaginal prolapse despite a lack of good quality data and consensus. Additionally, with the increased popularity of uterine conservation during primary native tissue prolapse repair, specialists will be faced with the dilemma of what to do with the uterus at the time of minimally invasive SCP for recurrent uterovaginal prolapse. In a review of over 125,000 robotic or laparoscopic SCP in the US between 2009 and 2011, nearly 50% of cases involved concomitant hysterectomy.(252) Thus, to further evaluate the data on SCP and uterine prolapse, we compared mesh exposure rates for studies describing results with no hysterectomy (post-hysterectomy or hysteropexy), total hysterectomy with SCP and supracervical hysterectomy with SCerP.(Table 13) Procedures were further subdivided into open and laparoscopic. Mesh exposure rates were 3.5-fold higher ($p < 0.0001$) after a SCP with concomitant total hysterectomy (7.3%) compared to no hysterectomy (2.1%). The differences in mesh exposure rates between SCP with hysterectomy versus no hysterectomy were greater for open procedures (9.8% vs 2.3%, $p < 0.0001$) compared to laparoscopic repairs (5.9% to 2.0%, $p < 0.0001$). Many of the open repairs use grafts other than polypropylene, such as polytetrafluoroethylene (Teflon) and polyethylene (Mersilene, some Marlex), which have been shown to increase risk of mesh exposure.(253) The rate of mesh exposure was significantly lower with SCerP and supracervical hysterectomy (0.6%).

If hysterectomy was considered at the time of SCP, techniques for graft attachment to the vaginal may also play a role. Three studies included in Table 8 contain subjects that underwent total vaginal hysterectomy or laparoscopic assisted vaginal hysterectomy with vaginal attachment of the mesh at SCP.(254-256) Two of these studies reveal a 2 to 4-fold decreased rate of mesh exposure (14% vs. 32% and 3% vs. 14%) with vaginal attachment of mesh compared to laparoscopic attachment of the vaginal portion of the mesh with concomitant total hysterectomy during laparoscopic SCP.(256-258) A third study showed a low rate of mesh exposure (1.6% vs. 1.7%) comparing total vaginal hysterectomy with vaginal attachment to laparoscopic supracervical hysterectomy (LSH) at the time of laparoscopic SCerP.(257) Alternatively, Visco et al evaluated mesh erosions after sacrocolpoperineopexy and demonstrated that when sutures (HR 5.4 95% CI 1.6-18) or mesh HR19.7 95% CI 4-101) was placed vaginally the risk of mesh erosions increased significantly when compared to traditional SCP.(259)

One potential explanation for the decreased rate of mesh exposure with vaginal compared to laparoscopic attachment of mesh when hysterectomy and SCP are conducted concomitantly is less vaginal cuff manipulation and disruption during the laparoscopic portion of the case. More long-term prospective data is needed to determine the role of hysterectomy at time of SCP.

Table 13 Rate of mesh exposures at sacrocolpopexy with and without total and supracervical hysterectomy

Reference	Follow-up months	SCP surgery	Mesh	Vault POP	SCP + total hyst	SCP+ Supracervical Hyst	P value
Jeon, 2008	36	Open	TEFLON MARLEX(PP) PP	0/35	5/63		
Jeon, 2009	66	Open	TEFLON MARLEX(PP)	0/31	4/26		
Cundiff 2008	24	Open	Mersilene(PE) PP GORETEX	8/239	12/83		

Reference	Follow-up months	SCP surgery	Mesh	Vault POP	SCP + total hyst	SCP+ Supracervical Hyst	P value
Wu, 2006	15	Open	GORETEX MERSILENE PP	10/212	7/101		
Costantini, 2005	51	Open	MARLEX(PP)	0/34	3/38		
Bai 2005	12	Open	Synthetic mesh	0/20	3/19		
Bensiger, 2005	12	Open	PP	0/35	4/49	0/37	
Brizzolara 2003	35	Open	80% PP 20% allografts	0/64	1/60		
Culligan 2002	24	Open	Synthetic mesh	3/234	3/11		
Cvach 2012(260)	17	Open	70% PP 30% Porcine	0/16	3/9 (33)		
Ginath 2013(261)	7	Open	PP	2/82		1/195	
Total for Open SCP				**23/1002 (2.3%)**	**45/459 (9.8%)**	**1/232 (0.4%)**	**<0.0001**
Stepanian 2008(262)	12	Lap	PP	2/272	3/130		
Tan Kim, 2011(263)	15	Lap ±RA	PP	5/110	13/57*	1/21	
Osmundsen 2012(264)	3	RA Lap	PP		8/49	0/31	
Bojahr 2012(265)	8	Lap	PP	0/19	MD	0/151	
Warner 2012(256)	6	Lap	PP	1/95	9/187*	0/92	
Crane 2014(266)	2	RA Lap	PP	6/118	3/79	0/33	
Myers 2015(241)	12	RA Lap	PP		3/40	1/43	
Pan 2016(199)	33	Lap	PP	0/65	0/34		
Gracia 2015(267)	12	Lap	PP	0/15		0/30	
Nosti 2016(254)	9	Lap ±RA	PP		2/123**	1/59	
Davidson 2019(268)	6	Lap ±RA	PP		1/45*	2/116	
Iliano 2020(269)	65	Lap ±RA	PP	2/54	6/82		
van Zanten 2020(270)	48	RA Lap	PP	1/34		2/61	
Campagna 2019(271)	12	Lap	Titanium coated PP	1/59	2/18	0/131	
Culligan 2020(272)	66	RA Lap	PP	0/76		0/240	
Total for Lap SCP				**18/917 (2.0%)**	**50/844 (5.9%)**	**7/1008 (0.7%)**	**<0.0001**
				40/1919 (2.1%)	**95/1303 (7.3%)**	**8/1240 (0.6%)**	**<0.0001**

PP polypropylene, PE polyester, Lap Laparoscopic, RA robotic assisted, SCP Sacral Colpopexy, MD=missing data
** A portion of these cases involves vaginal attachment of the mesh*
*** All of these cases involve vaginal attachment of the mesh*

5.3. Spread of unanticipated malignancy

There is insufficient data to compare laparoscopic SHP and LSH with SCerP. Cervical conservation appears to decrease mesh exposure risk when hysterectomy is performed with SCP (Table 13). A common concern with LSH involves the spread of unanticipated pathology associated with electronic power morcellation. On April 17, 2014, The U.S. FDA issued a safety communication discouraging the use of laparoscopic uterine power morcellation in hysterectomy and myomectomy for the treatment of uterine fibroids due to the "risk of spreading unsuspected cancerous tissue, notably uterine sarcomas beyond the uterus".(273) The FDA later issued an updated guidance communication November 24, 2014 recommending that manufacturers of power morcellators include a boxed warning with product labelling safety statements. This included the following contraindications: 1) removal of suspected fibroids in peri- or post-menopausal patients and 2) gynaecologic surgery with tissue known or suspected of malignancy. This prompted many manufacturers to withdraw their products from the market for fear of litigation. Many hospitals placed an immediate ban on laparoscopic power morcellation, while a smaller number of institutions crafted policies to permit usage under strict guidelines.

In women with fibroids, the risk of undiagnosed leiomyosarcoma is between 1:495 to 1:1100 according to the FDA. The prognosis is poor with this condition, and intraperitoneal spread of tissue may worsen the prognosis. This risk is presumably much lower in women without fibroids. Since the majority of women undergoing prolapse surgery do not have fibroids, the American Urogynecologic

Table 14 Risk of unanticipated pathology and malignancy during hysterectomy for prolapse

Reference	Number prolapse cases	Total unanticipated pathology N (%)	Endometrial Cancer	Sarcoma
Frick 2010(184)	644	17 (2.6)	2 (0.3)	0
Andy 2014(276)	324	3 (0.9)	0	0
Ackenbom 2016(277)	1196	10 (0.8)	3 (0.3)	0
Renganathan 2010(185)	517	MD	4 (0.8)	0
Grigoriadis 2015(278)	333	14 (4.2)*	0	0
Ouldamer 2014(279)	853	MD	4 (0.5)	0
Bojahr 2015(280)	635	MD	MD	0
Mahnert 2015(281)	670	5 (0.7)**	2 (0.3)	0
Kho 2016(282)	1113	MD	MD	0
Von Bargen 2017(283)	435	5 (1.1)	2 (0.5)	0
Total	**6720**	**54/3602 (1.5)**	**17/4972 (0.3)**	**0/6720**

** includes 1 case of cervical cancer (0.3%)*
*** includes 2 cases of cervical cancer and 1 metastatic cancer*

Society (AUGS) issued the following comments in a position statement in July 2014 that was updated in December 2018.(274) "After appropriate preoperative evaluation, supracervical hysterectomy facilitated by power morcellation during mesh SCP is a reasonable procedure. Shared decision making between a patient and her surgeon to perform power morcellation during supracervical hysterectomy for a minimally invasive mesh sacrocolpopexy should include the risks and benefits during the informed consent process." On February 25, 2020, the FDA issued a Draft Guidance: Product Labelling for Laparoscopic Power Morcellators.(275) One of the new labelling recommendations includes: "Laparoscopic power morcellators should only be used with a containment system. The containment system should be compatible with the laparoscopic power morcellator."

So, what is the true risk of unanticipated pathology and cancer in a population undergoing prolapse surgery? Table 14 includes data from several studies reporting the rate of unanticipated pathology and malignancy at the time of hysterectomy for prolapse repair. The studies were retrospective and evaluated low risk patients excluding cases involving preoperative symptoms of postmenopausal bleeding or abnormal findings on screening. The overall rates were low with only 1.5% unanticipated pathology, the majority of which were endometrial hyperplasia, and 0.3% of endometrial cancer. There were no cases of sarcoma identified during prolapse surgery. Consequently, for low-risk women, it is reasonable to perform laparoscopic power morcellation during prolapse repair after obtaining adequate informed consent. However, the recent FDA product labelling now mandates contained morcellation, which may result in increased usage of either mini-laparotomy or extracorporeal scalpel morcellation with a bag for containment through the expanded umbilical incision. Both of these options potentially increase the risk of wound complications, hernia formation and postoperative pain.

Conclusion

There are numerous options for primary treatment of uterovaginal prolapse. The following are evidence-based guidelines regarding uterine preservation.

- Hysteropexy is reasonable in women undergoing surgery for uterovaginal prolapse without contraindications to uterine preservation. However long-term data are limited and the need for subsequent hysterectomy unknown (GoR C).
- When considering relative contra-indications to uterine preservation, opportunistic salpingectomy which is not able to be performed at vaginal hysteropexy should be included in the shared decision-making process (GoR C).
- Large database studies demonstrated lower reoperation rates for recurrent prolapse and slightly higher complication rates in the hysterectomy group compared to hysteropexy (GoR C).
- Consistent Level one and two evidence reveal no differences in outcomes comparing sacrospinous hysteropexy to vaginal hysterectomy with native tissue prolapse repair with the exception of a single smaller RCT showing a higher risk of apical recurrence for patients with advanced prolapse undergoing hysteropexy (GoR B).
- Partial Colpocleisis is preferred over vaginal hysterectomy and total colpocleisis when there is no specific indication for hysterectomy and no interest in preserving coital function (GoR C).
- The role of the Manchester procedure for treatment of mild uterovaginal prolapse with or without cervical elongation has yet to be determined based on limited, poor Level two and three evidence (GoR D).
- The data are not supportive of transvaginal mesh and hysterectomy for uterine prolapse. Consistent Level two evidence shows no difference in anatomic success comparing sacrospinous hysteropexy with mesh graft to hysterectomy with graft; and, the mesh exposure rate was significantly higher after hysterectomy than hysteropexy (11% vs. 5%) (GoR C).
- Sacrohysteropexy (SHP) has a similar success rate and reoperation for prolapse when compared to vaginal hysterectomy and USLS, however lower success rates than sacrocolpopexy with total or supracervical hysterectomy (GoR C).

- Sacrocolpopexy with total hysterectomy is not recommended due to 3-5 fold higher mesh exposure rate (GoR C).
- In a single small study sacrocolpopexy with supracervical hysterectomy had a lower anatomic success rate than sacrocolpopexy with total hysterectomy (GoR D)
- Level three evidence reveals low rates of unanticipated pathology (1.5%) and endometrial cancer (0.3%) with no cases of sarcoma identified during hysterectomy in women with low risk of malignancy and dysplasia undergoing prolapse surgery. (GoR C)

V. APICAL PROLAPSE SURGERY

While anterior vaginal prolapse is most common, loss of apical support is usually present in women with prolapse that extends beyond the hymen.(284,285) There is growing recognition that adequate support for the vaginal apex is an essential component of a durable surgical repair for women with advanced prolapse.(286-288) There is a strong correlation between anterior vaginal prolapse and apical descent seen on anatomical studies.(289,290) While recognition of apical defects is one of the biggest challenges in the preoperative evaluation of pelvic support defects, surgical correction of the apex has several good options with relatively high success rates. Apical suspension procedures can broadly be separated into those performed transvaginally and those performed abdominally. Abdominal procedures, predominantly sacrocolpopexy, can be performed via laparotomy or using conventional laparoscopic or robotically assisted-laparoscopic techniques. Although precise estimates are not available, most studies suggest that the vaginal approach is most common with 80-90% of procedures being performed through this route.(1,31,33,77)[FDA] Transvaginal apical suspension procedures include both non-mesh (native tissue) procedures and mesh repairs. The individual woman's surgical history and goals, as well as her individual risks for surgical complications, prolapse recurrence and de novo symptoms affect surgical planning and choice of procedure for apical POP.

1. SACROSPINOUS LIGAMENT FIXATION (SSLF)

One of the most popular and widely reported native tissue transvaginal procedures for correcting apical prolapse is the SSLF. First described in 1958,(291) this procedure suspends the vaginal apex to the sacrospinous ligament either unilaterally or bilaterally, typically using an extraperitoneal approach. Observational series and clinical trials suggest that while apical recurrence after SSLF is uncommon (0.6% to 19%), recurrence of anterior vaginal prolapse is more problematic (3.7% to 28.5%) (Table 15). A meta-analysis by Morgan et al found an overall failure rate at any site of 28.8% (95% CI 18.4%-36.3%) with failure of the anterior segment seen in 21.3% (17-3-25.3%), apical segment of 7.2% (95% CI 4.0 – 10.4%) and posterior segment of 6.3% (95%CI 4.2-8.4%). Whether the relatively high rate of anterior vaginal prolapse recurrence seen with SSLS is due to the posterior deflection of the vaginal axis, as many authors suggest (78,94,292,293), or simply represents a general predilection of anterior support to fail after pelvic reconstructive surgery remains unknown.(294) The Pelvic Floor Disorders Network (PFDN) reported prospective longitudinal follow-up thru 5 years with strict composite criteria and "once a failure, always a failure" methodology.(295) Surgical failure rates (including symptoms and retreatment) reached 71.2% with a 59.7% anatomic failure rate, suggesting continued anatomic deterioration of this surgery over time, but low reoperation rates (4.6%) and high patient satisfaction rates. Reoperation rates after SSLF range from 1.3% to 37%, with all but three of the 30 series reporting rates less than 10%.

Maher et al demonstrated significant improvements in condition-specific and generic QOL after SSLF, similar to that after abdominal sacrocolpopexy.(95) A meta-analysis of randomised and observational studies found a pooled average for failure to provide relief of prolapse symptoms after SSLF of 10.3% (95% CI 4.4-16.2%).(296) The pooled average for failure to provide patient satisfaction after SSLF in this analysis was 13% (95% CI 7.4%-18.6%).(296) Although infrequent, serious complications associated with SSLF include buttock pain and sacral/pudendal neurovascular injury. Unilateral buttock/gluteal pain occurs in 3-15% of patients and typically resolves within 6 weeks after surgery.(142,297) In one multi-centre trial, neurological pain requiring medical or surgical intervention occurred in 12.4% immediately after SSLF and persisted in 4.3% at 4-6 weeks after surgery.(297) In a review of 22 studies that included 1229 SSLF procedures, three patients (0.2%) had life-threatening haemorrhage from sacral or pudendal vascular injury and the overall transfusion rate was 2%.(298)

Table 15. Outcomes of Sacrospinous ligament fixation (SSLF) procedures.

First Author, Year (year)	Study Design	No	Mean Follow-up Mo. (range)	Definition of Anatomic Success*	Anatomic success –all segments	Anatomic recurrence by segment	Reoperation for prolapse
Morley, (1988)(110)	retrospective	92	51.6 (1-132)	Not defined	90% (83/92)	Apex 4% Anterior 6%	4 (5%)
Imparato, (1992) (111) [53]	retrospective	155	Not stated	Not defined	90.3% (140/155)	Not reported	None reported
Shull, (1992)(112)	retrospective	81	(24 – 60)	Grade 0-1	82% (66/81)	Apex 4% Anterior 12% Posterior 1%	4 (5%)

First Author, Year (year)	Study Design	No	Mean Follow-up Mo. (range)	Definition of Anatomic Success*	Anatomic success –all segments	Anatomic recurrence by segment	Reoperation for prolapse
Pasley, (1995)(113)	retrospective	144	35 (6-83)	Asymptomatic and above hymen	67% (28/42)	Apex 12% Anterior 28.5% Posterior 2.3%	14 (37%)
Benson, (1996)(114)	RCT SSLF vs ASCP	42	30 (12-66)	Vaginal walls above hymen or apical descent less than 50% length	67% (28/42)	Apex 12% Anterior 28.5% Posterior 2.3%	14 (37%)
Paraiso, (1996)(115)	retrospective	243	76. (1-190)	Grade 0 or asymptomatic grade 1	79.7% (194/243)	Apex 4.9% Anterior 15.9% Posterior 4.9%	11 (4.5%)
Penalver, (1998)(116)	retrospective	160	40 (18-78)	'any symptomatic descent'	85% (136/160)	Apex 6% Anterior 6% Posterior 2.5%	11 (6.8%)
Colombo, (1998)(117)	retrospective	62	83 (48-108)	Grade 0-1	74% (46/62)	Apex 8% Anterior 14% Posterior 3%	0 (0%)
Meschia, (1999)(118)	retrospective	91	43 (12-86)	Grade 0-1	85% (77/91)	Apex 4% Anterior 13% Posterior 9%	None reported
Sze, (1997)(119)	retrospective	75	24 (3-72)	above hymen	71% (53/75)	Anterior 21% Other 8%	7 (12.9%)
Lantzsch, (2001)(120)	retrospective	123	58 (6 – 108)	Not defined	87% (107/123)	Apex 3.5% Anterior 8% Posterior 1.6%	2 (1.6%)
Lovatsis, (2001)(121)	Retrospective	293	(12-30)	At or beyond the introitus	97% (284/293)	Apex 3% Anterior NR Posterior NR	9 3%
Cruikshank, (2003) (122)	Prospective cohort	695	43 (6 – 60)	Reoperation for recurrence	89.4% (674/695)	Apex 5.1	105 (15%)
Niemenen, (2003) (123)	Retrospective	138	24	POPQ Stage 2 or greater	78.7% (107/138)	Apex 4.9% Anterior 11.5% Posterior NR	NR
Maher, (2004)(124)	RCT SSLF vs. ASCP	48	22 (6-58)	Grade 0-1	69% (33/480	Apex 19% Anterior 14% Posterior 7%	3 (6.3%)
Hefni, (2006)(125)	Prospective	305	57 (24-84)	Vaginal vault at least 6 cm distal to hymen	96% (292/305)	Apex 4% Anterior 13% Posterior 0%	NR
Toglia, (2008)(126)	Retrospective	64	26.5 (1-72)	Apex above introitus and no reoperation	78% (50/64)	Apex 9% Anterior 17% Posterior 0%	2 (3%)
Aigmueller, (2008) (127)	Prospective	55	84 (24-180)	Above the hymen	64% (35/55)	Apex 7% Anterior 29% Posterior 5%	5 (9%)
Chou, (2010)(128)	Retrospective	76	36 (12-60)	Grade 0	91% (69/76)	Apex 5.3% Anterior 3.7% Posterior NR	4 (5.3%)
Larsen, (2013)(129)	Retrospective	242	96 +/- 20	At or above hymen	86% (208/242)	Apex 0.6% Anterior 13.6% Posterior 1.2%	NR

First Author, Year (year)	Study Design	No	Mean Follow-up Mo. (range)	Definition of Anatomic Success*	Anatomic success –all segments	Anatomic recurrence by segment	Reoperation for prolapse
Qatawneh, (2013) (130)	Retrospective	114	40	Stage 0-1	77% (88/114)	Apex 11% Anterior 23% Posterior 10%	3 (2.6%)
Leone Roberti Maggoire, (2013)(131)	Retrospective	86	36	Stage 0-1	86% (74/86)	NR	NR
Barber, (2014)(132)	RCT SSLF vs USLS	186	24	"Absence of: 1)apical descent 1/3 into vaginal canal, 2) anterior or posterior prolapse beyond hymen 3) bothersome vaginal bulge symptoms and 4) retreatment"	63.1% (117/186)	Apex 2% Anterior 13.1% Posterior 3.3%	4 (2.6%)
Mothes, (2015)(133)	Retrospective	110	14+/-7	Apex Stage 0 or 1	94% (103/110)	Apex 5.5% Anterior 8.3%	NR
Sanses (2016)[i](134)	Retrospective	1642	12	Absence of reoperation for recurrence or pessary insertion	NR	NR	128/1642 (7.8%)
Chen (2016)(135)	Retrospective	95	24	POP stage 0 or 1	85% (81/95)	Anterior/Posterior 16% Apical 5.3%	NR
Jelovsek (2018)(136)	RCT Long-term study of SSLF vs USLS RCT above	134	60	"Absence of: 1)apical descent 1/3 into vaginal canal, 2) anterior or posterior prolapse beyond hymen 3) retreatment"	40% (54/134)	NR	5/110 (4.6%)
Castro (2021)(137)	RCT of SSLF with 2 anchoring systems	89	12	C<=-4; Ba<=0; Bp<= 0	77% (69/89)	NR	2/89 (2%)
Favre-Inhofer (2021) (138)	Retrospective	59	(12-120)	Leading edge < +1	71% (42/59)	Anterior 22% Apex 2%	4/59 (7%)
Wu (2020)(139)	Retrospective	453	66 (24-120)	Stage 0-1	82.5% (374/459)	Anterior 13% Apical 8%	36/459 (8%)
Total		**6152**			**84% (3806/4510)**		**6% (312/5176)**

2. IPSILATERAL UTEROSACRAL LIGAMENT SUSPENSION (USLS)

The USLS was first described by Miller (299) in 1927 and later popularised by Shull in the late 1990s. The USLS suspends the vaginal apex to the proximal remnants of the uterosacral ligaments using an intraperitoneal surgical approach. This procedure restores the vagina to a near normal axis, avoiding the more retroflexion associated with SSLF. The current evidence supporting the use of USLS is mostly retrospective case-series but now includes two recent RCT's by the Pelvic Floor Disorders Network (PFDN) (295, 300) In the OPTIMAL RCT of SSLF compared to USLS there was no significant difference in the rate of surgical failure at 5 years between the two procedures. In the SUPeR RCT comparing vaginal hysterectomy and USLS with a sacrospinous hysteropexy with graft, there was no statistically significant difference at 3 years,(136) but by 5 years the USLS was inferior.(230) In reviewing 36 studies with 5354 patients the mean anatomic success rate is 80% (range 46-96%) with a mean reoperation rate for prolapse of 5.7% (range 0-35 %) (Table 15a). Consistent with other prolapse surgeries, most failures are in the anterior segment. A meta-analysis performed by Margulies et al found pooled rates of anatomical success (POP-Q Stage 0-1) of 81.2% (95%CI 67.5-94.5%) for the anterior segment, 98.3% (95% CI 95.7-100%) for the apical segment and 87.4% (95% CI, 67.5%-94.5%) for the posterior segment.(301) Post-operative prolapse symptoms were reported in 5 of 11 studies in this review and were relieved in 82-100% of patients. These promising results are balanced against ureteric kinking/injury rate of 1%-11% with this procedure.(301) A review of 700 consecutive vaginal prolapse

Table 15a: Outcomes of transvaginal ipsilateral uterosacral ligament suspension (USLS) procedures.

First Author	Year	No. of Pts.	Mean Follow-up Months (range)	Definition of anatomic success*	Anatomic success – all segments	Anatomic Recurrence by Segment	Reoperation for prolapse
Jenkins(Jenkins 1997)	1997	50	(6-48)	Not defined	48/50 96%	Anterior 4%	NR
Comiter(Comiter, Vasavada et al. 1999)	1999	100	17 (6.5-35)	Grade 0-1	96/100 96%	Apex 4%	4/100 (4%)
Barber(Barber, Visco et al. 2000)	2000	46	15.5 (3.5-40)	Stage 0/1 or Stage 2 without symptoms	41/46 90%	Apex 5% Anterior 5% Posterior 5%	3/46 (6.5%)
Shull(Shull, Bachofen et al. 2000)	2000	289	Not stated	Grade 0-1	275/289 95%	Apex 1% Anterior 3.5% Posterior 1.4%	NR
Karram(Karram, Goldwasser et al. 2001)	2001	168	21.6 (6 -36)	Grade 0-1	148/168 88%	Apex 1% Anterior or posterior 11%	11/168(5.5%)
Amundsen(Amundsen, Flynn et al. 2003)	2003	33	28 (6-43)	Stage 0 or 1	27/33 82%	Apex 6% Posterior 12%	NR
Silva(Silva, Pauls et al. 2006)	2006	72	61.2 (42-90)	Symptomatic Stage 2 or greater	61/72 85%	Apex 3% Anterior 7% Posterior 14%	2/72 (3%)
Antovska (Antovska and Dimitrov 2006)	2006	32	25 (9-42)	Stage 0 or 1	NR	Apex 0% Anterior	NR
Wheeler(Wheeler, Richter et al. 2006)	2007	35	24 (0-46)	Stage 0 apical prolapse	28/35 80%	Apex 20%	0/0 (0%)
De Boer(de Boer, Milani et al. 2009)#	2009	48	12	Stage 0-1	23/48 48%	Apex 4.2% Anterior 47.9% Posterior 14.6%	NR
Doumaouchtsis(Doumouchtsis, Khunda et al. 2011)	2011	42	60	Grade 0 of vaginal vault	36/84 84.6%	Apex 15.4%	5/42 (11.9%)
Wong(Wong, Abet et al. 2011)	2011	57	12	Apical stage 0-1	4/57 93%	NR	1/57 (1.8%)
Cunjian(Cunjian, Li et al. 2012)	2012	31	14 +/- 6	Stage 0-1	31/31 100%	NR	NR
Edenfield (Edenfield, Amundsen et al.)	2013	219	14 (8.5-26.5)	Beyond the hymen or retreatment	54/219 24.7%	Apical 8.7% Anterior 17.4% Posterior 6.8%	33/219 (15%)
Barber (Barber, Brubaker et al. 2014)	2014	188#	24	Absence of: 1. apical descent 1/3 into vaginal canal, 2. anterior or posterior prolapse beyond hymen 3. bothersome vaginal bulge symptoms and 4. retreatment	100/155 64.5%	Apical 2% Anterior 12.9% Posterior 1.9%	5/161 (3.1%)
Unger(Unger, Walters et al. 2015)	2015	983	6.9	Beyond hymen	875/983 89%	NR	3.40%
Rondini#(Rondini, Braun et al. 2015)	2015	56	12	Apex Stage 0 or 1	46/56 82%	Apex 18% Anterior 34% Posterior 6.3%	10/56 (17%)
Vallabh-Patel(Vallabh-Patel, Saiz et al. 2016)	2016	42	9	Above the hymen and apex < ½ TVL	36/42 86%	NR	3/42 (7%)

First Author	Year	No. of Pts.	Mean Follow-up Months (range)	Definition of anatomic success*	Anatomic success – all segments	Anatomic Recurrence by Segment	Reoperation for prolapse
Richter(Richter, Park et al. 2016)	2016	125	23	Absence of: 1. apical descent 1/3 into vaginal canal, 2. anterior or posterior prolapse beyond hymen 3. bothersome vaginal bulge symptoms and 4. retreatment	NR	Apical 4% Anterior 10% Posterior 2%	2/125 (2%)
Rappa(Rappa and Saccone 2016)	2016	360	13	Above or at the hymen and no retreatment	289/360 80%	Apical 9% Anterior 17% Posterior 6%	36/360 (10%)
Spelzini(Spelzini, Frigerio et al. 2017)	2017	124	25	Stage 0 or 1	105/124 85%	Apical 1% Anterior 10% Posterior 6%	2/124 (2%)
Duan(Duan, Lu et al. 2017)	2017	104	109	Absence of: 1. apical descent 1/3 into vaginal canal, 2. anterior or posterior prolapse beyond hymen 3. bothersome vaginal bulge symptoms and 4. retreatment	95/104 91%	Apical 0 Anterior 7% Posterior 3% Multiple 1%	0/104 (0%)
Milani (Milani, Frigerio et al. 2018)	2018	533	32	Stage 0 or 1	448/519 86%	Apical 1% Anterior 9% Posterior 5%	5/519 (1 %)
Lavelle(Lavelle, Giugale et al. 2018)	2018	123	NR	Above or at the hymen and no retreatment	102/123 83%	NR	NR
Schiavi (Schiavi, Savone et al. 2018)	2018	214	107 61-170)	Stage 0 or 1	177/214 (83%)	Apical 1% Anterior 10% Posterior 6%	3/214 (1.4%)
Bastawros(Bastawros, Tarr et al. 2018)	2018	31	13.6	Apex C< -1/2 TVL Anterior= Ba<0	21/31 67%	Apex 3.2% Anterior 33.3%	4/31 (12.9%)
Bradley(Bradley, Bickhaus et al. 2018)	2018	242	11.8	Above the hymen and no retreatment	199/242 82%	Apex 1% Anterior 14% Posterior 4%	19/242 (7.8%)
Jelovsek (Long-term study of Barber study above.) (Jelovsek, Barber et al. 2018)	2018	147#	60	Absence of: 1. apical descent 1/3 into vaginal canal, 2. anterior or posterior prolapse beyond hymen 3. retreatment	65/133 49%	NR	12/147 (8.5%)
Deo (Deo, Bernasconi et al. 2019)	2019	353	60	Stage 0 or 1	300/353 85%	Apical 0.6% Anterior 11.6% Posterior 4.0%	4/353 (1%)
Novara (Novara, Sgro et al. 2019)	2019	69	13	Stage 0 or 1	NR	Apical 1% Anterior 13% Posterior 9%	NR

First Author	Year	No. of Pts.	Mean Follow-up Months (range)	Definition of anatomic success*	Anatomic success – all segments	Anatomic Recurrence by Segment	Reoperation for prolapse
Pedersen(Pedersen, Storkholm et al. 2019)	2019	95	86	Stage 0 or 1	62/95 65%	Apical 19% Other segment 9%	33/95 (35%)
Smith(Smith, Crisp et al. 2019)	2019	74	63	Above the hymen	69/74 93%	Anterior 4% Posterior 3%	NR
Zhang(Zhang, Lu et al. 2019)	2019	51	62	Absence of: 1. apical descent 1/3 into vaginal canal, 2. anterior or posterior prolapse beyond hymen 3. bothersome vaginal bulge symptoms and 4. retreatment	44/51 86%	Apical 0% Anterior 8% Posterior 2% Multiple 4%	0/51 (0%)
Shen(Shen, Lu et al. 2019) Probable duplicate to Zhang	2019	42	63	NS	39/42 93%	Apical 0% Anterior 7% Posterior 0%	0/42 (0%)
Nager (Nager, Visco et al. 2019)	2019	87#	36	Absence of: 1. prolapse beyond hymen 2. bothersome vaginal bulge symptoms and 3. retreatment	54/87 62%	NR	9/87 (10%) Includes pessary retreatment.
Total		5251			3998/5020 80%		206/3457 (6.0%)

Includes retrospective and prospective cohorts of intraperitoneal transvaginal USLS
NR, not reported
**POP staging systems, if used, are indicated as 'grade' for Baden-Walker or 'stage' for POPQ.*
 # RCT study, but number only Includes subjects who underwent USLS

surgeries found intraoperative ureteric kinking/injury rate of 5% directly attributable to USLS, however, 87% were identified at cystoscopy before the completion of the index surgery and corrected by removing suspension sutures intraoperatively with no long-term consequence to the patient.(302) Only three of 355 USLS (0.9%) performed in this series required additional procedures to relieve or correct ureteric obstruction or injury. A retrospective review of over 900 patients receiving USLS found an overall adverse event rate of 31.2% with 20.3% being attributed to peri-operative urinary tract infection.(303) Rates of pulmonary and cardiac events were 2.3% whereas the rate of ileus and small bowel obstruction were less than 0.5%. The intraoperative bladder injury rate was 1%. There were no intraoperative ureteric injuries; however, 4.5% of cases were complicated by ureteric kinking, all of which were resolved without subsequent sequelae with intraoperative suture removal with or without replacement of the vault suspension stitches. (303) Margulies et al identified 10 studies including a total of 820 women that reported on perioperative complications of USLS.(301) The ureteric reimplantation rate in this series was only 0.6%. Blood transfusions were reported in 1.3%, cystotomy in 0.1%, and bowel injury in 0.2%.

Abdominal and laparoscopic ipsilateral USLS techniques have also been described. Lowenstein et al reported a retrospective review of 107 women who underwent prolapse surgery that included an abdominal USLS.(304) In the 75 patients who completed one year follow-up, 12% reported recurrent or persistent prolapse symptoms and 7% had an anatomical failure (POP-Q stage 2 or greater). Complications were relatively few, however exposure of the apical sutures (expanded PTFT, Gore-Tex) occurred in 9% at an average time of 56 months (range 3-75 mo.).(304) In a retrospective comparative study, laparoscopic uterosacral suspension with uterine preservation had comparable anatomic outcomes to total vaginal hysterectomy with uterosacral ligament suspension.(227) Two retrospective comparisons between vaginal and laparoscopic USLS procedure found no significant differences in perioperative morbidity or anatomical or subjective outcomes.(305,306)

2.1. Sacrospinous Ligament Suspension versus Uterosacral Ligament Suspension

In 2014, the NICHD Pelvic Floor Disorders Network reported the results of the OPTIMAL trial whose primary objective was to compare the safety and efficacy of the SSLS to USLS in women with uterine or post hysterectomy apical prolapse.(297) To date, this is the only randomised trial to have compared these two commonly performed procedures. Success was defined as a composite outcome measurement and included the absence of: a) descent of the vaginal apex more than one third of the vaginal canal; b) anterior or posterior vaginal wall descent beyond the hymen, c) bothersome vaginal bulge symptoms as reported by the Pelvic Floor Distress Inventory and d) retreatment with surgery or a pessary. A total of 374 patients were randomised (188 USLS and 186 SSLF) from 9 U.S. centres. Two years after surgery, there was no statistical difference between the two groups for the composite outcome (USLS 64.5% vs SSLF 63.1%; adj. OR 1.1 95% CI 0.7 to 1.7). Additionally, bothersome vaginal bulge symptoms were seen in 18%, anterior or posterior prolapse beyond the hymen in 17.5% and retreatment with pessary or surgery 5.1% two years post-operatively with no differences between groups. Neurological pain requiring medical, behavioural or surgical intervention was higher in the SSLS group (12.4% vs 6.9%, p = 0.49) and persisted to 4-6 weeks in more participants (4.3% vs 0.5%). Intraoperative ureteric obstruction was noted in five patients (3.2%) in the USLS group and none in the SSLF. The long term (5 year) follow-up of this study showed steadily decreasing success rates of both procedures. At 5 years, using the same composite primary outcome the success rate was only 30% for SSLF and 38% for USLS (not statistically different).(295)

2.2. Midline plication USLS (Mayo/McCall's Culdoplasty)

Like the ipsilateral USLS, the midline plication USLS (commonly known as Mayo/McCall's culdoplasty) uses the proximal uterosacral ligaments to suspend the vaginal apex. The major difference is that with the midline plication USLS the uterosacral ligaments are plicated in the mid-line to obliterate the posterior cul-de-sac. While commonly performed, data describing the outcomes for this procedure are limited with almost no prospective studies (Table 16). Colombo and Milani retrospectively compared the outcomes of a modified-McCall's culdoplasty to the SSLS (n = 62 in each group). (292) Recurrence after the McCall's culdoplasty (Baden-Walker Grade $\geq$2) was 15% 4 to 9 years after surgery and not significantly different from the SSLS group. Recurrent anterior vaginal prolapse occurred less frequently in the McCall's group than the SSLS group (6% vs. 21%, p =.04; OR 4.1 (95% CI 1.3 to 14.2))(292) A large retrospective series of 693 women from the Mayo clinic described an 82% satisfaction rate on subjective follow-up with few complications.(307) The rate of subsequent prolapse repair in this population was 5.2%. A retrospective case series of 411 women undergoing Mayo culdoplasty found that a more dorsal "deep" placement of sutures through the uterosacral ligaments reduced the incidence of ureteric obstruction compared to other published series.(308) A retrospective long-term follow-up of 414 patients suggested that both the ipsilateral USLS and midline plication USLS had comparable effectiveness and safety. (309) Another retrospective review of 311 patients suggested that the midline plication USLS was as effective in advanced stage prolapse as in lesser degrees of prolapse.(310)

While the midline plication USLS is traditionally performed using an intraperitoneal approach, Dwyer and Fatton have described an extraperitoneal variant of the USLS.(311,312) In their series of 123 consecutive women undergoing an extraperitoneal USLS, 93 also received anterior and/or posterior synthetic mesh. The overall anatomical success (POP-Q stage 0 – 1) at a mean follow-up of 2 years (range 6 mo. – 5 years) was 85.5% with apical success of 95.4%. (312) The reoperation rate for recurrent prolapse was 7%. Urethral injury occurred in only 1.7%, however the blood transfusion rate was 4.9% and the rate of mesh exposure was 19.3%.

2.3. Levator Myorrhaphy

Francis and Jeffcoate described their retrospective series using levator myorrhaphy, in which a wide midline plication of the levator ani muscles is performed to which the vaginal cuff is fixed, in 1961.(313) A large sponge pack in the rectum is used to avoid over plication and bowel dysfunction. Five of 35 women responding to the questionnaire had transient ureteric complications, one requiring reoperation. Seventeen women were quite satisfied, while six were dissatisfied. Natale et al compared the levator myorrhaphy to the USLS in a randomised clinical trial of 229 women with stage 2-4 prolapse.(314) All women received a hysterectomy and all received placement of polypropylene mesh in the anterior vaginal segment. Anatomical success was not significantly different between groups. The mean total vaginal length was significantly shorter after levator myorrhaphy (7.9 cm vs. 8.9 cm, p = .04). Urinary, bowel and sexual function did not differ between groups post-operatively. Intraoperative ureteric obstruction was less common in the levator myorrhaphy group (0% vs. 7.9%); however all cases of ureteric obstruction in the USLS group were corrected intraoperatively with suture removal/replacement with no additional interventions required.(314) Other complications including mesh erosion were similar between groups.

2.4. Iliococcygeus Fixation

There are no randomised trials that support the use of this procedure. Several case series have provided some information. Shull reported that apical support was optimal in 39/42 (83%) of patients, but eight others had apical or other defects.(315) Meeks and colleagues reported a 96% objective cure in 110 women followed up to 13 years.(316) In a retrospective case-control study, Maher and colleagues reported similar subjective (91% vs 94%) and objective (53% vs 67%) cure rates with iliococcygeus fixation (n=50) compared to sacrospinous fixation (n=78).(317) A prospective cohort of 44 subjects receiving iliococcygeous fixation followed up for a median of 68.8 (range 60-92) months provides the longest-term data on this procedure.(318) Objective success (POP-Q stage 0 or 1) and subjective success (patient global impression of improvement < 2) were both 84%. Preoperative stage 4 vault prolapse was an independent predictor of failure (OR 8.8; 95% CI 1.3-9.4).(318)

3. SACROSPINOUS LIGAMENT FIXATION WITH GRAFT (TRANSVAGINAL MESH APICAL PROLAPSE)

Multiple commercially available transvaginal mesh devices have been marketed to correct apical prolapse, often designed to support both anterior and apical or anterior, apical and posterior vaginal segments. Table 16 summarises the results of 35 studies in 3270 patients. Early transvaginal mesh kits (Posterior Intravaginal Slingplasty (PIVS), Perigee, Apogee, and Prolift) used metal trocars to guide placement of mesh arms through the obturator foramen or the ischiorectal fossa. The PIVS was constructed of Type 3 multifilament polypropylene and because of mesh related complications this was removed from the market. The remaining studies in the table are Type 1 monofilament polypropylene meshes. Success rates of transvaginal meshes for apical prolapse from prospective and retrospective cohorts ranges from 61-100% for monofilament polypropylene meshes with mesh exposure rates vary from 0-17% (Table 16). Second generation device kits with typically lighter mesh loads and direct attachments to the Sacrospinous ligament (Uphold, Pinnacle, Boston Scientific, Elevate, AMS) demonstrate mesh exposure rates lower (0 to 8%) than those noted with older devices based on the limited data available.

Table 16. Outcomes from prospective and retrospective cohorts of transvaginal mesh kits used for apical repairs

Author	Year	Type	No.	Follow-up weeks	Success rate	Complications
Matox (140)	2006	PIVS	21	7	37%	1 proctotomy 1 haematoma
Vardy(141)	2006	PIVS	98	3	99%	2 erosions
Neuman(142)	2007	PIVS	140	120	99%	12 erosions
de Tayrac(143)	2007	PIVS	21	42	95%	2 haematomata
Biertho (144)	2007	PIVS‡,(Tyco)	34	12	91%	1erosion 1 haemorrhage
Foote (145)	2007	PIVS (Tyco)	52	20	83%	Erosion 11/52
Lee(146)	2010	PIVS	32	52	100%	1 transfusion
Belot F(147)	2005	Prolift Ethicon	277	Not stated	Not stated	Erosion 34/277
Amrute (148)	2007	Polypropylene H shaped	76	123	95%	erosion, 2 dyspareunia
Fatton (149)	2007	Prolift, Ethicon†	88	25	93%	2 haematoma
Gaurder-Burmester(150)	2007	Apogee AMS	48	52	100%	
Abdel Fattah(151)	2008	Prolift Ethicon	143	12	94%	1rectal injury, bladder injury, 16 vag erosion, 1 bladder erosion
Abdel Fattah(151)	2008	Apogee AMS*	38	12	95% (36/38)	Blood loss>400mls1, erosion 4, Dyspareunia 1, rectal injury 1
Milani(152)	2009	Total vaginal mesh Prolift	46	52	91% (41/45)	15% mesh exposure 2 blood loss>500mls
McDermott(153)	2011	Total vaginal mesh Prolift hysteropexy 24 Colpopexy 65	89	26-52	96%	10% mesh exposure 5% complications
Moore(154)	2012	Anterior/Apical Elevate AMS	60	57	92%	No extrusions
Vu(155)	2012	Uphold, Boston Scientific	115	12.1	96%	Mesh exposure 2.6%, neurologic injury 1,
Rapp (156)	2014	Anterior/Apical Elevate AMS	42	136	90%	Mesh exposure 5%, leg pain 3%, urinary retention 13%
Lo(157)	2015	Anterior/Apical Elevate AMS	65	24	97%	No mesh exposures noted, de novo stress incontinence 16%

Author	Year	Type	No.	Follow-up weeks	Success rate	Complications
Marschke(158)	2015	Anterior/Apical Elevate AMS	70	52	95.70%	Mesh exposure 5.7%
Letouzy(159)	2015	Uphold, Boston Scientific	115	92	93%	8% denovo dyspareunia reoperation for mesh complications- 3.4%
Stanford(160)	2015	Anterior/Apical Elevate AMS	142	104	93.8-100%	Mesh exposure 4.9% in those with prior hysterectomy and 13.8% with concurrent hysterectomy
Meyer(161)	2016	Prolift Ethicon	40	364	94% (at or above hymen)	6% Exposure
Hugele(162)	2016	Anterior/Apical Elevate AMS	218	104	61% Stage 0 or 1	6% Bleeding or hematoma
Altman(163)	2016	Uphold, Boston Scientific	164	52	94% Stage 0 or 1	4.3% (bladder perforations, bleeding)
Lamblin (164)	2016	Anterior/Apical Elevate AMS	84	104	74% Stage 0 or 1	4% bleeding
Song(165)	2016	Prolift Ethicon	120	384	Stage 0 or 1 Anterior 76% Apical 85% Posterior 82%	3% exposure
To(166)	2017	Anterior/Apical Elevate AMS	146	52	97% at or above hymen	1% exposure
Laso-Garcia (167)	2017	Prolift Ethicon	69	275	91% Stage 0 or 1	Dindo Grade 3 or 4 3% Mesh exposure 13%
Lo(168)	2017	Anterior/Apical Elevate AMS	59	156	90% Stage 0 or1	No exposures
Ubertazzi(169)	2018	Prolift Ethicon	72	276	86% (at or above hymen)	17% exposure
Palma(170)	2018	Calistar A Promedon	70	52	86% Stage 0 or 1	7% exposure
Brandt(171)	2019	InGYNious (AMI)	248	52	93% (above hymen)	5 % bleeding
Alas(172)	2019	Modified I-STOP sling (CL Medical)	47	24	100% Stage 0 or 1	1 transfusion
Allegre(173)	2019	Uphold LITE, Boston Scientific	121	52	72%	Dindo Grade 3 or 4 5.4%
Gauthier(174)	2019	Restorelle (Coloplast)	68	>52	72% Stage 0 or 1	3% mesh exposure
Falconer(175)	2021	Uphold LITE, Boston Scientific	205	260	85% Ba<0	1% mesh exposure
Galad (176)	2020	Anterior/Apical Elevate	46	156	87% Ba <1	8% mesh exposure
Total			**3589**			

** American Medical System, Minnetonka MN, USA † Ethicon, Sommerville NJ, USA ‡ PIVS Posterior Intravaginal Slingplasty Tyco Healthcare Norwalk CT*

The Cochrane Collaboration identified six randomised trials comparing native tissue vaginal repairs with transvaginal polypropylene mesh for apical prolapse in 589 women.(319) In all six of these trials, the native tissue repair included a SSLF or USLS and the mesh was polypropylene (Four trials monofilament weave (Prolift, Ethicon) and two trials multifilament weave). No significant differences in anatomical outcomes, vaginal bulge symptoms, repeat surgery for prolapse, dyspareunia or post-operative stress urinary incontinence were noted between groups. The average rate of mesh exposure after transvaginal mesh was 18% and surgery for mesh exposure was required in 9.5%. In that review. The Cochrane Collaboration authors concluded that the implication for clinical practice is that while the second generation newer mesh products may be as anatomically beneficial with a lower complication rate than their preceding mesh products this has not been rigorously evaluated and these products should be used cautiously until level one comparative data become available.(319) A summary of randomised trials comparing native tissue vaginal repair with monofilament mesh repair is in Table 17**.** In each study the SSLF with graft had a higher objective success rate, but mesh exposures were high (range 8.3- 42%) although they seemed to be lower (8%) with a second-generation mesh kit.(136) Since the 2011 FDA Public Health Notification on

surgical mesh for pelvic organ prolapse, many of these devices are no longer marketed and in 2019 all vaginal mesh kits were removed from the market in the U.S. by the FDA because at that time they did not conclusively show superiority over native tissue repairs. A more recent RCT comparing apical mesh and sacrospinous colpopexy for post-hysterectomy prolapse again demonstrated no significant advantage of the mesh intervention over the sacrospinous suspension .(320)

Table 17. Randomised Trials Comparing Native Tissue Apical Repair Versus Monofilament Polypropylene Transvaginal Mesh Apical Repair for Apical Prolapse

Author	Year	Group (N)	Mean Follow –up (Mos)	Objective Success rate (%)	Subjective Success rate (%)	Criteria for Objective (O) and Subjective (S) success*	Mesh exposure (%)	Comments
Sokol(177)*	2011	USLS (33)	14.7	66.20%	96%	O: Stage 0 or 1 S: Absence of bulge symptoms	NA	Reintervention in 15.6% of mesh group including 3 surgeries for prolapse recurrence and 2 for mesh exposure. None in ULS group
		Prolift (32)		70%	90%		15.60%	
Halaska(178)	2012	SSLF (83)	12	60.60%	-	O: Stage 0 or 1 S: QOL scores	NA	Post-hysterectomy vault prolapse only. Significant improvement in QOL questionnaires in both groups with no difference between groups.
		Prolift (85)		83.10%	-		20.80%	
Svabik(179)	2014	SSLF (34)	12	38.20%	-	O: Above hymen on POPQ or bladder descent less than 10mm below symphysis pubis on translabial US S: Pelvic Organ Distress Inventory Score (POPDI)	NA	Unilateral or bilateral levator avulsion required for inclusion. Significant improvement in POPDI with no difference between groups
		Prolift (36)		97.20%	-		8.30%	
De Silveira(180)	2015	SSLF (90))	12	Anterior 70.4% Apical 84% Posterior 91.4%	- -	O: less than or equal to hymen S: P-QOL (Portuguese version)	NA	Significant improvements in P-QOL with no difference between groups. Overall rate of reoperation in the native vaginal tissue repair group was 3.7 % (3 patients with recurrence) and in the mesh group was 7.9 % (2 patients with recurrence, 3 with exposure, 1 with wound dehiscence, and 1 with extrusion into the rectum)
		Prolift (94)		Anterior 86.4% Apical 92% Posterior 97.7%			20%	
Milani(181)	2018	Native tissue	84	82%	78%	O: Above hymen S: Absence of bulge sensation	NA	Composite success rate 54% for native tissue and 53% for TVM
		Prolift		85%	79%		42%	
Galad (2020)(176)	2020	SSLF (73)	36	66%	87%	O: Ba<-1 S: Satisfaction		P=.02 for 0bjective outcome at 3 years
		Elevate (73)		87%	91%		6%	
Nager(182)	2021	USLS	60	46% (36/78)		Composite Objective success: Absence of: 1)prolapse beyond hymen 2) bothersome vaginal bulge symptoms and 3) retreatment		P=0.03 for primary composite outcome. Both groups improved for 2o outcomes. 70% of participants remained masked at 5 years.
		SS hysteropexy with graft		63% (50/79)			8%	

*Trials using multi-filament mesh not included; Abbreviations: USLS: uterosacral ligament suspension, SSLF: sacrospinous ligament suspension, QOL: quality of life, US: ultrasound, Prolift: Prolift TM device, Ethicon Sommerville NJ, USA *This trial presents one year results of Iglesia, 2010.(183)*

4. SACROCOLPOPEXY

Since its introduction by Lane in 1962, (321) sacrocolpopexy has proven to be an effective and durable technique for correcting apical prolapse. In 2010, approximately 34,000 sacrocolpopexy's were performed in the U.S. representing 11% of all prolapse surgeries performed during that time period.(139) Traditionally, sacrocolpopexy has been performed via a laparotomy (i.e. abdominal sacrocolpopexy, ASCP) but the use of minimally invasive approaches, both laparoscopic (LSCP) and robotic (RSCP), has become the norm over the last decade. The 2016 Cochrane review identified six randomised trials comparing sacrocolpopexy to vaginal prolapse repair including three trials comparing abdominal sacrocolpopexy (ASCP) to SSLF (94,95,322), one trial comparing ASCP to USLS, (323) one trial comparing laparoscopic sacrocolpopexy (LSCP) to transvaginal mesh repair (324) and one comparing abdominal or laparoscopic sacrocolpopexy to USLS with mesh augmentation. (319) On meta-analysis, they concluded that overall a broad group of vaginal surgery with and without mesh is associated with higher risk of awareness of prolapse (RR 2.11 95% CI 1.1-4.2), recurrent prolapse on examination (RR 1.9 95% CI 1.3-2.7), repeat surgery for prolapse (RR 2.3 95% CI 1.2- 4.3), post-operative SUI (RR 1.9 95% CI 1.2-2.9) and dyspareunia (RR 2.5 95% 1.2- 5.5) when compared broadly with sacrocolpopexy.(319) A systematic review by the Society of Gynecologic Surgeons Systematic Review Group that included both randomised trials and cohort studies comparing sacrocolpopexy with native tissue (non-mesh) vaginal repairs found improved anatomic outcomes with sacrocolpopexy and no difference in reoperation rates or post-operative sexual function.(325) Adverse event data compiled from 79 studies (RCT, cohort and case series) found sacrocolpopexy associated with a higher rate of ileus or small bowel obstruction (2.7% vs 0.2%, p<.01), mesh or suture complications (4.2% vs 0.4%, p <.01) and thromboembolic disease (0.6% vs 0.1%, p = .03).(325)

4.1. Abdominal sacrocolpopexy (ASCP)

Observational studies and clinical trials suggest that ASCP is a highly effective procedure for apical prolapse. The success rate of ASCP, when defined as lack of apical prolapse, ranges from 75-100% (Table 18). When success is defined as no recurrent prolapse in any segment the published success rates are 56-100%. A systematic review of ASCP performed by Nygaard et al reported a median reoperation rate for recurrent prolapse of 4.4% (range 0 -18.2%) and for post-operative stress incontinence of 4.9% (range 1.2 -30.9%) and a mesh erosion rate of 3.4%.(326) Subjects enrolled in the long-term follow-up (5-7 years) of the CARE trial (E-CARE), demonstrated objective failure rates of 24-48% depending upon the definition of failure and a cumulative mesh erosion probability rate of 10.5% by 7 years.(327) Clinical trials demonstrate significant improvements in prolapse symptoms, urinary function and quality of life after ASCP.(68,95) There is Level 1 evidence that ASCP has superior anatomical outcomes when compared to SSLF but this is balanced by longer operating time, longer recovery and higher cost.(229) A single RCT has compared ASCP (n=63) to USLS (n=61) and found ASCP associated with greater anatomical success, fewer reoperations, greater post-operative complications but no difference in improvement in symptoms or quality of life.(323)

Beyond mesh erosion, reported complications of ASCP are generally consistent with other major open pelvic surgeries. The systematic review by Nygaard et al reported that wound complications occurred in 4.6% (range 0.4% to 19.8%), haemorrhage or transfusion in 4.4% (.2% to 16.9%), cystotomy in 3.1% (0.4% to 15.8%), ureteral injury in 1.0% (0.8% to 1.9%), bowel injury in 1.6% (0.4% to 2.5%) and incisional hernia repair in 5% (0,4 to 11%).(326) 1 in 20 women in the CARE trial experienced significant gastrointestinal morbidity after sacrocolpopexy. Of 322 women in the study, 19 had symptoms of possible ileus or small bowel obstruction; of these, four had reoperation for small bowel obstruction, 11 were readmitted for medical management, and four had a prolonged initial hospitalisation for gastrointestinal symptoms.(328) In long-term review after the CARE trial the subjective success rate remained acceptable at 75% however the mesh exposure rate was 9.9%.(327) The high rate of mesh exposure maybe explained by specific surgical techniques employed including high rates of multifilament mesh, concomitant hysterectomy and permanent sutures all of which are associated with increased rates of mesh exposure.(329,330) Indeed, authors have reported mesh exposure rates of less than 3% at 5 years when monofilament macroporous mesh and absorbable sutures were utilised at sacrocolpopexy. (270,331)

4.2. Abdominal sacrocolpopexy (ASCP) versus sacrospinous ligament fixation (SSLF)

To date, there are three RCTs that directly compare ASCP to SSLF. (66,94,95,322) The 2013 Cochrane review on the surgical management of POP summarises these studies and concludes that these trials provide Level 1 evidence that there were no statistically significant differences in objective failure at any site (any pelvic organ prolapse RR 0.77, 95% CI 0.39 to 1.53), subjective failure (RR 0.53, 95% CI 0.25 to 1.09), reoperation for POP (RR 1.46, 95% CI 0.19 to 1.11) or patient satisfaction (RR 0.82, 95% CI 0.32 to 2.06).(229) However, ASCP was superior to SSLF for the following outcomes: Prolapse $\leq$ stage 2 (RR 0.29, 95% CI 0.09 to 0.97), recurrent vault prolapse (RR 0.23, 95% CI 0.07 to 0.77), post-operative stress urinary incontinence (RR 0.55, 95% CI 0.32 to 0.95) and less post-operative dyspareunia (RR 0.39, 95% CI 0.18 to 0.86). In contrast, ASCP was associated with a longer operating time (Weighted Mean Difference (WMD) 21 minutes, 95% CI 12 to 30), longer time to recover (WMD 8.3 days, 95% CI 3.9 to 12.7) and was more expensive (WMD US $1334, 95% CI 1027 to 1641) than SSLF.(229)

4.3. Laparoscopic Sacrocolpopexy (LSCP)

The laparoscopic approach of sacrocolpopexy has been adopted by many surgeons over the last decade as an alternative to ASCP with the hopes of reproducing the high success rate of the ASCP while decreasing the morbidity and delayed recovery associated with laparotomy. Table 18 summarises 45 prospective and retrospective case series of 5584 patients. The results show acceptable short to mid-term success rates with mean objective success rate of 93% (range 60 -100%), mean total reoperation rate of 7%, and a mean reoperation rate for recurrent prolapse of only 3%. Mesh exposure rates are only 2% and the risk of spondylodiscitis seems to be in the 1% range. Subjective success rates of 79-98% (332-334) have been reported. Prospective studies demonstrate significant improvements in pelvic symptoms and quality of life after LSC.(324,335,336) Most RCTs observed that laparoscopic sacrocolpopexy is as effective as open abdominal procedure, with a reduced rate of intraoperative bleeding, hospitalisation and wound complications.(337,338) However, a recent RCT showed that LSCP provides outcomes as good as those of open procedure for anatomical correction but not for anterior pelvic organ prolapse.(339) A retrospective study assessed the complication rates in 402 LSCP cases.(262) This study compared patients who received concurrent laparoscopically-assisted vaginal hysterectomy with those that had previous hysterectomy. They showed no differences in intra- or perioperative complications and similar rates of mesh erosion between the two groups.(262) Overall the complication rates for this cohort were 0.75% for hematoma, 2.2% for ileus or small bowel obstruction, 1.5% for bladder injury, 0.75% for bowel injury and 0.25% ureteric injury. At 1 year, the overall mesh erosion rate

was 1.2%. In contrast, Tan-Kim et al reported on a retrospective series of 188 minimally invasive sacrocolpopexy and found a significantly higher mesh exposure rate in those who received concurrent total vaginal hysterectomy (TVH) (23%) compared with those who were post-hysterectomy (5%) or received a supracervical hysterectomy (5%).(340) TVH was found to be an in independent risk factor for mesh erosion on multivariable regression analysis in this study (OR 5.67; 95% CI 2.88-17.10).

Despite the clinical advantages of a laparoscopic approach, adoption of LSCP has been limited possibly related to the steep learning curve associated with attaining laparoscopic suturing and knot tying skills that are required to attach the mesh to the vagina and sacrum. Claerhout et al evaluated their learning curve in the first 206 cases performed by a single surgeon.(341) Operating times declined rapidly during the first 30 procedures in this series and reached steady state (175 minutes) after 90 cases. Using a cumulative sum (CUSUM) approach to evaluate operative time and failures (laparotomy, complication or anatomic failures) they found that adequate learning occurred after 60 cases.(341) Complication rates remained unchanged throughout this series. Other studies have shown a decrease in operating time after 15-24 cases.(342,343) In a large database study of 3852 non-mesh vaginal surgeries and 2538 minimally invasive sacrocolpopexy's, minimally invasive sacrocolpopexy was associated with similar rates of 30-day complications, prolonged hospitalisation, readmission, and reoperation compared with non-mesh vaginal surgeries for apical prolapse.(344) Similarly, in the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database of 1881 SSLF's, 975 USLS's and 4559 minimally invasive sacrocolpopexies, overall perioperative safety was comparable.(345)

Table 18. Outcomes for laparoscopic sacral colpopexy (LSCP) studies with at least 12 month follow up

Author, year	n (mesh)	Success Rate	f.u. months	Total reoperation rate	Reoperation rate recurrence	Reoperation rate complication	Vaginal mesh exposure	Spondylo-discitis	de novo dyspareunia
Cherot 2001(184)	44	43/44	18	0/44	0/44	0/44	0/44	0/44	0/44
Cosson, 200242*	83	78/83	11	2/83	1/83	1/83	1/83	0/83	MD
Antiphon, 200441	108	75/100	16	10/108	5/108	0/108	0/108	1/108	MD
Gadonneix, 200440*	46	38/46	24	0/46	0/46	0/46	0/46	0/46	MD
Higgs 2005(185)	103	39/66	60	15/103	11/103	4/103	6/103	0/103	MD
Ross, 200539	51	48/51	60	10/51	3/51	4/51	4/51	0/51	4/51
Rozet, 200537*	363	348/363	14	13/363	7/363	6/363	3/363	1/363	MD
Paraiso, 200536	56	MD	13	3/56	1/56	2/56	2/56	0/56	MD
Rivoire, 200735*	114	100/114	33	14/114	7/114	7/114	7/114	1/114	0/114
Agarwala, 200734	74	74/74	24	2/74	0/74	2/74	1/74	MD	1/74
Stepanian, 200831	402	380/402	12	14/402	0/402	11/402	5/402	0/402	4/402
Misrai, 2008(186)	43	37/43	48	3/43	1/43	2/43	2/43	0/43	MD
North, 2009(187)	22	22/22	27.5	1/22	0/22	1/22	1/22	0/22	0/12
Claerhout, 200946	132	127/132	12	9/132	0/132	9/132	6/132	0/132	10/53
Deprest, 200930	65	43/65	33	7/65	0/65	7/65	7/65	0/65	MD
Sarlos, 200829	101	98/101	12	4/101	1/101	1/101	1/101	0/101	1/101
Granese, 200928	138	131/138	43	1/138	0/138	0/138	0/138	0/138	2/138

Author, year	n (mesh)	Success Rate	f.u. months	Total reoperation rate	Reoperation rate recurrence	Reoperation rate complication	Vaginal mesh exposure	Spondylo-discitis	de novo dyspareunia
Akladios, 2010(188)	48	46/48	16	8/48	0/48	2/48	1/48	0/48	MD
Sabbagh, 2010 27**	186	122/132	60	8/186	2/186	6/186	5/132	0/132	9/170
Paraiso, 2011(189)	29	21/23	12	0/29	0/29	0/29	0/29	0/29	MD
Sergent, 201126 *	124	103/116	34	10/124	MD	3/124	4/116	1/124	1/85
Price, 201125	84	84/84	24	7/84	4/84	3/84	5/84	0/84	MD
Maher, 201111	53	41/53	24	3/53	0/53	1/53	1/53	0/53	MD
Perez, 2011(190)*	94	88/94	12	0/94	0/94	0/94	3/94	0/94	2/94
Freeman, 2013(191)	25	24/25	12	1/25	1/25	0/25	0/25	0/25	MD
Sarlos, 2014(192)	85	57/68	60	5/85	3/85	2/85	2/85	0/85	MD
Costantini, 2016(193)	60	60/60	41	3/60	0/60	3/60	3/60	0/60	1/60
Kenton, 2016(194)	33	MD	12	3/33	0/33	3/33	0/33	0/33	MD
Chen 2017 (Retrospective Cohort Study comparing LSH/LSCP v VSSLF)(135)	102	102/113	24	MD	MD	MD	1/113	MD	MD
Vandendriessche 2017 (195)	464	MD	54	49/391	20/391	11/391	11/391	MD	MD
Zhang 2017(196)	204	192/195	12	MD	MD	MD	1/204	MD	MD
Coolen 2017 (Prospective RCT)(197)	37	31/37	12	7/36	4/36	0/36	0/36	0/36	MD
Cormio 2017 (Prospective Cohort)(198)	21	20/21	17	1/21	MD	1/21	0/21	0/21	MD
Vidal 2018 (Prospective and observational study – included hysteropexy)(199)	72	71/72	18	7/72	0/72	0/72	0/72	0/72	2/72
Balsamo 2018 (Retrospective single center case control polyvinylidene fluoride mesh (PVDF) v standard polypropylene mesh (PP))(200)	73 (PP)	67/73	94	0/73	0/73	0/73	1/73	0/73	MD
	63(PVDF)	55/63	25.6	0/63	0/63	0/63	2/63	0/63	MD
Orhan 2019 (Prospective Cohort comparing Urologist v Gynecology LSCP technique)(201)	"96 Gyn"	83/96	48	11/96	6/96	0/96	2/96	0/96	MD
	"94 Urol"	82/94	48	10/94	5/94	0/94	2/94	0/94	MD
Andre 2018 (Prospective Cohort – may include hysteropexy, article in French(202)	63	62/63	18	MD	MD	MD	0		2/63
Wagner 2019 (Prospective single center study)(203)	82	53/75	60	7/75	4/75	3/75	3/75	0/75	MD

Author, year	n (mesh)	Success Rate	f.u. months	Total reoperation rate	Reoperation rate recurrence	Reoperation rate complication	Vaginal mesh exposure	Spondylo-discitis	de novo dyspareunia
Ozerkan 2019 (LSCP with polyester fiber suture – no Mesh)(204)	22	19/21	21	0/21	0/21	0/21	0/21	0/21	MD
Tibi 2019(Retrospective cohort comparing LSCP, native tissue repair and vaginal mesh repair(205)	70	63/66	12	MD	MD	1/70	0/70	0/70	MD
Bataller 2019 (RCT, Compared with transvaginal mesh)(206)	58	46/58	12	5/58	1/58	4/58	3/58	0/58	3/43
"Baines 2019 (Retrospective cohort study)(207)"	660	437/453	51	78/660	35/660	4/660	5/660	0/660	MD
Campagna 2019 (Retrosective Cohort – using light titanium coated polpropylene mesh)(98)	217	213/217	12	4/217	0/217	1/217	3/217	0/217	2/217
Kalis, 2020 (Retrospective cohort)(208)	128	97/114	12	MD	MD	MD	2/114	0/114	MD
Vanden Akker 2020(209)	124	62/118	36	17/124	3/124	3/124	4/124	0/124	1/61
Ferrando 2021(210)	44	35/44	24	2/44	2/44	0/44	0/44	0/44	0/44
Lamblin 2021 glue used for vaginal fixation (211)	30	22/30	36	3/30	3/30	0/30	1/30	0/30	MD
Lallemant(212) retrospective	160	138/160	33	8/160	2/160	2/160	1/160	1/160	MD
Total	**5818**	**"5467/ 5936 92.1%"**		**"265/ 5182 5.1%"**	**"147/ 5037 2.9%"**	**"110/ 5151 2.1%"**	**"116/ 5820 2.0%"**	**"44/ 4895 0.9%"**	**"45/ 1898 2.3%"**

*Abbreviations: MD: missing data, all mesh monofilament polypropylene except * PE: polyester, PPS, monofilament polypropylene-dimethyl siloxane (silicone)*

Table 19. Comparison of laparoscopic sacrocolpopexy (LSCP) and robotic sacrocolpopexy (RSCP)

Author, Year	Design (follow-up mos)	Group	No. patients	Operating time mins	Blood loss mls	Objective Success Rate (%)	Complications (%)	Mesh exposure (%)
Paraiso, 2011(213)	RCT (12)	LSCP	33	199	MD	91	12	0
		RSCP	35	265	MD	88	43	6
Chan, 2011(214)	Retrospective (RSCP 16; LSCP 39)	LSCP	20	185	155	90	0	0
		RSCP	16	230	131	93	12	0
Tan-Kim, 2011(86)	Retrospective (RSCP 36; LSCP 25)	LSCP	61	206	85	80	MD	2
		RSCP	43	281	86	90	MD	5
Seror, 2012(215)	Retrospective (RSCP 15; LSCP 18)	LSCP	47	231	280	100	40	0
		RSCP	20	128	55	95	30	0
Antosh, 2012(216)	Retrospective (3)	LSCP	23	325	100	91	8	0
		RSCP	65	334	50	87	MD	3
Awad, 2013(217)	Retrospective (3)	LSCP	40	176	205	100	5	0
		RSCP	40	186	48	100	5	0
Anger, 2014(218)	RCT (6)1 Follow up at 12 months reports no new serious adverse events (Kenton 2016)	LSCP	38	178	106	MD	2.6	0
		RSCP	40	202	85	MD	2.5	0
Mueller, 2016(194)	Retrospective	LSCP	232	215	114	92	8	0.8
		RSCP	226	255	99	86	7	0.9
Cucinella 2016(219)	Retrospective (6)	LSCP	20	85	125	100	0	0
		RSCP	20	141	56	100	0	0
Illiano, 2019(220)	RCT (24)	LSCP	51	193	59	100*	27.5 2	5.8
		RSCP	49	234	57	100*	20.42	4.1
Lallemant 2020(212)	Retrospective	LSCP	160	183	59	92.5	1.83	1.20%
		RSCP	54	203	57	74	1.83	0

Abbreviations: MD: missing data, RCT: randomized controlled trial, LSCP: laparoscopic sacrocolpopexy, RSCP: robotic sacrocolpopexy
[1] Apical Compartment: [2] Clavien-Dindo Grade 1 or 2: [3] Clavien-Dindo Grade 3

4.4. Robotic Sacrocolpopexy (RSCP)

Because of the relatively long learning curve required for LSCP, many surgeons have turned to robotic-assisted surgery in order to offer patients a minimally invasive approach to sacrocolpopexy. Robotic surgical systems have been developed with the goal of facilitating technically difficult procedures by improving the surgeon's vision, dexterity and ergonomics. Limited data suggest that operating time and efficiency improves significantly after performing 20 RSCPs.(346) A systematic review of 27 studies including 1488 RSCPs found that the robotic approach is associated with objective cure rates of 84%-100% and subjective cure rates of 92-95% with mesh erosion rates of 2% (range 0-8%)(347) Overall, the post-operative complication rate in this meta-analysis was 11% (range 0-43%) with severe complications occurring in 2%.(347) Conversion to open ASCP occurred in <1% (range 0-5%).

4.5. Laparoscopic versus Robotic Sacrocolpopexy

In the majority of comparative studies RSCP is associated with longer operating time but similar objective success (Table 19).

To date, three randomised trials have compared robotic to laparoscopic sacrocolpopexy. Paraiso et al reported a single-centre, blinded randomised trial comparing RSCP (n = 40) to LSCP (n=38) in women with stage 2-4 post-hysterectomy vaginal prolapse. Patients undergoing a RSCP experience longer operating time (mean difference + 67 minutes; 95% CI 43-89, p<.0001), increased post-operative pain up to six weeks following surgery and required longer use of non-steroidal anti-inflammatory medications (20 vs 11 days) compared with LSCP. At one year, there was no difference between anatomical and quality of life measures between the two groups. Additionally, the cost of RSCP was significantly higher (mean difference +$1936; 95% CI $417-$3,454).(335) In 2014, Anger et al conducted a multi-centre trial comparing 78 women with stage two or greater pelvic organ prolapse to RSCP (n=40) or LSCP (n=38) with a primary outcome of cost.(348) The robotic sacrocolpopexy group had higher initial hospital costs ($19,616 compared with $11,573, P<.001) and over six weeks, hospital costs remained higher for RSCP ($20,898 compared with $12,170, P<.001). However, when excluding costs of robot purchase and maintenance there was no difference in hospital costs over 6 weeks ($13,867 compared with $12,170; P=.060). The robotic group had longer operating room times (202.8 minutes compared with 178.4 minutes, P=.030) and higher pain scores one week after surgery (3.5+/-2.1 compared with 2.6+/-2.2; P=.044). At one year, there were significant improvements in sexual activity, quality of life and symptoms improved in both groups with no differences between groups.(349)

No reoperations for mesh complications occurred in either group. In a study of 100 randomised patients, Iliano found longer robotic operative times (234 vs 193 minutes) compared to laparoscopic procedures, but otherwise no difference in outcomes.(350) A recent systematic review by Yang et al of RCT's and comparative studies that compared RSCP and LSCP for uterine and vault prolapse included 49 studies with 3014 participants. The pooled results suggested that RSCP was associated with a significantly longer operative time, significantly less estimated blood loss and significantly lower conversion rate compared with LSCP without any difference in intra- and post-operative complications or anatomic success. Cost was not evaluated and they concluded that the choice of surgical procedure with either RSCP or LSCP is according to surgeon discretions and patient preferences(351).

4.6. Sacrocolpopexy versus transvaginal mesh

Maher et al reported results from a randomised trial comparing laparoscopic sacrocolpopexy (LSCP) (n=53) to a total vaginal mesh (TVM) (Prolift, Ethicon, Sommerville NJ, USA) (n=55).(324) LSCP was associated with longer operating time (mean difference +52 min (95% CI 41.5-62.6], decreased hospital stay (mean difference -0.5 days (95% CI -.93 to -.10) and quicker return to normal activities (mean difference -5.3 days (95% CI -8.4 to -2.3). Two years after surgery, objective success (overall POP-Q Stage 0 or 1) was seen in 77% of the LSCP group compared with only 43% of the TVM group, p <.001).(324) Also, reoperations were significantly higher in the TVM group (22%) than in the group that received LSCP (5%, p =.006). In a RCT comparing an open abdominal sacrocolpopexy with a vaginal hysterectomy/SSLF/and anterior polyvinylfluoride mesh, anatomic success rates were similar however reoperations were significantly higher in the vaginal mesh arm (14% vs 0%).(138)

4.7. Sacrocolpopexy with mesh versus biological grafts

Some surgeons have attempted to decrease mesh complications of sacrocolpopexy by using biological materials instead of synthetic mesh. However, Level 1 evidence supports the superiority of polypropylene mesh to fascia lata for objective anatomical support following ASCP.(46,352) A randomised trial of 106 women undergoing ASCP compared polypropylene mesh to cadaveric fascia lata and found superior anatomical outcomes in those who received polypropylene at one year (success 91% vs. 68%, p = .007) and five years after surgery (93% vs. 62%, p =.02).(46,352) There were no differences in graft related complications overall between the two groups. Several retrospective case series support these data. (353-355) While Level three evidence suggests that use of xenografts such as porcine dermis and small intestinal submucosa also have inferior anatomic success rates compared with polypropylene mesh,(356-358) a single randomised trial comparing polypropylene mesh to porcine dermis in women receiving LSCP found no difference in objective or subjective outcomes at one year.(359)

5. OBLITERATIVE PROCEDURES: LEFORT COLPOCLEISIS, TOTAL COLPOCLEISIS

Obliterative surgery, such as total colpocleisis (also called colpectomy/colpocleisis) or the LeFort partial colpocleisis, corrects POP by reducing the pelvic viscera back into the pelvis and closing off the vaginal canal either in part or whole.(360) Obliterative procedures are less commonly performed in the Europe, Asia, and Australia compared to the United States, and are usually reserved for women who are elderly, medically compromised, and no longer sexually active.(361) The purported advantages of obliterative surgery in this population are decreased operative time, decreased perioperative morbidity, and an extremely low prolapse recurrence risk. The obvious disadvantage is the elimination of the potential for vaginal intercourse. Preoperative counselling is essential when choosing between the obliterative and reconstructive options. A systematic review of colpocleisis published in 2006 noted colpocleisis appears to be nearly 100% effective for correcting pelvic organ prolapse. (360) However, a small cohort study of 47 elderly women undergoing LeFort colpocleisis found objective success to be 81% and symptomatic improvement at 91.5% with longer post-operative vaginal length and wider genital hiatus as risk factors for recurrence. (362) Multiple cohort studies have found high rates of patient satisfaction and significant functional improvement with low rates of regret for loss of sexual function (0-4.3%). (69,363-367)

Barber et al reported results from a multi-centre study of obliterative surgery using a prospective cohort design with a concurrent control group of age-matched women undergoing vaginal reconstructive surgery.(69) Despite permanent alterations in sexual function, significant improvements in bladder, bowel and prolapse symptoms as well as body image were noted after surgery with no differences between those who received colpocleisis and those who underwent reconstructive surgery. Additionally, significant and clinically important improvements were noted in bodily pain, vitality, social functioning, role-emotional, and mental health summary scales of the SF-36.(69) Another multi-centre prospective cohort of 90 women undergoing colpocleisis found significant improvement in pelvic floor symptoms and body image with high satisfaction and low levels of regret on validated questionnaires six months after surgery.(366) Similarly, a retrospective cohort of women over age 65 by Murphy et al comparing women who underwent colpocleisis (n=45) and similar group women who underwent reconstructive surgery with transvaginal mesh (Prolift, Ethicon Women's Health and Urology) found that improvements in condition-specific quality of life and post-operative patient satisfaction were comparable between the two treatment groups.(368)

The Pelvic Floor Disorders Network has reported on a large series of women undergoing colpocleisis (n=153) with one year follow-up. (202) All pelvic symptom scores and related bother significantly improved at three and 12 months, and 125 (95%) patients said they were either 'very satisfied' or 'satisfied' with the outcome of their surgery.(202) Bothersome stress and urgency incontinence were present before surgery in 54% and 41% of subjects respectively. Forty percent of subjects received a concurrent mid-urethral sling at the time of their colpocleisis and the rates of bothersome stress and urgency incontinence one year after surgery were 14% and 15% respectively. Similarly, bothersome bowel symptoms were present in 77% of subjects at baseline. One year after surgery, the majority of bothersome bowel symptoms resolved, particularly obstructive and incontinence symptoms, and development of new bowel symptoms was uncommon (0-14%).(369)

While obliterative procedures are predominantly performed in elderly, frail women who often have multiple co-morbidities, the rate of serious adverse events after this procedure appears to be low. In general, major complications due to performance of surgery on the elderly (e.g. cardiac, pulmonary and cerebrovascular complications) occur at a rate of approximately 2%.(360) Major complications due to the surgery itself (e.g. pyelonephritis, blood transfusion) occur at a rate of approximately 4%.(360) A systematic review of published series of colpocleisis from 1966 to 2004 reported a surgical mortality rate of approximately 1 in 400 cases. (360) One complication that appears to be uniquely associated

with obliterative surgery is development de novo rectal prolapse after surgery.(370,371) Collins et al in a retrospective cohort of 916 women undergoing vaginal POP surgery at one institution and found that the incidence of post-operative full-thickness rectal prolapse in women who were > or = 65 years old who underwent obliterative surgery was 3 of 74 (4.1%; 95% CI, 1.4-11), with an estimated odds ratio of 22 (95% CI, 2.3-196; P < .002) compared with women who were > or = 65 years old who underwent reconstructive surgery.(370)

CONCLUSIONS

- A single large RCT suggests USLS and SSLF have similar anatomical, functional and adverse event outcomes. (GoR B)
- Level one evidence demonstrates transvaginal mesh procedures offer no significant advantage over vaginal native tissue apical repairs and are associated with mesh erosions. (GoR A)
- Level one evidence suggests that overall sacrocolpopexy is associated with lower risk of awareness of prolapse, recurrent prolapse on examination, repeat surgery for prolapse, post-operative SUI and dyspareunia when compared broadly with vaginal prolapse repairs with and without mesh augmentation. (GoR A)
- Level one evidence suggest ASCP has a higher success rate as compared to SSLS with less SUI and post-operative dyspareunia. ASC had greater morbidity including operating time, inpatient stay, slower return to activities of daily living and higher cost. (GoR A)
- In a single RCT, ASCP associated with greater anatomical success, fewer reoperations, greater post-operative complications than USLS but no difference in improvement in symptoms or quality of life. (GoR B)
- LSCP is associated with lower blood loss, longer operating time and shorter hospital stay than ASCP with no difference in objective or subjective cure rates. (GoR B)
- Compared to LSCP, RSCP is associated with longer operating times, greater post-operative pain and cost with similar rates of anatomic success and complications. (GoR B)
- ASCP performed with polypropylene mesh has superior outcomes to fascia lata. (GoR B)
- In a single RCT, LSCP had a superior objective and subjective success rate and lower reoperation rate compared to polypropylene transvaginal mesh for vault prolapse. (GoR B)
- Level three evidence suggest McCall culdoplasty, Iliococcygeus fixation and colpocleisis are relatively safe and effective interventions. (GoR C)

VI. SURGERY FOR POSTERIOR VAGINAL WALL PROLAPSE

Almost 200,000 women undergo prolapse surgery in the United States each year, with one-third to one-half including a posterior wall prolapse repair.(32) Prolapse of the posterior vaginal wall may be secondary to the presence of rectocele, sigmoidocele, enterocele, or a combination of these. This section will focus on the current understanding of the posterior vaginal anatomy, pathophysiology and anatomic defects which contribute to posterior vaginal wall prolapse, and will update the previous ICI report regarding outcomes after surgical repair of rectocele.

Anatomy of the Posterior Vaginal Wall

The vagina is made up of fibromuscular tissue extending as a tube from the abdominal cavity to the perineal body. Support of the posterior vaginal wall includes a complex interaction of the vaginal tube, connective tissue support, and muscular support of the pelvic floor.

The connective tissue support of the vagina can be divided into three levels based on work by DeLancey.(178) All three levels require evaluation when considering the surgical management of the posterior vaginal compartment. Level I includes the apical portion of the posterior vagina supported primarily by the cardinal-uterosacral ligaments, originating at the sacrum and inserting onto the posterior cervix and upper vagina.(372) Level II includes support to the mid-section of the vagina, which is provided by the endopelvic fascia, attaching the lateral posterior vaginal wall to the aponeurosis of the levator ani muscles. The fibres of the endopelvic connective tissue extend from the lateral edge of the vaginal tube to the pelvic sidewall. The proximal half of the posterior vagina is supported by endopelvic attachment to the arcus tendinous fasciae pelvis.

Finally, Level III includes the distal support of the posterior vaginal wall and is primarily provided by the perineal body. This level of support has strong attachments to the levator ani complex and is thus less susceptible to pelvic pressure transmission that may cause prolapse: it imparts a physical barrier between the vagina and rectum.

The puborectalis muscle provides a sling of support, enclosing the genital hiatus. Typically, the puborectalis is in a state of chronic contraction and the anterior and posterior vaginal walls are in direct apposition. In normal defaecation, there would be no increased pressure or stress placed on the endopelvic fascial attachments, as the puborectalis muscle relaxes and any increased pressure on the posterior vaginal wall is equilibrated by the opposing anterior vaginal wall.

The rectovaginal space is the potential space between the vaginal tube and the rectum. It consists of areolar tissue, and allows the vagina and rectum to function independently. Histological studies have noted that there is no specific layer of “fascia” between these two structures.(373)

Disruption of this complex interplay of bony, muscular, and connective tissue support can result in posterior vaginal wall prolapse resulting in both physical discomfort as well as negative impact on a woman’s functioning.

Surgical Repair of Posterior Vaginal Prolapse

Posterior vaginal prolapse can be associated with a bothersome vaginal bulge as well as emotional, sexual, and defaecatory dysfunction. Surgical treatment should be primarily driven by patient symptoms and bother. Goals include restoration or maintenance of normal anatomy, bowel function, and/or sexual function. Of note, many patients may present with both defaecatory symptoms as well as posterior vaginal prolapse leading to the assumption that the prolapse is causing the problems. However, data are conflicting regarding the efficacy of posterior vaginal repair on improving defae-

Table 20. Midline plication or traditional posterior colporrhaphy without levatorplasty

Study (year)	N	Review (Months)	Anatomic Cure (%)	Vaginal Bulge (%)	Vaginal Digitation (%)	Defecatory Dysfunction (%)	Dyspareunia (%)
Arnold (379) Preoperative Post-	29 24		19/24(80)		20	9/24(36)	6/24(23)
Mellgren (376) Preoperative Post	25 25	12	24/25(96)	21 4	50 0/25 (0)	8 2/25(8)	2/25(8)
Kahn I(380) Preoperative Post	231 171	42	130/171(76)	64 31	56/171(33)	4 19/171(11)	27/171(16)
Weber (381) Preoperative Post	53 53	12					14/53(26)
Sand.(56) (16) Preoperative Post	70 67	12	67/70(90)				
Maher(382) Preoperative Post	38 38	12	33/38(87)	100 5	100 6/38(16)	3 6/38 (16%)	37 2/38(5)
Abramov.(383) Preoperative Post	183 183	>12	150/183(82)	100 4		17 33/183 (18)	8 31/183 (17)
Paraiso.(384) Preoperative Post	37 28	17.5	24/28 (86%)			80 9/28 (32)	56 13/28(45)
Total			**447/539 (83%)**		**61/234 (26%)**	**78/469 (17%)**	**95/522 (18%)**

catory symptoms and the association is incompletely understood. (374,375)

Types of surgical repair for posterior vaginal prolapse include midline plication (native tissue), site specific technique (native tissue), graft/mesh augmentation of midline or site-specific repairs, transanal repair, ventral rectopexy, and sacral colpopexy in which mesh is extended to the distal portion of the posterior vaginal wall and/or perineum.

1. MIDLINE PLICATION (TRADITIONAL POSTERIOR COLPORRHAPHY)

Midline plication of the fibromuscularis in the posterior compartment, or posterior colporrhaphy, was introduced in the 19th century. Plication in the midline decreases the width of the posterior vagina wall, creates a shelf of support, theoretically increasing the strength of the fibromuscularis layer. Reported anatomical “success rates” of this technique range from 76-96% (Table 20).

The vaginal epithelium of the posterior vaginal wall is incised in the midline and flaps are created by dissecting the vaginal epithelium off the underlying fibromuscularis layer. Plication of the fibromuscularis then starts proximally towards the hymen. Dyspareunia rates range from 5-45% in the literature.

Of note, midline plication may include plication of the levator ani muscles as well. This can help to close the genital hiatus, although it is not a normal anatomical position of the levator muscles. This may overly constrict the vaginal calibre and cause post-operative pain and dyspareunia.(376-378) Thus, in general levator plication has fallen out of favour especially in sexually active women.

2. SITE-SPECIFIC POSTERIOR VAGINAL REPAIR

This technique is similar to the traditional posterior colporrhaphy, except for the plication step. After the epithelium is dissected off of the underlying connective tissue, discrete defects in the connective tissue are identified by the surgeon by placing a finger in the rectum. Any identified discrete breaks in the connective tissue are then approximated and closed using interrupted sutures. If there is remaining laxity after the site-specific repair, a midline plication can then be performed over the site-specific repairs. Levator plication is not performed. The mean anatomic success rate is 83% (range 56-100%) with 18% post-operatively needing vaginal digitation to defecate and 18% experiencing post-operative dyspareunia (Table 21).

Abramov et al retrospectively compared the midline fascial plication and discrete site specific repair for rectoceles.(385) They noted a significantly higher recurrence rate of rectoceles following the discrete site-specific repair 32% as compared to 13% following the

Table 21. Site-specific posterior vaginal repair

Study (year)	N	Review (Months)	Anatomic Cure (%)	Vaginal Bulge (%)	Vaginal Digitation (%)	Defecatory Dysfunction (%)	Dyspareunia (%)
Cundiff et al (387) Preoperative Post-operative	69 61	12	50/61 (82%)	100 11/61(18)	39 11/61(18)	13 5/61(8)	29 12/61(19)
Porter et al(388) Preoperative Post-operative	125 72	6	59/72 (82)	38 10/72(14)	24 15/72/ (21)	24 15/72(21)	67 33/72(46)
Kenton et al(386) Preoperative Post-operative	66 46	12	41/46 (90)	86 4/46(9)	30 7/46(15)	30	28 4/46(8)
Glavind and Madsen(389) (23) Preoperative Post-operative	67 67	3	67/67 (100)				12 2/67(3)
Singh et al(390) Preoperative Post-operative	42 33	18	30/33(92)	78 2/33(7)		9 2/33(5)	31 5/33(15)
Abramov et al(385) Preoperative Post-operative	124 124	>12	69/124 (56)	100 14/124(11)		15 24/124(19)	8 20/124(16)
Paraiso et al(391) Preoperative Post-operative	37 27	17.5	21/23 (78)		58 6/27(21)		48 8/27(28)
Sung et al(392) Preoperative Post-operative	80 70	12	63/70 (90)	4/58(7%)	9/58 (15.5%)	12/57 (21)	4/57 (7)
Total			**410/496 (83%)**	**45/394 (11.4%)**	**48/264 (18%)**	**58/347 (17%)**	**88/487 (18%)**

midline fascial plication (P=0.015). The correction of the rectovaginal fascia defect that allows entrapment of faeces on straining in significant rectoceles may be too large to be repaired with the discrete approach (386) and appears to be corrected by the more robust midline fascial plication.

3. GRAFT (ABSORBABLE) OR MESH (PERMANENT) AUGMENTATION OF POSTERIOR VAGINAL REPAIR

Graft or mesh can be used in the rectovaginal space. This is often combined with either a midline colporrhaphy or site-specific repair. Although there is variation in the surgical technique typically, after creating vaginal flaps, the dissection is extended laterally on both sides to the pelvic sidewall. A midline colporrhaphy or site-specific repair is then typically performed. The graft or mesh is then placed over the repair and anchored along the sidewall. The vaginal epithelium is then closed over the graft or mesh. Of note, commercial transvaginal mesh kits are no longer widely available.

There are four comparative studies suggesting no difference in anatomical and quality of life outcomes when using synthetic absorbable mesh or biological graft compared to native tissue transvaginal repair, including three randomised trials and one retrospective cohort study.(392-394,415) Graft-augmented repair outcomes are presented in Table 22**.**

Paraiso et al compared three techniques for rectocele repair in a prospective randomised trial.(391) Patients were randomised to receive either a traditional repair (N=37), a site specific repair (N=37) or a site-specific repair augmented with porcine small intestine mucosa (N=32). All patients had Stage II or greater posterior vaginal wall prolapse at baseline. The objective anatomical failure rate was highest in the graft augmented group (12/26) at 1 year which was statistically significantly worse than the site-specific group (6/27) and traditional repair (4/28). There was no significant difference in subjective symptoms (worsening prolapse or colorectal symptoms) or dyspareunia between the three groups. No graft exposures were reported.

Sung et al conducted a double blind, multicentre randomised trial comparing native tissue repair (70) versus native tissue with porcine small intestine submucosal (SIS) graft (67) for symptomatic stage 2 rectocele.(392) The native tissue repair involved either a midline plication or site specific repair at the surgeon's discretion, with the majority undergoing site-specific repair. In the graft group the native tissue repair was augmented with porcine SIS overlay. At one year, there was no difference between the groups in objective and subjective success rates or in resolution of defaecatory symptoms. Post-operative dyspareunia rates were not significantly

different at 7% in the native tissue group and 12.5% graft group. No graft exposures were reported.

Grimes et al conducted a retrospective review of 193 posterior repairs performed between 2001-2008 from the Kaiser Permanente San Diego Pelvic Floor Database.(394) 124 (64%) native tissue (including 38% traditional colporrhaphy and 62% site-specific repair) and 69 (36%) graft augmentation procedures were included. Minimum follow up was approximately 12 months. Graft augmentation was at the discretion of the surgeon and included noncross-linked cadaveric dermis, cross-linked porcine dermis, and noncross-linked porcine dermis. Anatomical success was similar between native tissue vs. graft (Bp <-1, 86% vs. 80%). Post-operative splinting and incomplete evacuation was greater in the graft group compared to native tissue (splinting, 85% vs. 68%; p=0.04).

There was one comparative study evaluating patient-reported outcomes after native-tissue versus nonabsorbable mesh augmentation for isolated primary rectocele by Madsen et al.(395) The authors used prospective data from the Swedish National Register for Gynaecological Surgery, including 3988 women who underwent primary operation for rectocele between 2006-2014. 3908 women had a native-tissue repair and 80 had nonabsorbable mesh. No concurrent procedures were included and follow up was 12 months. The authors found no difference in vaginal bulge sensation (78% vs. 90% “cure” for native tissue vs. mesh), or feeling satisfied/very satisfied (74% vs. 70% native tissue vs. mesh). There was no statistically significant difference for de novo dyspareunia (33% vs. 10% for native tissue vs. mesh). Reoperation rate was 1.1% in both groups.

Glazener et al (396) conducted two pragmatic, parallel-group multicentre randomised trials (PROSPECT) in 35 centres in the UK. Women were randomised to native tissue (N=430) vs synthetic mesh augmentation (N=435), or native tissue (N=367) vs biological graft augmentation (N=368). Women were followed for 2 years. Prolapse severity symptoms, quality of life and serious adverse events was not different between groups. The cumulative number of women who had a synthetic mesh complication at 2 years was 12%.

More recently Nussler et al interrogated the Danish surgical database and evaluated those undergoing traditional posterior colporrhaphy (n=433) and permanent polypropylene mesh (n=193) for recurrent isolated rectocele at I year. Those undergoing permanent mesh had significantly greater stage ¾ prolapse than the native tissue group however the awareness of bulge (OR 2.1 95% CI 1.03-4.35) and patient satisfaction (OR = 2.4; CI 1.2-4.97) remained superior in the mesh group. Patient reported complications and reoperation at 12 months remained similar in both groups.(397)

4. VENTRAL RECTOPEXY

For rectal prolapse both perineal and abdominal procedures are described. While the transanal Delorme’s procedure has been performed for many years Level three evidence suggests that perineal approaches seem to be associated with a higher post-operative faecal incontinence and recurrence rate and therefore an abdominal procedure is preferred by most surgeons.(398-400) In the search to reduce this high rate, laparoscopic ventral mesh rectopexy (LVMR) was introduced (401) and mobilises just the anterior aspect of the rectum, and thereby the risk for autonomic nerve damage and associated dysmotility with impaired evacuation is minimised. The dissection is followed by a mesh suspension of the distal rectum to the sacral promontory, correcting the descent of the rectum and reinforcing the rectovaginal septum. Although no high quality comparative research exists so far, VMR is being progressively performed internationally and proposed as the treatment of choice for rectal prolapse.(402)

To date, only one small randomised controlled trial (RCT) Emile et al compared LVMR with Delorme’s operation (n= 25 vs. 25) for ERP with mean follow-up of 18 ± 5 months (range, 9-30).(403) Baseline characteristics differed from the literature with a low mean age (39.7 years) and a high percentage of males (38%). The trial demonstrated no difference between the groups in recurrent prolapse (16% Delorme’s, 8% LVMR) or difference in change in Wexner continence or constipation scores post-operatively. The Delorme’s procedure had a shorter operating time and longer admission stay than the LVMR. With a larger sample size, the non-significantly higher recurrent rectal prolapse rate after the Delorme procedure may become significant.

The vast majority of the current literature regarding LVMR comprises observational studies and often differ in patient selection and outcome measures. This heterogeneity makes it difficult to interpret the results. Most studies lack a systematic approach and follow-up is usually short.

Emile et al have however performed a systematic review of LVMR and found a complication rate of 12% and a recurrence rate of 3% with a median follow up of 23 months. There was a 79% improvement of faecal incontinence and a 71% improvement in constipation.(404)

There is currently no evidence that robotic ventral mesh rectopexy has any benefit over laparoscopy.

4.1. Recurrence

Since the first description of LVMR, recurrence rates for external rectal prolapse (ERP) range between 1.5 to 15.4% (Table 23). Most recurrences are seen within 36 months’ post-operatively, but not all studies demonstrate this time interval. Studies including all rectal

Table 22. Graft-augmented (absorbable) posterior vaginal repair (does not include synthetic mesh)

Author	N	Review (mo)	Anatomic cure (%)	Vaginal bulge (%)	Vaginal digitation (%)	Defecatory dysfunction (%)	Dyspareunia (%)
Paraiso(393) 2006	29	12 mo	14/26 (54%)	-	2/29 (7%)	5/24 (21%)	3 (6%)*
Sung(392) 2012	67	12 mo	59/67 (88%)	2/64 (3%)	6/62 (10%)	28/64 (44%)	7/56 (12.5%)
Grimes(394) 2012	69	71 mo range 9-80)	55/69 (80%)	-	35/41 (85%)	33/41 (80%)	5/23 (22%)
Total			**128/162 (79%)**		**43/132 (33%)**	**66/129 (51%)**	

prolapse syndromes as an indication for LVRM, report a recurrence rate of 2.6 to 14.3% Only three trials evaluated IRP as the indication for LVRM with recurrence ranging from 5.3 to 7.1%. Recurrence rates following RVMR are generally comparable to LVMR series (Table **23).**

4.2. Functional Outcome

4.2.1. External rectal prolapse

External Rectal Prolapse (ERP) is considered a definitive indication for LVMR.(405) Functional outcome in rectal prolapse surgery is usually assessed with validated faecal incontinence and constipation scores. The LVMR articles included in this guideline either used the Cleveland Clinic Constipation Score (CCCS, range 0-30), (406) Obstructed Defaecation Syndrome (ODS) Score (range 0-31),(407) Fecal Incontinence Severity Index (FISI, range 0-61),(408) or the Cleveland Clinic Incontinence Score (CCIS, range 0-30).(409) For all four grading systems, a decrease in score correlates with an improvement of symptoms. A median improvement in CCCS ranged from 4.8-11 points with between 52-84% reporting a general reduction of obstructed defaecation complaints is noted following LVMR (Table 24). Post-operatively 50-93% of patients reported a reduction in faecal incontinence and an improved median FISI ranged from 12 to 36 points**.** New-onset complaints are described in 4.8 to 17.6% of patients for obstructed defaecation and in 1.5 to 3.2% of patients for faecal incontinence (Table 24). The only robotic VMR study including patients with an ERP showed a mean CCCS gain of 3.2 points.(410)

4.2.2. Internal rectal prolapse

In general, for an Internal Rectal Prolapse (IRP) Oxford Grade 1 and 2 (recto-rectal intussusception) pelvic floor physiotherapy is indicated.(411) Significant functional symptoms in combination with an Oxford Grade 3 or 4 IRP (recto-anal intussusception) failing to conservative therapy, could be an indication for VMR.(405) Studies including patients with a symptomatic grade 3 or 4 IRP describe a median reduction of CCCS (range 3.1-9.0 points) and a reduction in obstructed defaecation complaints (range 55-86% of patients) Post-operatively between 20-92% reported a reduction in faecal incontinence with a median improved FISI ranging from 16 to 25 points as seen in Table 24. No, *de novo* faecal incontinence was described.

Median gain of CCIS was non-significantly equivalent between the two techniques. Functional results following RVMR are comparable to the literature on LVMR for various indications (Table **22)**.

5. VENTRAL MESH RECTOPEXY MORBIDITY

Multiple studies have been performed to assess the safety of LVMR. At present, thirty studies report a post-operative complication rate between 0-23.4% (Table 25). The vast majority of those complications were minor, as classified according to the Clavien-Dindo (CD) classification. Major complications following VMR are described from 0-7.7% with a mortality rate of 0-1.1%. In recent years, there was serious controversy about the use of permanent mesh in pelvic floor surgery. In 2015 Evans et al combined data collated from prospective databases in five hospitals (2203 patients) and described an overall mesh erosion rate of 2% (42 synthetic, three biological) after a median of 23 months.(412)

Currently 34 observation studies (range median follow-up 3-74 months) mention mesh-related morbidity following LVMR with mesh complication rates from 0-6.7% and mesh erosion percentages between 0-3.7%.(403, 412-430) Five studies (range median follow-up 3-24 months) evaluated robotic VMR and the rate of synthetic mesh-related complications was 0%.(410, 431-434) Based on these figures, it appears that the concerns about mesh complications following a transvaginal mesh procedure are not applicable to the VMR.

6. BIOLOGICAL GRAFT RECTOPEXY

In 2008 and 2011 the US Food and Drug Administration (FDA) published official warnings for the use of mesh in POP surgery.(435) Although similar figures following an abdominal approach have never been described, an aversion to synthetic mesh in POP surgery was created. In the search for an alternative, biological meshes became more popular. To date, erosion rates and functional outcome following VRM for synthetic and biological mesh are comparable.(436) The material characteristics of a biological mesh could in theory result in a higher recurrence rate. Currently, recurrence rates are quite comparable. One report, however, noted a high recurrence rate of 14% after 20 months of follow-up.(437) Ogilvie et al published the only (case-matched) study comparing biological with synthetic mesh for LVMR (n= 29 vs 29).(420) No significant difference in mesh-related morbidity, functional outcome and recurrence after a median follow-up of 15.4 months was found. One article comparing LVMR with RVMR (34 vs 17) using biological mesh showed no mesh-related morbidity or recurrences in either cohort after 12 months.(438) Functional outcome was approximately equivalent between the two groups. McLean et al found, in a cohort study of 224 LVMR's with biological mesh, a complication rate of 11%, recurrence rate of 11% and a mesh related morbidity of 0.45%.(439)

The use of a biological mesh for LVMR appeared to be safer in a systemic review performed by Balla et al.(440)

7. RECTOCELE AS AN INDICATION FOR VENTRAL MESH RECTOPEXY

Rectocele has been described as an indication for VMR. (413,416,417,419,441) As early as 2008 a Dutch group retrospectively reported on 16 women undergoing LVMR for obstructed defaecation syndrome. Many had an enterocoele or rectocele preoperatively with 25% also having internal rectal prolapse.(442) The mean operating time was 199 minutes and the mesh was secured to the anterior rectum and posterior vagina. Post-operative complications included two ileus, one of which required reoperation, one wound infection, 1 neurological injury to left leg, two incisional hernia and one infected mesh that was removed. The obstructed defaecation score was not significantly different post-operatively and in fact deteriorated in 75%. The authors reported the LVMR to be a feasible approach in selected patients, without identifying the group.

In 2011 Wong et al (441) reported a retrospective case series on ventral rectopexy (n=38) for complex rectocele (defined as one or more of: rectocele greater than 3cm diameter on imaging, associated enterocele or internal rectal prolapse), with 12 months' review.

The surgical technique was unorthodox for ventral rectopexy with "mesh secured to pelvic floor musculature on either side of the rectum, taking care not to place the sutures directly into the rectal wall". This single leaf procedure was performed in (14/38) and closely resembles a single leaf sacral colpopexy. The majority (24/38) actually underwent a classical dual leaf sacral colpopexy.(443) The authors not surprisingly reported a significant reduction in vaginal prolapse symptoms, (45 to 5%) and dyspareunia (27 to 10%) results that have been well recognised in level one data on sacral colpopexy.(444) There was no difference in post-operative scores for obstructed defaecation syndrome, Cleveland clinic incontinence score or Gastrointestinal quality of life score.

Formijne Jonkers et al retrospectively reported on 233 patients undergoing LVMR and who completed postal validated bowel function questionnaires.(413) Indications for surgery were divided into three groups. Group one included external rectal prolapse (15%), group two internal rectal prolapse and or rectocele (68%) and group three internal rectal prolapse or rectocele and enterocele (17%). Sixty-four percent (n=150) completed the questionnaires which demonstrated significant improvement in faecal incontinence and constipation scores post-operatively in all three subgroups. Unfortunately, it is not possible to determine how many of patients in groups two and three are included due to rectocele and how many due to internal rectal prolapse. Furthermore, the study methodology results in an overestimation of impact of the surgery. No attempt was made in the study methodology to account for the 36% that failed to respond and then persisted in including 233 patients in the post-operative review. These oversights in the study methodology served to overestimate the impact of the intervention. Thus, it is not possible to discern from this report if the LVMR is effective for rectocele.

Lauretta et al retrospectively described a modified laparoscopic ventral rectopexy for 30 women with external or internal prolapse and 26 for some degree of rectocele.(417) At surgery the mesh was secured to both the anterior rectum and posterior vaginal wall. Pre- and post-operatively rectocele and internal prolapse were defined at proctography. At a median review of 14 months one patient had a suture erosion and one a recurrent rectal prolapse. Excellent functional outcomes were reported with constipation significantly improved in 93%, a significant reduction in the Altomare obstructed defaecation score and preoperative incontinence improved after the procedure in all patients affected. Unfortunately, no post-operative vaginal prolapse assessment or report of defaecography findings were reported and the reader is unable to determine if the functional outcomes reported are due to correction of the internal and or rectal prolapse or the possible correction of a rectocele.

A French group prospectively evaluated 33 patients undergoing a traditional LVMR for external rectal prolapse (n=20), rectocele and internal rectal prolapse (n=10), and rectocele (n=3).(419) At median review of 42 months constipation was improved in 72% (13/18) and two patients (7%) presented de novo constipation. The patients' Wexner score and quality of life improved significantly post-operatively and two patients developed recurrent rectocele (7%). Despite there being no pre or post-operative vaginal prolapse assessment recorded and that only three patients with rectocele alone were included, the authors concluded LVMR was an effective and safe treatment for external rectal prolapse and or rectocele.

Horisberger et al (416) retrospectively evaluated 27 women undergoing LVMR for complex pelvic floor conditions including symptomatic rectocele (79%), enterocele (64%) and grade 1-2 rectal prolapse (43%). At 22 months significantly improved constipation scores and quality of life scores on the SF-12 questionnaire were demonstrated without improvement in Wexner Incontinence score. Over 50% of preoperatively sexually active women reported a deterioration in sexual function and no post-operative assessment of vaginal prolapse was reported. Again, it is impossible to determine if the improvement in constipation scores are due to treatment of grade 1-2 rectal prolapse or correction of the rectocele.

Due to the significant heterogeneity of the included conditions the reader is unable to determine if the changes reported are due to correction of external and or internal rectal prolapse or due to correction of the rectocele. No trial has demonstrated that the LVMR or modifications employed are successful in correcting rectocele. One trial demonstrated that a procedure that more closely resembles a sacral colpopexy than ventral rectopexy, was successful in correcting vaginal prolapse symptoms with little impact upon functional bowel symptoms.

8. COMBINED VAGINAL AND RECTAL PROLAPSE

Logically women with rectal prolapse may also suffer vaginal prolapse and or bladder dysfunction. As early as 2007 Lim et al (445) retrospectively reported on 29 women undergoing open combined mesh sacral colpopexy, ventral rectopexy and urinary continence surgery performed by urogynaecologist and colorectal surgeons working together for combined pelvic floor dysfunction. The authors demonstrated significant improvement in the validated Pelvic Floor Distress Inventory and in all three subscales including vaginal, urinary and rectal related symptoms. Three patients (10%) required reoperation, one for removal of mesh and two for recurrent vaginal prolapse.

More recently Van Iersel et al prospectively describe 51 patients undergoing robotic ventral rectopexy, sacral colpopexy and urinary continence surgery as required performed in collaboration between colorectal and urogynaecology surgeons for combined vaginal and rectal prolapse.(436) They demonstrated a significant improvement not only in faecal incontinence (Pescatori incontinence scale 4 vs 3, p=0.002) and constipation (73.3%, p<0.0005) but also in the Urinary Distress Inventory (27.8 vs 22.2; p<0.0005) and on sexual function (Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire score 31.8 vs 35.9; p = 0.002. Quality of life for bowel and bladder function (p < 0.0005) was also observed. Anatomical vaginal reconstruction was demonstrated by the simplified POP quantification p< 0.0005). One patient (2%) developed mesh erosion and a single recurrent rectocele was observed.

9. PROLAPSE SURGERY AND COEXISTENT BOWEL SYMPTOMS

Women with vaginal prolapse frequently have coexistent bowel dysfunction including obstructed defaecation, constipation and faecal incontinence. The prevalence of associated bowel symptoms in women with vaginal prolapse was recently reviewed by the International Urogynaecology Consultation and reported obstructed defaecation in 53% (33-95%), constipation 40% (10-83%) and faecal incontinence in 19% (12-69%).(446)

We were unable to identify an evidence-based pathway for the management of pelvic organ prolapse and associated bowel symp-

toms. So utilising the wide clinical and academic experience of the committee we established using the Delphi process clinical guidance on the management of women with vaginal prolapse and associated bowel symptoms as seen in Figure 4. As the success rate of posterior colporrhaphy in those with rectocele and impaired defaecation is over 80% as described above the algorithm points to those entering the standard pathway for vaginal prolapse. Those with obstructed defaecation without significant rectocele and those with faecal incontinence are referred to colorectal colleagues who will differentiate between those with neurological causes that typically would undergo sacral neuromodulation and those with high grade rectal prolapse who maybe considered for ventral rectopexy/resection. Finally, those with constipation are actively managed to minimise straining as constipation is an acknowledged risk factor for the development and possible recurrence of vaginal prolapse.

Table 23. Recurrence rates following LVMR and RVMR with synthetic mesh

Laparoscopic studies	n	FU (median)	Recurrence	Type of recurrence	Presentation of recurrence (months)
Indication ERP and significant IRP					
D'Hoore(401) 2004	42	61	2 (4.8%)	2 ERP	54, 91
Verdaasdonk(447) 2006[a]	13	7	2 (15.4%)	2 ERP	-
Auguste(427) 2006	54	12	4 (7.4%)	3 ERP, 1 IRP	26 (7-54) [b]
D'Hoore(448) 2006	109	-	5 (4.6%)	4 ERP, 1 enterocele	-
Cristaldi(449) 2007	63	18	1 (1.7%)	ERP	-
Boons(450) 2010	65	19	1 (1.5%)	ERP	12
Wijffels(451) 2011	80	23	2 (2.5%)	2 ERP	6, 16
Faucheron(452) 2012	175	74/60[c]	2 (3%)c	2 ERP	6, 24
Randall(421) 2014[d]	190	29	9 (4.7%)	1 ERP, 8 IRP	25, 30, 31, 60[e]
Gosselink(415) 2015[f]	41	12	1 (2.3%)	ERP	12
Tsunoda(426) 2016	31	25	3 (9.7%)	3 IRP	10, 17, 31
Emile(403) 2016	25	18[g]	2 (8%)	ERP	-
Chandra(429) 2016	15	22	0 (0%)	-	-
Indication IRP and/or rectocele					
Collinson(453) 2010	75	12	4 (5.3%)	4 IRP	-
Wong (441) 2011	84	29	6 (7.1%)	6 rectoceles	-
Gosselink(415) 2015[f]	50	12	3 (5.8%)	3 IRP	-
Indication both ERP and IRP and/or rectocele					
Lauretta(417) 2012	2 ERP, 28 IRP	13.9[g]	1 (3.3%)	1 IRP	19
Formijne Jonkers[16] 2013	36 ERP, 197 IRP	30	6 (2.6%)	-	-
Badrek-Amoudi[18] 2013	11 ERP, 37 IRP	33	4 (8.3%)	4 IRP	22 (median)
Maggiori[19] 2013	33[h]	42[g]	2 (6.7%)	2 rectocele	11, 14

Laparoscopic studies	n	FU (median)	Recurrence	Type of recurrence	Presentation of recurrence (months)
Mackenzie[25] 2014	149 ERP, 487 IRP	21	60 (9.4%)	-	-
Owais[61] 2014[i]	18 ERP, 60 IRP	42	2 (2.9%)	2 IRP	-
Consten/van Iersel(430) 2015	242 ERP, 677 IRP	33.9/120[c]	68 (14.3%)[c]	15 ERP, 53 IRP	24.1 (1–139.4)[b]
Tsunoda(425) 2015	19 ERP, 25 IRP	26	2 (3.4%)	2 IRP	10, 15
Horisberger(416) 2016	12 ERP, 15 IRP	22	1 (3.7%)	ERP	2
Robotic vs. Laparoscopic – various indications					
De Hoog(410) 2009	20 ERP robot	23.4	4 (20%)	-	-
Wong(441) 2011	23 IRP lap 15 IRP robot	12	1 (4.3%) 1 (6.7%)	Rectocele Rectocele	3 7
Wong(434) 2011	40 IRP lap 23 IRP robot	6	0 (0%) 0 (0%)	- -	- -
Mantoo(433) 2013[j]	23 ERP, 51 IRP lap 12 ERP, 32 IRP robot	16[g]	6 (8%) 3 (7%)	- -	- -
Mäkelä-Kaikkonen(431) 2014	14 ERP, 6 IRP lap 13 ERP, 7 IRP robot	3	1 (5%) 0 (0%)	- -	- -

[a] One patient was excluded from further analysis, therefore n=13 instead of n=14 is used; [b] mean (range); [c] Recurrence percentage is KM estimate at 60 and 120 months of follow-up; [d] Study group included the first 44 cases from Slawik et al. [55]; [e] Only 4 time intervals are described; [f] The results of Gosselink et al. is displayed per indication; [g] Mean instead of median; [h] Of the 33 patients (ERP n = 20, n = 13 IRR) 3 lost to follow-up. For the remainder of patients, the surgical indication was not given; [i] Only men included; [j] A modified version of the D'Hoore rectopexy used; Lap: laparoscopic

Table 24: Functional Results following LMVR and RVMR with synthetic mesh

Laparoscopic studies	N	Median FU (mo)	Improvement OD	P value	Improvement FI	P value	Median Gain CCCS	P value	Median gain CCIS	P value
Indication ERP										
D'Hoore(401) 2004	42	61	84.2%. De novo 4.8%	-	90.30%	-	-	-	13	<0.001
Auguste(427) 2006	54	12	70%. De novo 17.6%		72.40%		-	-	5.8[a]	-
Verdaasdonk(447) 2006[b]	13	7	66%	-	69%	-	-	-	-	-
Cristaldi[63] 2007	63	18	78%	-	90%. De novo 3.2%	-	5	<0.0001	32 (FISI)	<0.0001

Laparoscopic studies	N	Median FU (mo)	Improvement OD	P value	Improvement FI	P value	Median Gain CCCS	P value	Median gain CCIS	P value
Boons(450) 2010	58[c]	19	72%	-	83%. De novo 1.5%	-	5	< 0.0001	36 (FISI)	< 0.0001
Formijne Jonkers(413)2013[d]	36	30	57.90%	0.01	76.20%	<0.001	-	-	-	-
Randall(421) 2014	190	29	-	-	93%	-	-	-	8	< 0.0001
Gosselink(415) 2015[d]	41	12	-	-	50%	<0.01	4.8	<0.01	12 (FISI)	<0.01
Tsunoda(425) 2015[d,e]	19	12	52%	-	62%	-	7	<0.0001	23 (FISI)	<0.0001
Consten/van Iersel[26] 2015[d]	242	33.9	63.30%	<0.0001	73.20%	<0.0001	-	-	-	-
Tsunoda(426) 2016	31	12	-	-	-	-	5	0.005	22 (FISI)	<0.0001
Emile(403) 2016	25	6	62.50%	-	75%	-	8.7	-	5	-
Chandra(429) 2016	15	22	-	-	-	-	11	< 0.001	24 (FISI)	0.007
Indication IRP and/or rectocele										
Collinson(454) 2009	30	3	83%	-	92%	-	9	<0.0001	25 (FISI)	<0.0001
Collinson(453) 2010	75	12	86%	-	85%	-	7	< 0.0001	20 (FISI)	<0.0001
Wong (434)2011	84	29	45%	< 0.001	20%	> 0.05	-	-	-	-
Formijne Jonkers[16] 2013[d]	197	30	76.90%	< 0.001	65.40%	< 0.001	-	-	-	-
Gosselink(414) 2013	72	12	-	-	-	-	5	< 0.001	16 (FISI)	<0.01
Gosselink(415) 2015[d]	50	12	-	-	48%	<0.01	3.1	<0.01	17 (FISI)	<0.01
Tsunoda(425)2015[d,e]	25	12	55%	-	63%	-	6	<0.0001	22 (FISI)	<0.0001
Tsunoda(455) 2015	26	16	-	-	-	-	7	< 0.01	24 (FISI)	<0.01
Consten/van Iersel(430) 2015[d]	242	33.9	61%	<0.0001	73.20%	<0.0001	-	-	-	-
Indication both ERP and IRP and/or rectocele										
van den Esschert(442) 2008	1 ERP, 16 IRP	38[a]	-	-	-	-	+2.7[g] (ODS)	0.091	-	-
Lauretta(417) 2012	2 ERP, 28 IRP	13.9[a]	92.80%	-	85.70%	-	9.1 (ODS)[a]	<0.05	7.1[a]	<0.05
Badrek-Amoudi(428) 2013	11 ERP, 37 IRP	33	68%	< 0.0001	-	-	17 (ODS)[h]	<0.0001	4	< 0.0001
Maggiori(419) 2013	33[i]	42a	72%. De novo 7%	-	90%	-	-	-	8	0.002
Mackenzie(418) 2014	149 ERP, 487 IRP	21	56.7%[j]. De novo 1.4%	0.119	89.7%[k]. De novo 1%	0.04	12 (ODS)[40]	-	8	-
Owais(456) 2014[l]	18 ERP, 50 IRP	42	82%	-	82%	-	12.5 (ODS)	< 0.001	4	< 0.001
Horisberger(416)2016	12 ERP, 15 IRP	22	-	-	-	-	3[m]	0.007	2	0.735

Laparoscopic studies	N	Median FU (mo)	Improvement OD	P value	Improvement FI	P value	Median Gain CCCS	P value	Median gain CCIS	P value
Robotic vs. Laparoscopic studies – various indications										
De Hoog(410) 2009[a]	20 ERP R	23.4	-	-	-	-	3.2[a]	-	-	-
Mantoo(433) 2013[n]	23 ERP, 51 IRP L 12 ERP, 32 IRP R	16[a]	-	-	-	-	6 (ODS)[o] 14 (ODS)[o]	0.004 0.004	4[p] 4[p]	0.604 0.604

[a] Mean instead of median; [b] One patient excluded from further analysis, therefore n=13; [c] complete functional data in 58/65 patients; [d] Results of Formijne Jonkers et al., Gosselink et al., Tsunoda and Consten/van Iersel et al. are displayed per indication; [e] Postop. functional data were fulfilled in 44/59 patients; [f] preoperatively mean CCIS is given, postoperatively the median; [g] Mean ODS score was 2.7 higher after surgery meaning; [h] Pre- and postoperative ODS scores were available for n=36; [i] Of the 33 patients (ERP n=20, n=13 IRR) 3 lost to follow-up. For the rest the surgical indication was not given; [j] Based on n=602; [k] Based on n=276; [l] Only men included; [m] Herold obstipation score; [n] A modified version of D'Hoore rectopexy used; [p] estimation based on bar chart. OD: obstructed defecation, FI: faecal incontinence, ODS: obstructed defecation syndrome score, L: laparoscopic, R: robot.Based on expert opinion, the committee developed a treatment algorithm (Figure 4) for the management of women undergoing pelvic organ prolapse surgery and an associated array of bowels symptoms that frequently co-exist. The algorithm guides those with a rectocele with and without obstructed defaecation symptoms towards standard prolapse surgery as outlined in Figure 10. Those with faecal incontinence and obstructed defaecation without a rectocele, require colorectal evaluation and if due too internal or rectal prolapse

Table 25 Conversion, intra- and post-operative complications following LVMR and RVMR with synthetic mesh

Laparoscopic studies	n	Median FU (months)	Intra-operative complications	Conversion	Post-operative complications Total	Minor (CD 1-2)	Major (CD 3-4)	Mortality (CD 5)
D'Hoore(401) 2004	42	61	0	2 (4.8%)	2 (4.8%)	2 (4.8%)	0	0
D'Hoore(448) 2006	109	-	0	4 (3.7%)	8 (7.3%)	8 (7.3%)	0	0
Slawik(457) 2008	80	54	-	1 (1.3%)	7 (8.8%)	7 (8.8%)	0	0
van den Esschert(442) 2008	17	38[a]	0	1 (5.9%)	4 (23.5%)	3 (17.6%)	1 (5.9%)	0
Boons(450) 2010	65	19	-	1 (1.5%)	11 (16.9%)	6 (9.2%)	5 (7.7%)	0
Collinson(453) 2010	75	12	0	1 (1.3%)	4 (5.3%)	3 (4%)	0	0
Wijffels(451) 2011	80	23	-	1 (1.3%)	10 (12.5%)	9 (11.3%)	1 (1.3%)	0
Wong(441) 2011[b]	40	6	0	4 (10)	5 (12.5%)	5 (12.5%)	0	0
Wong(434) 2011	84	29	4 (4.8%)	3 (3.6%)	3 (3.6%)	2 (2.4%)	1 (1.2%)	0
Lauretta(417) 2012	30	13.9[a]	-	0	2 (7.7%)	0	2 (7.7%)	0
Faucheron(452) 2012	175	74/60[c]	0	3 (1.7%)	8 (4.6%)	5 (2.9%)	3 (1.7%)	0
Formijne Jonkers(413) 2013	233	30	0	6 (2.6%)	11 (4.7%)	7 (3%)	4 (1.7%)	0
Badrek-Amoudi(428) 2013	48	33	-	0	9 (18.8%)	8 (16.7%)	1 (2.1%)	0
Maggiori(419) 2013	33	42[a]	0	1 (3%)	0	0	0	0

Laparoscopic studies	n	Median FU (months)	Intra-operative complications	Conversion	Post-operative complications Total	Minor (CD 1-2)	Major (CD 3-4)	Mortality (CD 5)
Mantoo(433) 2013 [b]	74	16[d]	0	3 (4.1%)	15 (20%)	15 (20%)	0	0
Mäkelä-Kaikkonen(431) 2014[b]	20	3	0	0	1 (5%)	0	1 (5%)	0
Mackenzie(418)2014	953	21	-	8 (1.3%)	63 (6.6%)	53 (5.6%)	8 (0.8%)	2 (0.2%)
Ogilvie(420) 2014	29	15.4	1 (3.4%)	0	3 (10.3%)	2 (6.9%)	1 (3.4%)	0
Randall(421) 2014	190	29	1 (0.5%)	5 (2.6%)	22 (11.6%)	11 (5.7%)	8 (4.2%)	2 (1.1%)
Owais(456) 2014	68	42	0	0	11 (16.2%)	10 (14.7%)	1 (1.5%)	0
Gosselink(415) 2015	91	12	0	0	5 (5%)	4 (4.4%)	0	0
Tsunoda(455) 2015	26	16	0	0	2 (7.7%)	2 (7.7%)	0	0
Consten/van Iersel[26] 2015	919	33.9/120[c]	3 (0.3%)	20 (2.2%)	203 (23.4%)	153 (19.3%)	50 (4.1%)	1 (0.1%)
Tsunoda(426) 2016	31	25	0	0	2 (6.5%)	2 (6.5%)	0	0
Emile(403) 2016	25	18[a]	0	0	5 (20%)	5 (20%)	0	0
Chandra(429)2016	15	22	1 (6.7%)	0	3 (20%)	3 (20%)	0	0
Robotic studies								
Wong(441) 2011[b]	23	6	0	1 (4.3%)	1 (4.3%)	0	0	0
Mantoo(433) 2013[b]	74	16d	0	1 (2.3%)	5 (11%)	5 (11%)	0	0
Mäkelä-Kaikkonen(431) 2014[b]	20	3	1 (5%)	0	1 (5%)	1 (5%)	0	0
Mäkelä-Kaikkonen(432) 2016	16	3	1 (6.3%)	0	2 (12.5%)	2 (12.5%)	0	0

[a] Mean instead of median; [b] The results of Wong, Mantoo and Mäkelä-Kaikkonen et al. are displayed per technique; [c] Percentages are Kaplan-Meier estimates at 60 and 120 months of follow-up; [d] not specified whether mean of median was used. n: no. of patients, FU: follow-up; -: not specified of not applicable.
maybe suitable for combined surgery for vaginal and rectal prolapse.

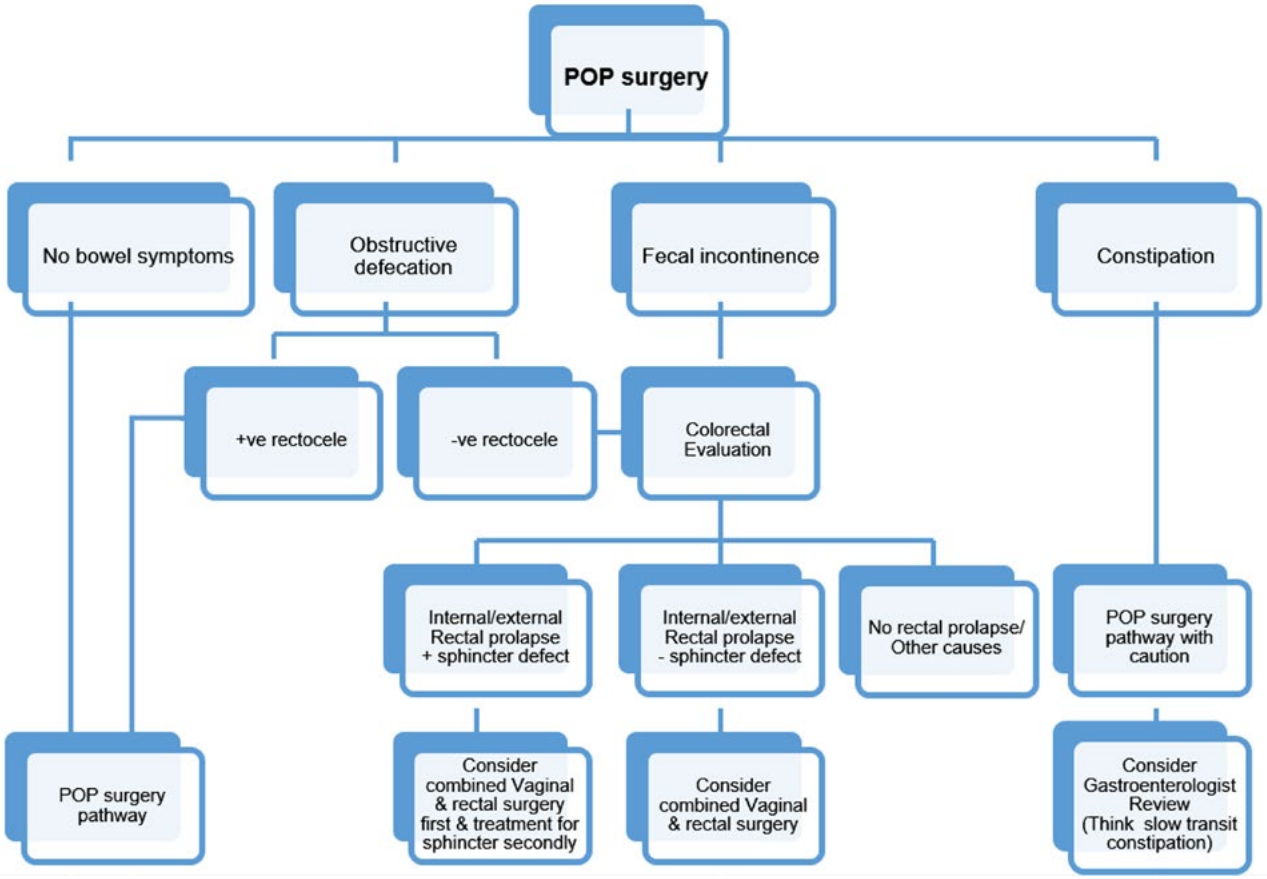

Figure 4. Prolapse surgery pathway and coexistent bowel symptoms.

CONCLUSION

Level one and two evidence suggest midline plication posterior repair without levatorplasty has superior objective outcomes as compared to site-specific posterior repair. (GoR B)

Higher dyspareunia rate is reported when levatorplasty is performed. (GoR C)

Transvaginal approach is superior to the transanal approach for repair of posterior wall prolapse. (GoR A)

To date no study has shown any benefit to graft or mesh overlay or augmentation of a suture repair for posterior vaginal wall prolapse. (GoR B)

While modified abdominal sacrocolpopexy results have been reported, data on how these results would compare to traditional transvaginal repair of posterior vaginal wall prolapse is lacking.

The data comparing Delorme's procedure and VMR for external rectal prolapse are conflicting with a single RCT demonstrating no statistical difference, while level 3 data is supportive of VMR performed laparoscopically or robotically, with low rates of recurrent rectal prolapse and improved rates of faecal incontinence and constipation. (GoR D)

VMR appears superior to other abdominal rectopexies (posterior mesh rectopexy, Ripstein, Orr-Loygue) with different rectal mobilisations to treat ERP in terms of functional outcome. (GoE C)

LoE 3 supports ventral rectopexy for Oxford grade 3-4 internal rectal prolapse. The data is not conclusive regarding graft material or route of surgery. (GoR C)

No data demonstrates ventral rectopexy with or without graft attachment to the posterior vaginal wall is effective in management of rectocele. (GoR D)

Limited level three evidence suggest that patients with combined rectal and vaginal prolapse benefit from colorectal surgeons and urogynaecologist collaborating closely. (GoR C)

VII. SURGERY FOR PELVIC ORGAN PROLAPSE AND BLADDER FUNCTION

Patients with POP often present with bladder symptoms like urinary incontinence or voiding difficulties: In women with stage II POP about 55% have concurrent SUI. This prevalence decreases with increasing POP stages to 33% in women with stage IV POP (458) and proves that preoperatively, many women with advanced POP do not experience SUI. However, if the prolapse is reduced

digitally or with the help of a pessary, sponge holder or speculum, SUI might be demonstrated in 10 to 80%.(459-462) This type of SUI, which is demonstrable with the prolapse reduced in otherwise continent women, is termed occult, masked or latent SUI. The importance of this finding remains ambiguous (463): the test itself is not optimal (463) as it does not necessarily mimic prolapse surgery and may obstruct or put undue tension on the urethra. Although different techniques to reduce the prolapse have been described, a gold-standard has not been established.(462,463) Neither the speculum nor the pessary test to reduce the prolapse had acceptable positive predictive values to identify women in need of a concomitant continence procedure. The negative predictive values however were 92.5% (95%CI 90.3–1.00) and 91.1% (95%CI 88.5–99.7), respectively. Therefore, women with preoperatively negative tests for occult SUI are at low risk to develop SUI postoperatively.(462,464) After POP surgery, women might experience new SUI because the operation for POP unkinked the previously obstructed urethra.(465,466) The term de novo stress urinary incontinence is used to describe SUI that develops following surgical correction of the prolapse, amongst women who were continent prior to surgery.

If women remained continent during pessary insertion for 2 months prior to POP surgery, most of them (84%) continued to be continent postoperatively.(467) The number needed to treat was 11. The authors concluded that overtreatment was avoided by this longer-term pessary test.(467) Such an “extended pessary trial” might be very helpful counselling women regarding concomitant continence procedures.(468) A further method to expose occult SUI was described by Song et al.(469) They performed a standard 1-hour-pad-test after pessary fitting. After vaginal POP repair 22/45 women (49%) had new SUI compared to only 30/161 (19%) women who did not have occult SUI preoperatively. The cut-off point was calculated at 1.9 g.(469)

In a secondary analysis of the CARE trial the authors revealed that a more distal preoperative POPQ-point Ba was associated with a higher incidence of postoperative de novo SUI.(470)

One third of women with stage II or more POP experience difficulties emptying the bladder.(458) Reducing the prolapse during preoperative urodynamics may restore normal voiding function.(471) Voiding difficulties might disappear postoperatively because the obstruction caused by the prolapse has been corrected.(471) In contrast, they might develop because of kinking of the urethra due the surgical technique.

Urinary symptoms belong to the patient-centred outcome measures after POP surgery. Accordingly, bladder symptoms including persistent or de novo stress and urge urinary incontinence as well as voiding symptoms should be discussed with the patient when counselling for a POP operation. Should women with or without accompanying SUI and POP receive an additional continence procedure when the prolapse is repaired? Which prolapse operation would be best to prevent de novo or persisting symptomatic postoperative SUI? This section of the chapter assesses the available evidence regarding the effect of POP surgery on bladder function including stress urinary incontinence, overactive bladder and voiding dysfunction. Fig. 5 summarises data from randomised, prospective and retrospective studies. They were included if they clearly described preoperative examinations including testing for occult SUI and adequately analysed data to fit the categories of stress incontinent women and continent women with and without occult SUI.

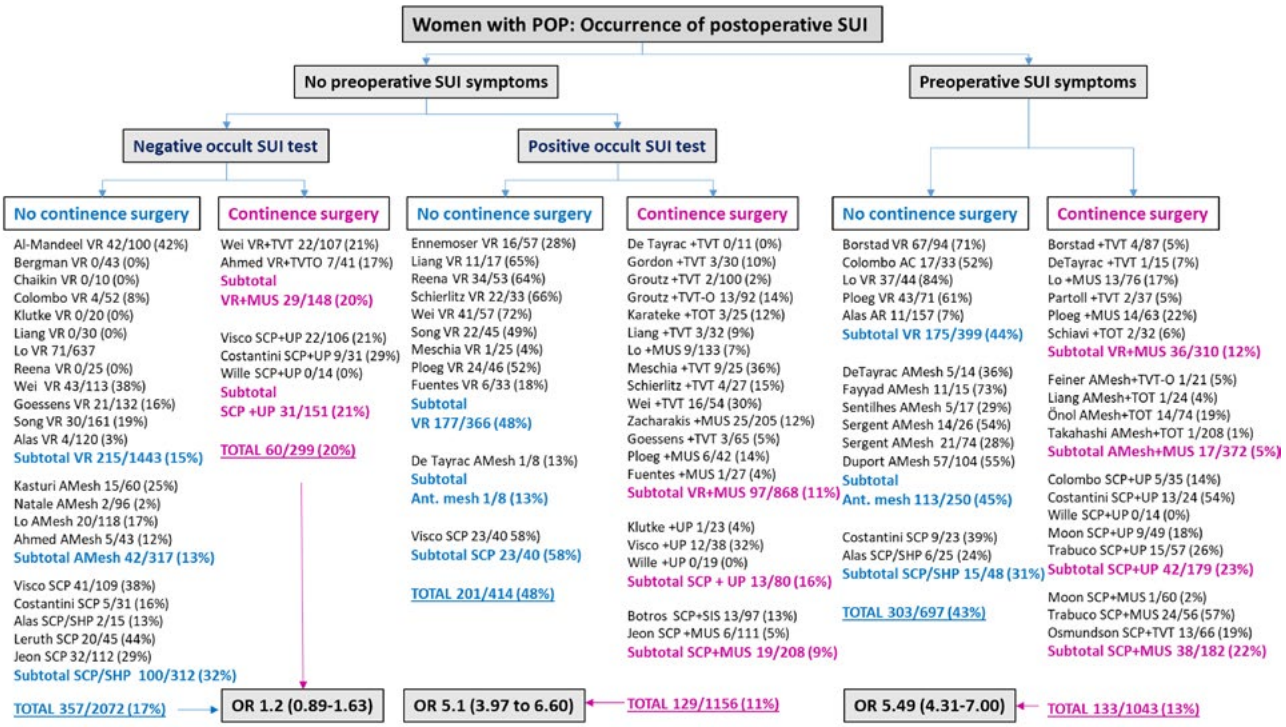

Figure 5. Postoperative SUI rates after POP surgery with and without continence procedures based on preoperative SUI symptoms and presence of occult SUI. *(AC=anterior colporrhaphy, VR= vaginal repairs, AMesh=anterior mesh, TVT=tension-free vaginal tape, TVT-O=tension-free vaginal tape-transobturator, TOT=transobturator tape, MUS=mid-urethral sling, UP=urethropexy, SCP=sacrocolpopexy, SHP=sacrohysteropexy)*

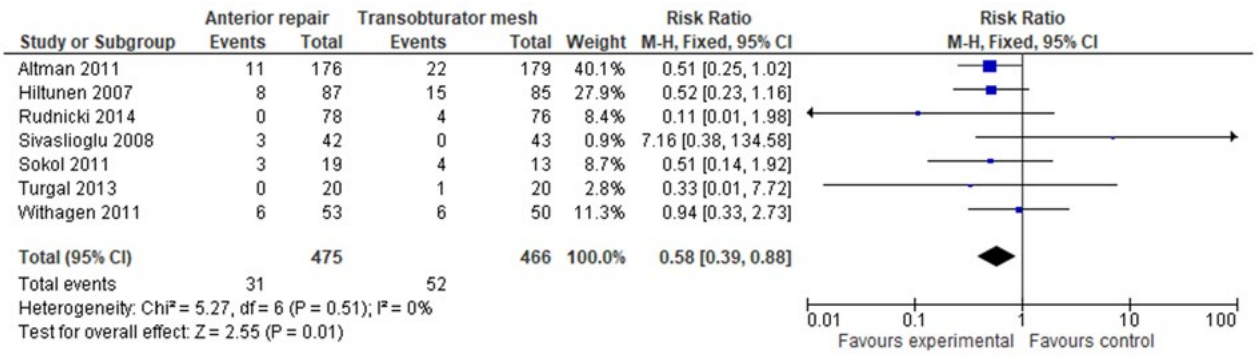

Figure 6. De novo SUI: Forrest plot of seven RCT´s comparing anterior repair and transoburator mesh repairs.

1. CONTINENT WOMEN UNDERGOING POP SURGERY

In women undergoing POP surgery without preoperative SUI symptoms but unclear occult SUI testing, de novo SUI was detected after vaginal POP repairs in 37/550 (7%) women in nine randomised controlled trials (RCT) (125,173,472-478) and in 13/189 women (7%) in 6 non-RCTs (459, 462, 479-482). After armed anterior mesh procedures the de novo SUI rate was significantly higher at 14% (212/1475; p=0.0045, chi-square; OR 2.31, 95% CI 1.68 to 3.19) with a rate of 16% (110/708) in nine RCT arms, (125, 173, 472-476, 483, 484) and 13% (102/767) in 12 prospective or retrospective trials.(485-493)

Seven RCT´s directly compared anterior colporrhaphy and transobturator mesh procedures (mesh kits or self-fashioned) in continent women and reported 12-months results.(125,173,472-475,494) Anterior repair significantly decreased the risk of de novo SUI (RR 0.58, 95%CI 0.39, 0.88; Fig. 6).

The 3-year follow-up results of two RCTs (132,473) corroborate the 12 months findings: 24/144 (17%) versus 13/145 (9%) women developed SUI after anterior mesh versus native tissue repair (RR 1.88, 95%CI 1.01-3.49).(121,132,494) Similar rates of de novo SUI occurred if the anterior compartment prolapse was repaired using a polypropylene transobturator mesh in 2/96 (2%) or a porcine dermis graft 1% (1/94).(163)

New SUI was significantly more common after sacrospinous fixation and vaginal repairs compared with abdominal sacral colpopexy (8/24, 33% versus 2/22, 9% in a single RCT),(66) however, in the sacral colpopexy group some women received paravaginal repairs which may be effective in limiting de novo SUI postoperatively. One trial considered concomitant sacrospinous fixation as a risk factor for de novo OAB.(495)

Although the risk of developing SUI after POP surgery without a concomitant continence procedures is not higher for continent women without occult SUI (357/2072; 17%) (163,459,463,467,469,477,478,480-482,484,496-504) compared to POP surgery with a continence procedure (60/299; 20%), (463,484,498,505,506) there are differences between surgical approaches as displayed in Fig. 5. Sacrocolpopexy alone significantly increases the risk for de novo SUI (100/312; 32%) compared with vaginal repairs (215/1443, 15%; OR 2.92, 95%CI 0.47-1.11) and vaginal anterior mesh procedures (42/317, 13%; OR z3.34, 95%CI 2.22-5.03).

Summarising all studies assessing de novo SUI rates in continent women with negative testing for occult SUI who underwent sacrocolpopexy or sacrohysteropexy, 100/312 (32%) developed SUI (Fig. 5) (463, 499, 503-505) compared to 31/151 (21%) with an additional urethropexy (OR 1.98; 95 % CI: 1.25 to 3.13).

In the large multicentre randomised controlled CARE trial (Colpopexy and urinary reduction efforts), preoperatively continent women were randomly allocated to undergo sacral colpopexy with (n=157) or without Burch colposuspension (n=165). Brubaker et al demonstrated at 2 years that an additional Burch colposuspension significantly reduced the risk for de novo SUI. Subjective SUI was reported by 38/147 (26%) after additional Burch colposuspension and by 63/155 women (41%) after sacrocolpopexy alone. However, objective testing yielded similar findings in the two groups: 11/116 (9%) and 9/134 women (7%), respectively, demonstrated SUI. The study was terminated prematurely because of the high postoperative SUI rate in women who did not receive concomitant Burch colposuspension and as result of early termination was underpowered. Unfortunately, surgery was only standardised for colposuspension but neither for the paravaginal repair nor for sacral colpopexy with significant variations in use of suture type and graft materials.(67,507) After a follow up of 8 years, Costantini et al in another smaller RCT reported contrary results with 9/31 women (29%) developing SUI after additional Burch colposuspension compared to 5/31 (16%) after sacrocolpopexy alone.(502, 505) A meta-analysis using a random-effects model summarises these two RCT´s with results after more than 12 months (505, 507) According to this model, continent women do not benefit from prophylactic Burch colposuspension when undergoing sacral colpopexy (RR 1.41, 95%CI 0.24-8.21)

De novo SUI is clearly disappointing to women and a validated risk calculator has been developed “The Model Predicting De Novo Stress Urinary Incontinence in Women Undergoing Pelvic Organ Prolapse Surgery” (https://riskcalc.org/FemalePelvicMedicineandReconstructiveSurgery) . It is based on the OPUS and CUPIDO randomised controlled trials evaluating vaginal surgery with or without a mid-urethral sling in women with and without SUI and POP. The model takes into account age, vaginal birth, BMI, diabetes, OAB and preoperative stress test.(508,509) On external validation the accuracy of this model in predicting de novo SUI after prolapse surgery was only slightly higher than that achieved with flipping a

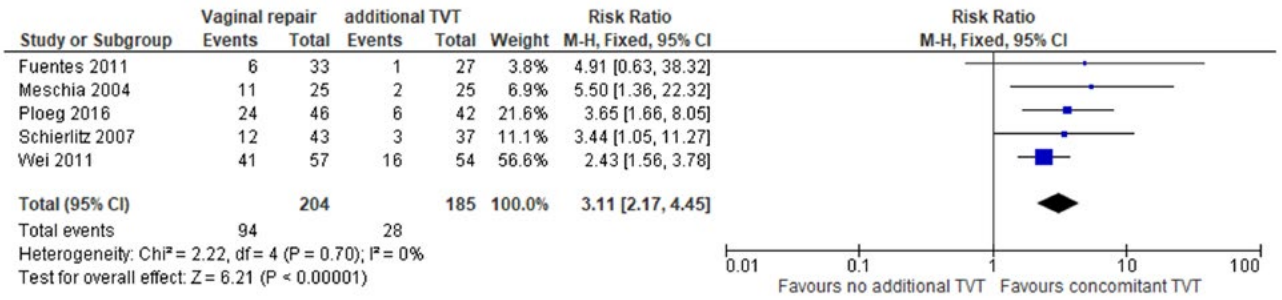

Figure 7: An additional mid-urethral sling at the time of vaginal prolapse repairs in women with occult SUI significantly reduces the risk of new postoperative symptomatic SUI.

coin with a concordance). an index of 0.57; 95% CI 0.46-0.67, P=.048).(509)

2. WOMEN WITH POP AND OCCULT SUI

Women with preoperative occult SUI benefit from the addition of continence surgery to their POP surgery. Five randomised trials assessed postoperative SUI rates in women who were symptomatically dry preoperatively but had a positive stress test with the prolapse reduced.(510-514) With a mid-urethral sling in addition to vaginal prolapse repairs, significantly fewer women complained of SUI (28/185, 15% versus 94/204, 46%; chi-square P<0.001). The meta-analysis of these five trials calculated that a concomitant MUS significantly increased postoperative SUI rates (RR 3.11, 95%CI 2.17-4.45; Fig. 7).

If non-randomised studies are included, the meta-analyses corroborate these findings: In general, a concomitant continence procedure (463, 467, 481, 482, 497, 498, 504, 506, 510, 512-521) improves postoperative SUI rates in women with POP and occult SUI compared to POP surgery alone (459, 463, 469, 482, 498, 510, 512-515, 522) (OR 5.1, 95%CI 3.97 to 6.60; Fig. 4). A concomitant urethropexy (463, 481, 506) at the time of sacrocolpopexy decreases the risk of postoperative SUI (OR 0.14, 95%CI 0.06-0.34) which is also true for a concomitant MUS (504, 521) (OR 0.07, 95%CI 0.03-0.16).

2.1. Women with SUI and POP

Colombo et al (105) compared Burch colposuspension and anterior repair for the treatment of women with anterior vaginal wall prolapse and SUI. While women benefited more from Burch colposuspension with regards to SUI (cure of SUI 30/35, 86% versus 17/33, 52%), anterior repair better corrected the anterior prolapse (cure of cystocele 23/35 versus 32/33).(105) Most urogynaecologists would deem a Burch colposuspension an operation for SUI and not necessarily for anterior vaginal wall prolapse and an anterior repair would be considered for POP rather than for SUI.

Two randomised trials compared vaginal POP repairs with and without an additional MUS in incontinent women.(523,524) As expected, the concurrent continence procedure significantly reduced postoperative SUI rates (RR 0.30, 95%CI 0.19, 0.48). Whether a mid-urethral tape (TVT) is inserted concomitantly or after three months did not result in significantly different success rates based on an “on-treatment” analysis of Borstad et al (83/87, 95% versus 47/53, 89% three months later).(524) Twenty-seven/94 (29%) women were cured of SUI after prolapse surgery alone and did not receive a TVT three months later.(524) As a concomitant MUS represents an additional risk and may not be necessary in a significant number of women, a staged procedure might be considered and adequate counselling appears paramount.

Overall, in women with POP and SUI, compared to POP surgery without a continence procedure, (486,488,489,497,499,512,515,524-528) a concomitant continence procedure increases postoperative SUI cure rates (105,487,490,491,497,506,512,515,524,528-534) (OR 5.49, 95% CI 4.31-7.00; Fig. 5). This was particularly evident for vaginal native tissue repairs with or without MUS (44% versus 12%; OR 5.95, 95% CI 3.99-8.87) and anterior vaginal mesh procedures with or without MUS (45% versus 5%; OR 17.2, 95%CI 9.97-29.75).

In the meta-analysis including non-randomised studies (Fig. 5), concomitant Burch colposuspension or urethropexy at the time or sacrocolpopexy did not significantly reduce postoperative SUI rates in women with POP and SUI (15/48, 31% versus 42/179, 23%; OR 1.48, 95%CI 0.73-2.99). This also applied to MUS and sacrocolpopexy (38/182, 22%; OR 1.65, 95%CI 0.78-3.52).(532-535) One retrospective trial assessed the effect of fascial sling, retropubic or transobturator mid-urethral tapes inserted at the time of abdominal sacral colpopexy (536): The transobturator sling was inferior with an SUI cure rate of 67% in comparison to 84% and 83%, respectively.

It remains unclear why an additional urethropexy at the time of sacrocolpopexy proved beneficial in continent women and not in women with POP and SUI. Based upon the available evidence Fig. 8 represents a decision flow analysis of women undergoing POP surgery with and without SUI.

3. OVERACTIVE BLADDER SYMPTOMS

OAB symptoms may be associated with POP (458) and prolapse surgery may cure or improve OAB but it may also result in new OAB symptoms. The Cochrane review on the surgical management of POP in women with or without incontinence (494) calculated that de novo overactive bladder symptoms developed in 71 of 221 women (32%) undergoing prolapse surgery.

The reported cumulative rate of de novo OAB in women who underwent a transobturator anterior mesh procedure in non-RCTs is 13% (90/712), (483,486-488,491,527,531,537,538) whereas it is 10% (7/71) in the few studies reporting data after anterior repair with or without a mid-urethral tape.(510,539) After sacrocolpopexy with Burch colposuspension de novo OAB occurred in 12/83 (14%) (505, 532) and 2/60 (3%) after sacrocolpopexy with a MUS.(532)

OAB seems to resolve in approximately half of women after any POP operation (259/525, 49%).(495, 514, 527, 533, 539, 540) In a large prospective Finish cohort (n=2933: 81% native tissue repair, 12% vaginal mesh, 7% abdominal mesh with those undergoing concomitant continence surgery excluded) preoperative OAB was identified in 40% and decreased to 18% at 2 years. Reduction in preoperative OAB was more apparent after anterior/apical interventions than posterior compartment surgeries. Preoperative medical treatment of OAB was utilised in 3.3% and vaginal or systemic oestrogen in 82%. De novo OAB occurred in 1-3% and the study methodology did not allow for analysis of associated treatments of OAB symptoms.(541)

Overall, there is wide variation in the rate of de novo OAB (2-32%) after prolapse surgery which may be impacted by undisclosed rates of treatment instigated.

4. URINARY VOIDING DYSFUNCTION

The Cochrane review (494) noted new voiding dysfunction in 57 of 456 (12%) women in seven randomised trials with various prolapse surgeries with or without continence procedures. (105,125,474,505,528,533,542) However, significant heterogeneity exists in defining and reporting urinary voiding problems so a meaningful meta-analysis was not able to be performed and most voiding difficulties are transient.

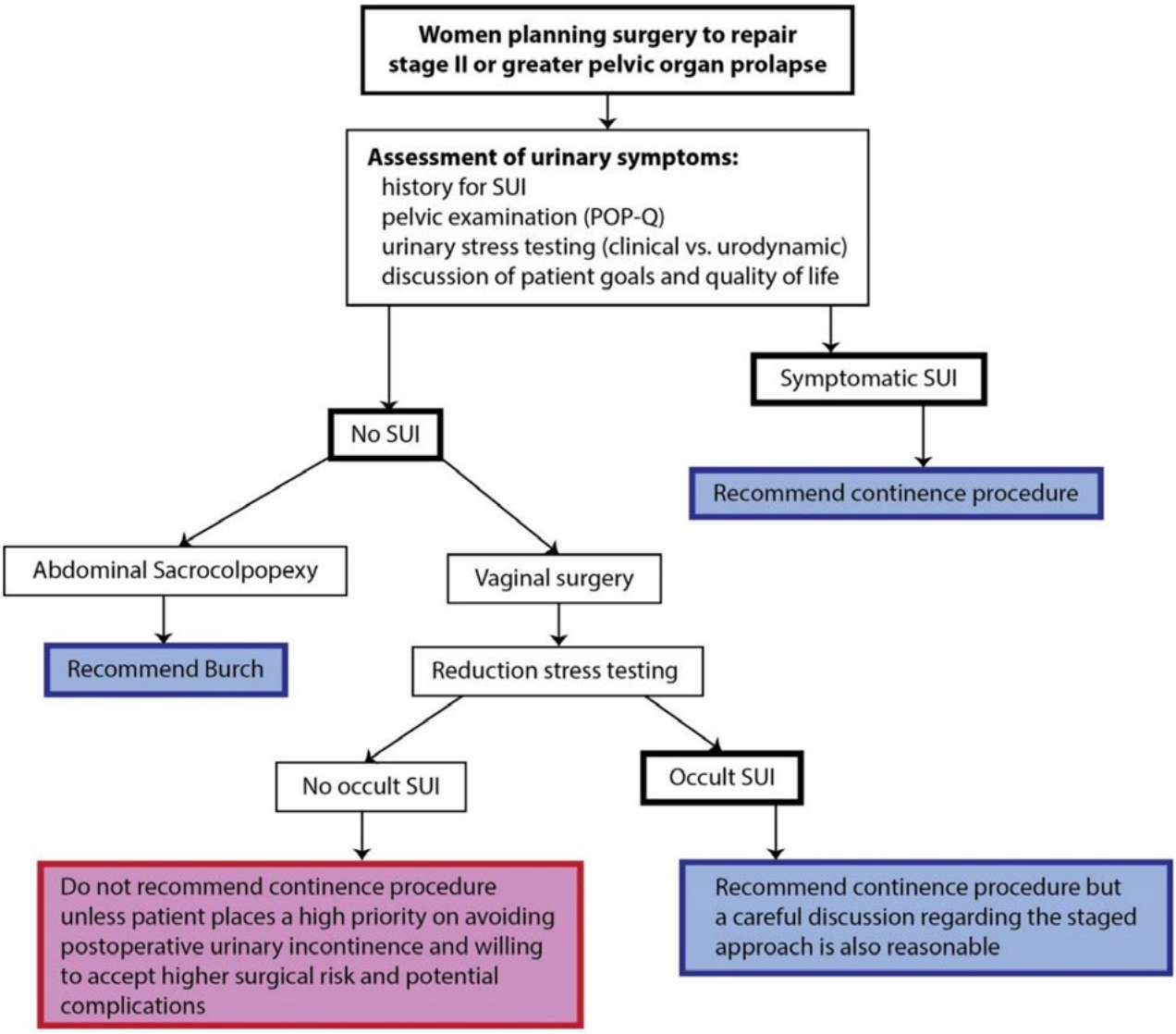

Figure 8. Decision making flow chart for women undergoing prolapse surgery with and without SUI.

After anterior repair, voiding dysfunction ranges from 0% to 37%. (105,150,156,173,510,543)

Anterior repair with or without concomitant vaginal POP surgery resulted in postvoid residuals exceeding 150 ml in 27/126 (21%) in an RCT comparing transurethral and suprapubic catheterisation. (543) After anterior mesh repair, voiding difficulties occur between 5% and 42%.(66,173,487,544-547)

One study looked at postoperative urinary retention defined as the need to discharge the patient with an indwelling catheter because of a failed trial of void.(545) Voiding dysfunction ranged from 34% (10/29) after isolated anterior mesh repair to 42% (30/71) cases after combined anterior and posterior repairs. After isolated posterior repair 8/42 (19%) developed urinary retention. At the 3-months follow up, there were no more voiding complaints.(545)

If there are postoperative voiding problems with residuals exceeding 150 ml, clean intermittent catheterisation is superior to an indwelling catheter for three days with regards to bacteriuria, urinary tract infection and length of required catheterisation according to one RCT(548) and intermittent transurethral catheterisation is equivalent to a suprapubic catheter regime.(543) Insertion of a suprapubic catheter however resulted in more related complications like loss and blockage of the catheter and haematuria.(543) Another RCT (549) reported on the duration of postoperative urethral catheterisation between two and four days after anterior repair and found no differences in voiding dysfunction. This was confirmed by an RCT comparing two and five days of indwelling catheter placement. Longer hospital stay and more urinary tract infections were associated with the five days protocol.(550) Patients do not seem to benefit from postoperative urethral catheterisation beyond two days.(549,550)

Whether preoperative voiding dysfunction resolves after POP repair is rarely adequately described. Lo et al reported that 37/380 women (10%) continued to have voiding dysfunction after native tissue vaginal POP surgery whereas it developed in only 1%. Expectedly, concomitant MUS increased the risk of postoperative voiding dysfunction (OR 3.12, 95 % CI 1.79 - 5.46, $p < 0.001$) (551). Similarly, voiding dysfunction improved in most women after vaginal mesh repairs (40% preop versus 1% postop).(552)

CONCLUSIONS

- Continent women with negative testing for occult SUI do not require a concurrent prophylactic continence procedure. (GoR B)
- In continent women with negative occult SUI testing undergoing sacrocolpopexy, an additional Burch colposuspension may reduce postoperative SUI. (GoR C)
- Anterior mesh repair increases the risk for SUI as compared to anterior repair without mesh in continent women. (GoR B)
- Continent women with occult SUI benefit from POP surgery with concomitant continence procedures as compared to POP surgery without continence intervention. (GoR B)
- In women with POP and SUI, a concomitant continence procedure increases postoperative SUI cure rates. (GoR A)
- Preoperative OAB (40%) resolves in approximately 50% post prolapse surgery although the impact of concomitant non- surgical treatment on this date has not been clarified. (GoR C)
- The rate of de novo OAB varies widely (2-32%). (GoR C)
- Rates of Urinary retention following POP surgery varies from 0-34% and is nearly always temporary. (GoR C)
- Pre-operative urinary retention resolves in as many as 90% post prolapse surgery. (GoR C)

VIII. PELVIC ORGAN PROLAPSE SURGERY AND SEXUAL FUNCTION

The prevalence of sexual dysfunction in patients with pelvic organ prolapse (POP) and other pelvic floor disorders is high, approximately 64%.(553) Therefore, changes to sexual function (SF) are important to women considering prolapse surgery. When women with POP were asked to prioritise the importance of outcomes after surgery, they ranked improvement in sexual function just below resolution of bulge symptoms and improvement in physical function.(554) Other qualitative studies in a urogynaecologic population show that worsening sexual function after surgery is viewed by women as a severe adverse event.(555)

Prior reviews have shown that overall sexual function either improves or remains unchanged after POP surgery.(556-558) Dyspareunia can be reported in clinical trials in a variety of ways, in that it can be due pain with intercourse prior to surgery, postoperative, persistent, or de novo. Many randomised trials on POP surgery report overall sexual function based on validated sexual function questionnaires and dyspareunia, but there is a lack of data on sexual function domains such as: sexual desire, arousal, lubrication, and orgasm. It is not clear how POP surgeries affect these other domains of sexual function and further research in this area is warranted.

It is important to assess sexual function in patients undergoing reconstructive surgery for prolapse in general practice and in research trials. According to the IUGA-ICS Joint Report on the Terminology and Assessment of Sexual Health of Women with Pelvic Floor Disorders, trials should report both on preoperative AND postoperative outcomes for: sexual activity, dyspareunia, and validated sexual function questionnaire scores.(559) Few randomised POP studies report on all these measures, and the overall quality of sexual function outcome reporting is low (Table 26-29).

To measure sexual function, validated questionnaires on sexual function are necessary. Some validated quality of life and symptom questionnaires are inclusive of sexual function, but there are several sexual function questionnaires that are specific to a urogynaecologic patient population. They include the Pelvic Organ Prolapse/ Incontinence Sexual Questionnaire (PISQ), PISQ-12 short form, and PISQ-IR.(560) The PISQ-12 is the most commonly used sexual function questionnaire in prolapse randomised trials. The Female Sexual Function Index (FSFI) is another questionnaire that is commonly used in clinical research on female sexual function, and is commonly utilised, but is not specific to women with prolapse.(561) Unfortunately, in nearly all of the trials that report sexual function post-surgical intervention the primary outcome is not sexual function and as such the trials are frequently under-powered to assess

this outcome. So meta-analysis of data is required to obtain meaningful sexual function results and this is performed understanding that definitions of dyspareunia and evaluation of sexual function may vary creating challenges in data interpretation.

1. SEXUAL FUNCTION AFTER PROLAPSE SURGERY WITH NATIVE TISSUE REPAIRS

Overall, sexual function usually improves or remains unchanged after prolapse surgery with native tissue repairs. Since many vaginal pelvic reconstructive surgeries utilise a combination of apical suspension native tissue repairs and repairs in other vaginal compartments, it is difficult to separate these repairs individually to analyse effects of sexual function. The most level I data in the prolapse surgical literature involves comparing transvaginal synthetic mesh to a variety of native tissue repairs, most commonly in the anterior compartment.

There are several RCTs that look at sexual function in women after sacrospinous ligament fixations (SSLF), and all show an improvement in overall sexual function scores based on PISQ-12 scores. (216, 217, 562) Similar to this, surgical trials for uterosacral ligaments suspensions show improvement in overall sexual function, as all PISQ-12 scores increased postoperatively.(216,217,323)

Posterior colporrhaphy/repairs previously involved levator-ani plication which is associated with high rates of dyspareunia.(377) However, modern posterior repairs avoid this step while still plicating the rectovaginal muscularis. Two randomised trials look specifically at posterior repairs, and although total postoperative dyspareunia ranges from 20-27%, this is still lower than dyspareunia preoperatively in the same patient population.(392,393) It would be more important to examine the rate of de novo dyspareunia in the these RCTs, but neither trials report on this. Another RCT comparing women undergoing posterior repairs with standard postoperative recovery to women with posterior repairs using postoperative vaginal dilators, showed a de novo dyspareunia rate in the control group to be 3.8% at 6 months.(563) As for overall sexual function scores, one RCT reported PISQ-12 scores remained similar while the other reported significant improvement after posterior repairs.(392,393)

2. SEXUAL FUNCTION AFTER PROLAPSE SURGERY WITH MESH

Although transvaginal synthetic mesh has been controversial and banned in several countries internationally, significant quality data is available regarding changes in sexual function. Meta-analysis of sexual function outcomes from 16 RCTs with 24 publications evaluating 3243 women with follow-up ranging from 6-84 months, comparing transvaginal mesh and native tissue repairs are summarised in Table 26. While, based on 16 studies included, the rates of dyspareunia (11.2 versus 9.9%, RR 1.13 95%CI 0.84, 1.51 P=0.42) and de novo dyspareunia (7.1 versus 6.5% RR 1.1 95%CI 0.68,1.77 p=0.61) were similar between the groups post intervention, the sexual function outcomes based upon PISQ scores were significantly higher in the non-mesh group than after the transvaginal mesh interventions as seen in Forrest plot Figure 9. These results suggest that while the rate of dyspareunia, new and or persisting is similar after vaginal repair with or without transvaginal mesh that sexuality and sexual function more generally as measured in PISQ is better after vaginal repairs without mesh than in those with transvaginal mesh. Risk factors for pelvic pain and dyspareunia after TV mesh surgery includes younger age, fibromyalgia, poorer physical health, and somatisation.(564)

Details on 10 RCTs evaluating sexual function in 1462 women comparing vaginal biological grafts to native tissue repairs are listed in Table 27. There was no difference between biological grafts and native tissue repairs in the rates of dyspareunia (11.4 versus 10% RR 1.1 95% Ci 0.7,1.6 p=0.68) and de novo dyspareunia (2.7 versus 3.0% RR 0.9 95% CI 0.2,5.2 p=0.9). In four RCT's comparing anterior colporrhaphy to porcine skin graft or porcine small intestine submucosa mesh, no differences were found in dyspareunia and improvement on PISQ-12 scores.(156,565-567)

For mesh in the posterior compartment specifically, fewer RCT's were performed comparing native tissue repair to mesh repair. Paraiso et al compared three techniques (posterior colporrhaphy, site-specific repair and use of porcine small intestine sub mucosa). (393) No differences in sexual outcome were found between the groups and PISQ scores improved after surgery in all three groups.

3. SEXUAL FUNCTION AFTER PROLAPSE SURGERY WITH SACROCOLPOPEXY

Meta-analysis of three RCTs evaluating 325 women comparing abdominal sacrocolpopexy to native tissue repairs are listed in Table 28 and demonstrated a non-significantly lower rate of dyspareunia (17.5 versus 28.6% RR 0.61 95% CI 0.3, 1.4 p=0.23) and de novo dyspareunia (4.8 versus 8.1%, RR 0.6 95% CI 0.1, 3.3 p=0.66) after sacrocolpopexy as compared to native tissue repairs.

Table 29 is a meta-analysis of data on sexual function from 5 RCTs evaluating 514 women ranging from 6 to 48 months between transvaginal mesh and sacrocolpopexy for apical prolapse. The results demonstrate a higher rate of dyspareunia (30 versus 14% RR 2.1 95% CI 1.1, 4.2 p=0.04) and a non-significantly higher rate de novo dyspareunia (19 versus 7% RR 2.95 95% CI 0.82, 10.6 p=0.1) following transvaginal mesh as compared to sacrocolpopexy.

Culligan and Salamon et al reported laparoscopic sacrocolpopexy procedures have a positive impact on sexual function. In this trial comparing mesh to biologic grafts, laparoscopic sacrocolpopexy with mesh showed dyspareunia decreased from 51% preoperatively to 20% postoperatively.(568, 569) Another trial by Maher et al, concluded that sexual function remains similar after sacrocolpopexy, although dyspareunia rates tend to decrease.(66,570) De novo dyspareunia ranges 5-8%.(66,569,571)

CONCLUSION

- While synthetic transvaginal mesh and non-mesh vaginal repairs have similar rates of de novo and total dyspareunia the transvaginal mesh repair has poorer sexual function as measured by PISQ when compared to non-mesh repairs. (GoR B)
- Synthetic transvaginal mesh has higher rate of total dyspareunia when compared to sacrocolpopexy (GoR B)

- When comparing vaginal biologic grafts to vaginal native tissue repairs, there are similar decreases in postoperative dyspareunia and similar changes in sexual function (GoR B)
- Sexual activity preoperatively in patients undergoing POP reconstructive surgery ranges 42-65%, while postoperative sexual activity ranges 32-62%. (GoR C)
- De novo dyspareunia rates for native tissue vaginal repair and sacrocolpopexy range from 2-8% (GoR C)
- Total dyspareunia rates generally decrease following native tissue repairs and sacrocolpopexy from 15-30% preoperatively to 8-20% postoperatively (GoR C)
- It is essential to use validated questionnaires measuring sexual function in women before and after prolapse surgery. We also recommend reporting sexual activity and dyspareunia rates de novo, pre-, and post-intervention in all patients. (GoR C)

Table 26: Sexual function Data from RCT's Comparing Transvaginal Mesh to Native Tissue Repairs

RCT	Sexual Activity		De novo dyspareunia		Total dyspareunia		PISQ-12 Score or other SF questionnaire	
	TVM	NT	TVM	NT	TVM	NT	TVM	NT
Altman 2011 (572)	Pre 80/200 Post MD	Pre 73/189 Postop MD	-	-	Pre MD Post 8/110	Pre MD Post 2/101	Pre 32. (7.2) Post 35(34-36)	Pre 33.1 (6.7) Post 35 (34 -36)
Vollebregt 2011 (122) (573)	Pre 32/50	Preop 31/48	3/20	2/21	MD	MD	FSFI Pre 20.3 (12) Change 1.5	FSFI Pre16.22 Change 4.51
Sivaslioglu 2008 (474)	MD	MD	2/43	0/42	MD	MD	MD	MD
Ngyuyen 2008 (119)	Pre 27/37 Post 23/37	Pre 28/38 Post 26/37	2/23	4/26	Pre MD- Post 6/27	Pre MD- Post 6/28	Pre 33 (3) Post 34 (6)	Pre 32 (4) Post 33 (3)
Sokol 2012 (574) 1 yr	Pre op 14/25	Pre op 11/26	1/11	3/14	Pre 3/17 Post 1/15	Pre 3/18 Post 3/16	Pre 31 (19- 44) Post 34 (27- 44)	Pre 32 (16 to 42) Post 35 (29 to 45)
Gutman (575) 3yr	Post 13/25	Post 14/26	3/12	1/11	Post 8/12	Post 6/10		
Rudnicki 2014 (476)1yr	Pre MD Post 36/76	Pre MD Post 48/78	2/76	0/76	-	-	Pre MD Post 11.9 (5.5)	Pre op - Post op 13.1 (5.6)
Rudnick (132)(3yr	Pre MD Post 23/70	Pre MD Post 39/68	2/70	0/68				
El-Nazer 2012 (576)	Pre 17/20 Post 18/20	Pre 18/20 Post 17/20	0/18	1/17	Prep 7/17 Post 7/18	Pre 8/18 Post 8/17	-	-
deTayrac 2013 (577) 1yr Allegre 2019 (128)(7yr)	Pre 28/75 Post 31/75	Pre 21/72 Post 28/72	3/13	1/14	Pre 10/28 Post 6/22) Post 1/39	Pre 3/21 Post 5/24 Post 2/36	Pre 28.5(6.5) Post 33.3 (5.6) Post 31 (5.3*)	Pre 30.3 (7.5) Post 34.5 (5.9) Post 35.6 (5.8*)
Lamblin 2014 (131)	Pre 15/33 Post18/33	Pre 12/35 Post 15/34	1/34	1/33	-	-	-	-
Delroy 2013 (126) Dias 2016 (578)	Pre 21/40 Post 23/40 Pre 21/43 Post MD	Pre 19/39 Post 19/39 Pre 23/43 Post MD	- 2/43	- 4/43	Pre MD– Post 2/21	Pre MD – Post 4/19	-	-
Menefee 2011 (124)	-	-	2/28	3/24	-	-	PISQ change 0 (-28 to 36)	PISQ Change 0 (-32 to 16)
Nieminen 2008 (579) (2 yr) Nieminen 2010 (121) (3 yr)	Pre 49/105 Post 51/105 Post 51/104	Pre 48/97 Post 45/96 Post 44/96	-	-	-	-	-	-
Carey 2009 (580)	Pre 34/69 Post 30/63	Pre 36/70 Post 33/62	5/18	5/12	Pre 11/34 Post 12/30	Pre 20/36 Post 13/33	-	-

RCT	Sexual Activity		De novo dyspareunia		Total dyspareunia		PISQ-12 Score or other SF questionnaire	
	TVM	NT	TVM	NT	TVM	NT	TVM	NT
Withagen 2011.(173) (581) (1 yr) Milani 2018.(174) (7 yr)	Preop 52/93 Postop 53/93 Post 30/66	Pre 49/97 Post 51/97 Post 30/72	3/37	3/29	Pre 13/52 Post 9/53 Post 13/64	Pre 16/49 Post 12/51 Post 12/72	Pre op 35 (5) Post op 34 (6.7) Change 0 (4.2)	Pre op 31.5 (7.2) Post op 34.7 (5.7) Change 2.9 (6.8)
Dos Reis Brandão da Silveira 2015 (582)	Pre 25/88 Post 25/88	Pre 14/81 Post 14/81	-	-	Pre MD- Post 3/88	Pre MD Post 5/81	QS-F Pre22 (12) Post 21.8 (10)	QS-F Pre 30.1 (13.3) Post 22.4 (13.8)
Halaska 2012 (583)	-	-	-	-	Pre MD Post 6/79	Pre MD- Post 2/72	Pre op 30.89 Post op 33.44	Pre op 29.8 Post op 36.53
Svabik 2014 (584)	-	-	-	-	Pre MD Post 2/36	Pre MD Post 1/34	Pre 30.3 (9.52) Post 32.6 (6.26)	Pre 33.1 (6.31) Post 35.6 (5.07)
de Tayrac 2008 (585)	Pre op 8/24 Post op 9/24	Pre op 12/25 Post op -	-	-	-	-	Pre 0.5 (5.9) Post 13.6 (9.3)	Pre 12.5 (5.1) Post 12.5 (9.3)
Damiani 2016 (586)	-	-	4/30	0/59	Pre 5/30 Post 6/30	Pre 12/59 Post 3/59	MD	-MD
Glazener 2016 (587) Primary POP	Pre 148/399 Post 169/360	Pre 152/407 Post 175/360	-	-	Pre 13/197 Post9/173 (12 mo)	Pre 18/217 Post 8/186	ICIQ-VS Pre 22.2 (9.4) Post 7.5 (8.1)	ICIQ-VS Pre 22.1 (9) Post op 7.2 (7.2)
Glazener 2016 (587) Recurrent POP	Pre 26/50 Post 20/41	Pre 16/53 Post 18/45	-	-	Pre 5/32 Post 3/23	Pre 1/22 Post 0/18	ICIQ-VS Pre2 2.2 (9.5) Post 7.9 (8.6)	ICIQ-VS Pre 21.1 (10) Post op 8.3 (7.4)
Glazener 2016 (587) Trial 4 Recurrent POP	Pre 14/41 Post 16/39	Pre op 6/24 Post op 6/20	-	-	Pre 0/20 Post 1/18	Pre 0/8 Post 0/6	ICIQ-VS Pre 23.4 (7.8) Post 5.8 (4.8)	ICIQ-VS Pre 17.5 (9.2) Post 6.7 (6)
Ignjatovic 2010 (588)	-	-	-	-	-	-	FSFI Pre 23 Post 27	FSFI Pre 24 Post 29
Nager et al 2019 (300)	Pre 30/88 Post 26/88	Pre 40/87 Post 31/87	2/57	3/52	Pre 10/26 Post 5/26	Pre 17/37 Post 5/31	Pre op 3 (0.5) Mean change 0.3 (0.1 to 0.5	Pre op 2.9 (0.4) Mean change 0.3 (0.1 to 0.5)
Total*	**Pre op 620/1437 (43.1%) Post op 561/1206 (46.5%)**	**Pre op 586/1408 (41.6%) Post op 539/1154 (46.7%)**	**32/451 (7.1%)**	**30/462 (6.5%)**	**Pre op 77/453 (17%) Post op 86/769 (11.2%)**	**Pre op 98/485 (20.2%) Post op 77/776 (9.9%)**		
	RR 1.0 (0.91,1.09) P=0.92		**RR 1.1 (0.68,1.77) p=0.61**		**RR 1.13 (0.84, 1.51) P=0.42**		**PISQ MD -1.24(-2.11,-0.37)**	

RCT: randomized controlled trial, SF: sexual function, TVM: transvaginal synthetic mesh, NT: vaginal native tissue repairs, Ant: anterior, AR: anterior repair, Pre op: pre-operative, Post op: post-operative,
PR: posterior repair, TVH: total vaginal hysterectomy, USLS: uterosacral ligament suspension, SS: sacrospinous, SSLF: sacrospinous ligament suspension, FSFI: female sexual function index, PISQ: Pelvic organ prolapse/Urinary Incontinence Sexual Questionnaire, QS-F:Sexual Quotient Female Version, ICIQ-VS: International Consultation on Incontinence Questionnaire-Vaginal Symptoms Module. PISQ-IR: PISQ: Pelvic organ prolapse/Urinary Incontinence Sexual Questionnaire- IUGQ Revised
**personnel written communication from Dr deTayrac*

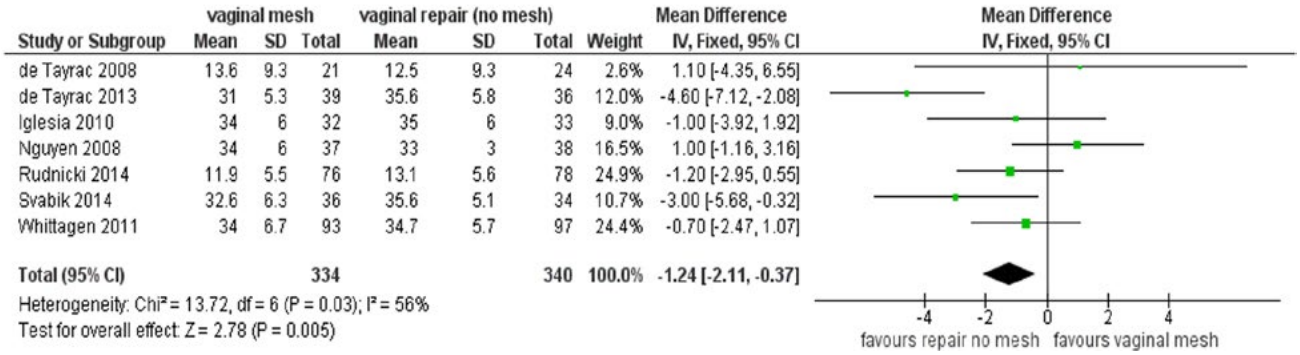

Figure 9. Forrest plot PISQ scores comparing vaginal repairs with and without transvaginal mesh.

Table 27: Sexual Function Data from RCT's Comparing Vaginal Repairs with Biologic Grafts to Vaginal Native Tissue Repairs

RCT	Sexual Activity		De novo dys-pareunia		Total dyspareunia		PISQ-12 Score or other SF questionnaire	
	BG	NT	BG	NT	BG	NT	BG	NT
Paraiso 2006 (393)	Pre 17/32 Post 16/32	Pre 17/37 Post 19/33			Pre 12/32 Post 3/32	Pre 13/37 Post 9/33	Pre 33 (8) Post 37 (5)	Pre 29 (8) Post 36 (5)
Meschia2007 (156)	Pre 12/65 Post MD	Pre 11/74 Post MD -	-	-	Pre MD Post 7/47	Pre MD Post 5/48		
Guerette 2009 (160)	MD	MD	0/20	1/16	Pre MD Post 3/20	Pre MD Post 3/16	Pre 16 Post MD	Pre 13.9 Post MD
Feldner 2010, 2012 (589, 590)	Pre op 23/29 Post op -	Pre op 22/27 Post op -	-	-	Pre MD Post 5/29	Pre MD Post 4/27	FSFI Pre 5.5 (7.2) Post 24.9 (7.5)	FSFI Pre 15.3 (6.8) Post 24.2 (7)
Dahlgren 2011 (565) (57)	Pre 33/69 Post 35/69	Pre 29/64 Post 34/64	-	-	Pre 19/69 Post 6/65	Pre op 9/64 Post op 8/60	-	-
Menefee 2011 (591)	-	-	2/26	3/24	-	-	Change 1 (-35 to 24)	Change 0 (-32 to 16)
Sung 2012 (392)	Pre 50/75 Post MD	Pre 54/75 Post MD	-	-	Pre MD Post 7/56	Pre MD Post 4/57	-	-
Robert 2014 (592)							Pre op 31 (7) Post op 38 (10)	Pre op 33 (8) Post op 38 (8)
Damiani 2016 (586)	-	-	0/28	0/59	Pre op 6/28 Post op 9/28	Pre op 12/59 Post op 3/59	-	-
Glazener 2016 (587) Trial 2	Pre 135/337 Post 152/312	Pre 119/339 Post 138/313	-	-	Pre 21/186 Post 8/165 (	Pre 20/175 Post 9/149	ICIQ-VS Pre 22.8 (9.1) Post 9 (9.1)	ICIQ-VS Pre 21.7 (8.7) Post 7.1 (6.9)
Total*	**Pre op 270/607 (44.5%) Postop 203/413 (49.2%)**	**Pre op 252/484 (52%) Postop 191/410 (46.6%)**	**2/74 (2.7%)**	**3/99 (3%)**	**Pre op 58/315 (18.4%) Post op 48/442 (11.4%)**	**Pre op 54/334 (16.2%) Post op 45/449 (10%)**		
	RR 1.1 (0.91, 1.21) p=0.50)		**RR 0.9 (0.2,5.2) p=0.9**		**RR 1.1 (0.7, 1.6) p=0.68)**		**No difference**	

RCT: randomized controlled trial; BG: biologic graft; NT: native tissue repairs, Ant: Anterior; Post: Posterior; Pre op: preoperative, Post op: postoperative, TV: transvaginal, AR: anterior repair, PR: posterior repair, SIS: small intestine submucosa FSFI: female sexual function index, PISQ: Pelvic organ prolapse/Urinary Incontinence Sexual Questionnaire, ICIQ-VS: International Consultation on Incontinence Questionnaire-Vaginal Symptoms Module

**Totals were calculated on 1 year outcomes. If 1 year outcomes were not reported, the longest follow up reported was used for totals.*

Table 28: Sexual Function Data from RCT's Comparing Sacrocolpopexy to Native Tissue Repairs

RCT	Sexual Activity		De novo dyspareunia		Total dyspareunia		PISQ-12 Score or other SF questionnaire	
	SCP	NT	SCP	NT	SCP	NT	SCP	NT
Maher 2004 (66) Abd SCP vs SSLF	Pre op 29/47 Post op 19/42	Pre op 31/48 Post op 17/37	2/42	3/37	Pre op 9/29 Post op 6/29	Pre op 9/31 Post op 7/31	-	-
Rondini 2015 (323) Abd SCP vs USLS	-	-	-	-	-	-	Pre op 25 Post op 29.7 No change	Pre op 28 Post op 33.4 Improved No difference between groups
Lo 2009 (593) Abd SCP vs SSLF	Pre op – Post op 11/52	Pre op – Post op 18/66	-	-	Pre op – Post op 1/11	Pre op – Post op 7/18	-	-
Total	**Preop 29/47 (61.7%) Post op 30/94 (31.9%)**	**Pre op 31/48 (64.6%) Post op 35/103 (34%)**	**2/42 (4.8%)**	**3/37 (8.1%)**	**Pre op 9/29 (31%) Postop 7/40 (17.5%)**	**Pre op 9/31 (29%) Postop 14/49 (28.6%)**		
	RR 0.94(0.63, 1.40) p=0.76		**RR 0.6 (0.1, 3.3) p=0.66**		**RR 0.61 (0.3, 1.4) p=0.23)**		**No difference**	

RCT: randomized controlled trial, SF: sexual function, SCP: sacrocolpopexy, NT: vaginal native tissue repairs, Abd: abdominal, SSLF: sacrospinous ligament fixation, USLS: uterosacral ligament suspension. Pre op: pre-operative, Post op: post-operative.
**Totals were calculated on 1 year outcomes. If 1 year outcomes were not reported, the longest follow up reported was used for totals.*

Table 29: Sexual Function Data from RCT's Comparing Transvaginal Mesh to Sacrocolpopexy

RCT	Sexual Activity		De novo dyspareunia		Total dyspareunia		PISQ-12 Score or other SF questionnaire	
	TVM	SCP	TVM	SCP	TVM	SCP	TVM	SCP
Maher 2011 (570)	Pre op 18/55 Post op -	Pre op 20/53 Post op -	-	-	Pre op 2/18 Post op -	Pre op 3/20 Post op -	APFQ Sex Pre op 1 (1.7) Post op 1	APFQ Sex Pre op 1.3 (2.1) Post op 0.9 (0)
Lucot 2018 (137)	-	-	-	-	Pre op – Post op 18/61	Pre op – Postop 10/71	FSFI Post 26.7 (25-28)	FSFI Post 27.8 (26-29)
Ow 2018 (594)	Pre 17/39 Post 17/32	Pre 21/43 Post 13/32	-	-	-	-	Pre op 32.4 (6.1) Post 32.8 (6.6)	Pre op 32 (7) Post op 24.9 (4.9)
Bataller 2019 (571)	Pre 37/60 Post 37/58	Pre 43/60 Post 43/58	7/37	3/43	Pre 4/37 Post -	Pre 3/43 Post	ICIQ-SF Change 2.7 (7)	ICIQ-SF Change 2.6 (6)
de Castro 2020 (138)	Pre 19/35 Post-	Pre 15/36 Post op -	-	-	-	-	ICIQ-SF Pre 7.2 (7.7) Post 2.4 (4.6)	ICIQ-SF Pre 7(7.2) Post 1.8 (3.8) I
Total	**Pre 91/189 (48%) Post 54/90 (60%)**	**Pre 99/192 (52%) Post 56/90 (62.2%)**	**7/37 (18.9%)**	**3/43 (7%)**	**Pre op 6/55 (10.9%) Post 18/61 (29.5%)**	**Pre op 6/63 (9.5%) Post op 10/71 (14.1%)**	**No difference between groups**	
	RR 0.96 (0.8, 1.2) p=0.76		**RR 2.95 (0.82, 10.6) p=0.1**		**RR 2.1 (1.1, 4.2) p=0.04**			

RCT: randomized controlled trial, SF: sexual function, TVM: transvaginal mesh, SCP: sacrocolpopexy, ASC: Abdominal sacrocolpopexy, Pre op: pre-operative, Post op: post-operative, APFQ: Australian Pelvic Floor Questionnaire, Ant: anterior, Post: posterior, LSC: laparoscopic sacrocolpopexy, FSFI: female sexual function index, ICIQ-SF: International Consultation on Incontinence Questionnaire
**Totals were calculated on 1 year outcomes. If 1 year outcomes were not reported, the longest follow up reported was used for totals.*

IX. COMPLICATIONS AND METHODS OF PREVENTION

While pelvic reconstructive surgery for genital prolapse, with or without mesh, results in improved prolapse related symptoms and quality of life in most cases (595) (Level 1) complications are inevitable.

A national Scottish database cohort study has been done between 1997 and 2016 on 18 986 women underwent a first single prolapse procedure, 1279 (7%) of which used mesh.(596,597) Compared with non-mesh repair, mesh repair of anterior compartment prolapse was associated with a similar risk of immediate complications (aRR 0.93 [95%CI 0.49-1.79]); an increased risk of further incontinence (aIRR 3.20 [2.06-4.96]) and prolapse surgery (1.69 [1.29-2.20]); and a substantially increased risk of later complications (3.15 [2.46-4.04]). Compared with non-mesh repair, mesh repair of posterior compartment prolapse was associated with a similarly increased risk of repeat prolapse surgery and later complications. No difference in any outcome was observed between vaginal and, separately, abdominal mesh repair of vaginal vault prolapse compared with vaginal non-mesh repair.

Many countries (US, UK, Australia, France) have prohibited access to vaginal meshes due to an unfavourable risk/benefit ratio and a high incidence of mesh-related complications.

On April 16, 2019, the FDA ordered all manufacturers of surgical mesh intended for transvaginal repair of vaginal prolapse to immediately stop selling and distributing their products.(598) The FDA has determined that the manufacturers have not demonstrated reasonable assurance of safety and effectiveness for these devices, which is the premarket standard that now applies to them since the agency reclassified them into class III (high risk) in 2016. Women who have received transvaginal mesh for the surgical repair of pelvic organ prolapse should continue with their follow-up care. There is no need to take additional action if they are satisfied with their surgery and are not having any complications or symptoms. They should notify their health care provider if they have complications or symptoms, including persistent vaginal bleeding or discharge, pelvic or groin pain, or pain with sex.

In 2011, the IUGA (International Urogynecological Association) and the ICS (International Continence Society) published a specific classification of complications related to pelvic reconstructive surgery using prostheses.(80) That classification has been developed to encompass to all possible physical complications involving the use of a prosthesis or graft in a female pelvic floor surgical procedure. Both insertion complications (e.g. trocar related) and healing abnormalities are covered. Whilst this creates a large number of possible complication scenarios, appropriate organisation has still been possible by category (C), time (T) and site (S). A key advantage of a standardised classification is that all parties involved in female pelvic floor surgery will be referring to the same clinical issue. It has been shown in several studies that this classification can significantly add to clarity in reporting mesh related complications,(141, 599, 600) even if training is necessary to optimise inter-observer reliability,(601) which has been criticised by others. (602-604)

Other classification, such as Clavien-Dindo classification, has also been used. (137) In a French multicenter randomised controlled trial on 262 women with cystocele stage ≥2, without previous prolapse surgery, laparoscopic mesh sacropexy (LS) and transvaginal mesh repair (TVM) were compared on the rate of complications ≥ grade II according to the modified Clavien-Dindo classification at one-year. The rate of complications ≥ grade II was lower after LS than after TVM, but did not meet statistical significance (17% vs 26%, treatment difference 8.6% [95%CI -1.5 to 18]; p=0.088). The rate of complications of grade III or higher was nonetheless significantly lower after LS (LS=0.8%, TVM=9.4%, treatment difference 8.6% [95%CI 3.4%; 15%]; p=0.001).

Using the same complication classification after transvaginal mesh repair for prolapse Barski et al (605) performed a systematic review and reported much higher rates of complications than reported above for native tissue POP repairs. Eleven randomised controlled and nine prospective studies from 2008 to 2013 with 2,289 patients (most POP-Q ≥ II, median follow-up 12 months) were included. The total complication rate was 27% in anterior, 20% in posterior, and 40% in combined mesh repair group. Complications of at least Clavien-Dindo grade 3 (requiring surgical, endoscopic or radiological intervention) occurred in 8% anterior, 3.5% posterior, and 13% of combined mesh repairs. No differences were found for reoperation rates for POP in mesh repairs as compared to non-mesh repairs (2 versus 3%).

1. REOPERATION AFTER VAGINAL SURGERY

Mairesse et al have recently published a retrospective population-based cohort study of all French surgical procedures for prolapse from 2008 to 2014.(248) A total of 310,938 patients were studied. Rates of death, admission to intensive care unit, readmission for early (30-day) complications, and reoperation for recurrent prolapse were 0.07%, 0.45%, 2.5% and 4.4%, respectively. Concomitant hysterectomy at the first surgery was associated with a significantly lower risk of reoperation for recurrence (HR 95%CI = 0.51 [0.49-0.53]. The most frequent reasons for early readmission were local infection (32.8%), haemorrhage (21.4%) and pain (17.2%). Risk factors for complications were obesity, low surgical volumes hospital and associated incontinence surgery.

Table 30 shows the reoperation rates after vaginal polypropylene mesh surgery versus native tissue repair for specific (linked to the mesh) complications from randomised controlled trials. The mean rate of reoperation for mesh-related complications was 6.6%, mainly for vaginal mesh exposure. The rate of reoperation for prolapse was similar in both the transvaginal mesh group and native tissue repair, 23/871 (2.6%) vs 33/861 (3.8%) (p=0.16) (Level 1), but follow-up was less than 36 months in the majority of trials.(119, 121, 122, 129, 131, 132, 173, 472, 474, 575, 577, 578, 606, 607)

In a retrospective study of 524 Prolift mesh, with a median follow-up of 38 months (range, 15-63), global reoperation rate was 11.6%, including surgery for urinary incontinence (6.9%), mesh-related complications (3.6%), and prolapse recurrence (3%) (Level 4).(608)

To estimate the risk of repeat surgery for recurrent prolapse or mesh removal after vaginal mesh versus native tissue repair for anterior vaginal wall prolapse, Jonsson Funk et al had utilised longitudinal, healthcare claims from 2005 to 2010 to identify women ≥18 years who underwent an anterior colporrhaphy with or without concurrent vaginal mesh. They identified 27,809 anterior prolapse surgeries with 49,658 person-years of follow-up. Of those, 6,871 (24.7%) included vaginal mesh. The 5-year cumulative risk of any repeat surgery was significantly higher for vaginal mesh versus na-

tive tissue (15.2 % vs 9.8 %, p<0.0001) with a 5-year risk of mesh revision/removal of 5.9%. The 5-year risk of surgery for recurrent prolapse was similar between vaginal mesh and native tissue groups (10.4 % vs 9.3 %, p=0.70) (Level 3). The use of mesh for anterior prolapse was associated with an increased risk of any repeat surgery, which was driven by surgery for mesh removal.(609)

In a study based on prospectively collected data from the Swedish National Register for Gynaecological Surgery, including 6247 anterior colporrhaphy and 356 non-absorbable mesh, reoperation rate within 12 months was higher in the mesh group, OR = 6.87 (CI 3.68-12.80) (Level 3).(610)

In a retrospective study based on 445 patients (including 43.5% for pelvic organ prolapse) with complications whom underwent mesh removal laparoscopically, via groin dissection and/or transvaginally in three tertiary referral centres in the US.(611) In patients who had POP mesh removal, 42.3% had an anterior TVM, 30.6% had a posterior TVM, 14% had both anterior and posterior TVMs, and 13.1% underwent sacrocolpopexy mesh removal. Complications encountered during mesh revision/removal surgery were: two ureteral injuries during anterior vaginal wall mesh removal, and two rectal injuries during posterior vaginal wall mesh removal.

In the recent French multicentre randomised controlled trial Prospere, on 262 women with cystocele stage ≥2, without previous prolapse surgery, the total reoperation rate was lower after laparoscopic mesh sacrocolpopexy (LS) compared to transvaginal mesh repair (TVM), but did not meet statistical significance (LS=4.7%, TVM=10.9%, treatment difference 6.3% [95%CI -0.4 to 13.3]; p=0.060).(137) (Level 2).

In the UK Prospect study, a pragmatic, parallel-group, multicentre, randomised controlled trials, on 1348 women, serious adverse events such as infection, urinary retention, or dyspareunia or other pain, excluding mesh complications, occurred with similar frequency in the different groups (vaginal standard repair alone, mesh augmentation and graft augmentation) over 1 year (mesh trial: 31/430 [7%] with standard repair vs 34/435 [8%] with mesh, RR 1.08, 95%CI 0.68 to 1.72; p=0.73; graft trial: 23/367 [6%] with standard repair vs 36/368 [10%] with graft, RR 1.57, 0.95 to 2.59; p=0.08). The cumulative number of women with a mesh complication over 2 years in women actually exposed to synthetic mesh was 51 (12%) of 434.(396)(Level 2)

Table 30. Prevalence of reoperation after vaginal polypropylene mesh surgery vs native tissue repair (RCT with anterior mesh)

Author	Year	No. mesh surgery & NTR (n/n)	Mesh / Surgical Technique	f.u. (months)	Vaginal exposure n (%)	Reoperation for vaginal exposure n (%)	Reoperation for mesh-related Complication (incl exposure) n (%)	Reoperation for POP recurrence No mesh vs Mesh n (%) / n (%)
Allegre (612)	2020	75/72	Ugytex® Collagen-coated PP / 4 arms TO	86	4 (13)	3 (8)	4 (13)	4 (11) / 3 (8)
Tamanini(129)	2020	33/43	Nazca TC® / 2 arms TO + 2 prepubic arms	60	2 (6.1)	0 (0)	0 (0)	0 (0) / 0 (0)
Steures(613)	2019	77/80	Prolift +M® / 4 arms TO	24	4 (5.6)	1 (1.4)	1 (1.4)	1 (1) / 5 (7)
Glazener(396)	2017	435/430	type 1 PP (19 to 44 g/m²) coated mesh	24	/	/	17 (4)	16 (5) / 15 (4)
Rudnicki (132)	2016	70/68	Avaulta Plus® Collagen-coated PP / 4 arms TO	36	10 (14.7)	5 (7.4)	5 (7.4)	7 (10.3) / 0 (0)
Dos Reis Brandão da Silveira (582)	2015	94/90	Prolift® / 4 arms TO	12	18 (20.5)	3 (3.4)	5 (5.6)	3 (3.7) / 2 (2.2)
Dias (578)	2015	43/43	Nazca TC® / 2 arms TO + 2 prepubic arms	24	5 (13.5)	2 (4.7)	3 (8.1)	10 (30.3) / 3 (8.1)
Lamblin (131)	2014	31/32	Perigee® / 4 arms TO	24	2 (6)	1 (3)	1 (3)	0 (0) / 0 (0)
Gutman (575)	2013	25/26	Prolift® / 4 arms TO	36	5 (15.6)	3 (9.4)	3 (9.4)	0 (0) / 3 (11.5)

Author	Year	No. mesh surgery & NTR (n/n)	Mesh / Surgical Technique	f.u. (months)	Vaginal exposure n (%)	Reoperation for vaginal exposure n (%)	Reoperation for mesh-related Complication (incl exposure) n (%)	Reoperation for POP recurrence No mesh vs Mesh n (%) / n (%)
Vollebregt (122)	2011	61/64	Avaulta® / 4 arms TO	12	2 (4)	1 (2)	1 (2)	4 (7) / 3 (6)
Altman (472)	2011	200/189	Prolift® / 4 arms TO	12	21 (11.5)	6 (3.2)	6 (3.2)	1 (0.5) / 0 (0)
Withagen (173)	2011	93/97	Prolift® / 4 arms TO	12	14 (16.9)	5 (5)	5 (5)	4 (4.1) / 0 (0)
Iglesia (606)	2010	32/33	Prolift® / 4 arms TO	10	5 (15.6)	3 (9)	3 (9)	0 (0) / 4 (6.5)
Nieminen (121)	2010	105/97	4 arms non TO	36	20 (19)	14 (13)	14 (13)	1 (1%) / 6 (5.8)
Nguyen (119)	2008	37/38	4 arms TO	12	2 (5)	2 (5)	2 (5)	MD
Sivaslioglu (474)	2008	45/45	4 arms TO	12	3 (6.9)	3 (6.9)	3 (6.9)	MD
Total	-	-	-	-	117/979 (11.9%)	52/979 (5.3%)	73/1423 (5.1%)	51/1329 (3.8%) vs 44/1338 (3,3%) (p=0.46)

Abbreviations: NTR: native tissue repair, MD: missing data, PP: monofilament polypropylene

2. REOPERATION AFTER ABDOMINAL SURGERY

Several techniques have been described (with the use of non-absorbable sutures and with or without mesh placement) concerning the treatment of pelvic organ prolapse (POP) by abdominal route: sacrocolpopexy (SCP), sacrocervicopexy (SCerP), sacrohysteropexy, anterior abdominal wall hysteropexy, uterosacral hysteropexy and uterosacral ligament suspension (USLS) . These procedures can be performed by an open laparotomy, a laparoscopy or a robotic-assisted laparoscopic approach (614) and lateral suspension.(615) Data are lacking concerning comparative studies between these different procedures and between abdominal and vaginal procedures. However, in 2020, sacrocolpo/cervico/hysteropexy was the most evaluated procedure and this procedure was considered to be the standard treatment of POP via the abdominal route.

Rates of anatomical recurrence following laparoscopic sacral colpopexy or hysteropexy range from 4 to 18% at 12-14 months of follow-up (Level 2). Mean rates of reoperation for prolapse recurrence and for de novo stress urinary incontinence after open abdominal sacral colpopexy are 2% and 5%, respectively (Level 3).(46,156,326,616-619)

Population-based cohort studies observed similar rates of reintervention following abdominal and vaginal POP surgeries, with or without the use of a mesh (597,620) (Level 3). Nevertheless, RCTs observed that the total reoperation rate was lower after laparoscopic mesh sacropexy compared to transvaginal mesh repair.(137,570)(Level 2)

RCTs observed similar reoperation rates following open or laparoscopic route for sacral colpopexy (339,621)(Level 3).

Table 18 demonstrates that the total reoperation rate for laparoscopic sacral colpopexy is 5.1%, with 2.1% representing complications and 2.9% representing reoperations for prolapse.

Higher recurrence rates (up to 60% at 6 years follow-up) have been reported in some retrospective series.(622)

The rate of reoperation for recurrences after laparoscopic sacrocolpopexy is significantly higher with the use of porcine dermis grafts in comparison to polypropylene mesh.(623) (Level 3)

3. VAGINAL MESH EXPOSURE

According to AUGS/IUGA,(614) only the term “mesh exposure” with a description of where that exposure is located (e.g., “vaginal mesh exposure” or “rectal mesh exposure”) should be used.

3.1. Prevalence of vaginal mesh exposure after vaginal mesh surgery

It is difficult to know the exact rate of vaginal mesh exposure, as the definition of exposure is variable between studies and meshes used are different. Table 31 shows the rate of exposures after vaginal polypropylene mesh surgery in the 14 currently available randomised controlled trials, mainly with different kinds of four-arm trans-obturator meshes. In these trials, the mean rate of exposure was 12%, and the mean rate of reoperation for vaginal mesh exposure was 6% (Level 1).

According to the available literature, polypropylene collagen-coated mesh does not seem to give any advantage in comparison to classic non-absorbable mesh regarding the vaginal mesh exposure rate (Level 1)(132,135,624,625). Furthermore, vaginal mesh exposure has also been reported as high as 6.9% with the use of biological implant,(626) even if others have found low rates using biological implants, between 0 to 1.4%.(627,628)

Partially absorbable meshes are also associated with a risk of vaginal mesh exposure. In a RCT conducted in 163 women comparing native tissue surgery and partially absorbable mesh vaginal surgery, the prevalence of vaginal mesh exposure was 6%.(613)

In recent series, ultra-light weight meshes (<30gr/m²) used with trans-obturator arms (OPUR) (Enikeev et al, Urologia, 2020) or anterior sacrospinous fixation were associated with a low rate of mesh exposure (1%) at medium-term review (Level 4).(135) However, a comparative retrospective series showed very low but similar rates of mesh exposure following UPHOLD (ultra-lightmesh) and PROLIFT (non ultra-light mesh) placement (1/330 (0.3%) vs 17/2258 (0.7%), respectively; p=0.72) (Level 3) (Kato et al, Int J Urol, 2021).

Furthermore, several case series have reported a low rate of vaginal mesh exposure after anterior-apical single incision techniques, from 0 to 3.4% (Level 4), (134,135,629-632) which was significantly lower in comparison to trans-obturator meshes,(633) although there is no available RCT showing that these rates are due to the technique, rather than to the surgeons experience or the lightweight mesh.

A recent RCT has compared vaginal hysteropexy using light-mesh and vaginal hysterectomy with uterosacral ligament suspension on 175 postmenopausal women at 9 clinical sites in the US between 2013 and 2015, and followed up to 3-year for 97% of the initial population.(136) While vaginal mesh exposure was higher in the mesh group (8% vs 0%), other complications were higher in the non-mesh group (ureteral kinking 7% vs 0%, granulation tissue after 12 weeks 11% vs 1%, and suture exposure after 12 weeks 21% vs 3%).

Although there is a lack of evidence supporting the use of posterior mesh vaginally for rectocele or enterocele repair,(595) a few studies have reported a low vaginal mesh exposure rate in the posterior compartment, between 2 to 3.8%.(634,635)

Data is becoming available of long-term rates of mesh exposure. Letouzey et al, who used the Gynemesh® on 63 patients with a mean follow-up of 6.5 years, the vaginal mesh exposure rate was 16% (10/63), all of which underwent surgical correction.(636) In the study by Heinonen et al, who used the Prolift® mesh on 140 patients with a mean follow-up of 7 years, the vaginal mesh exposure rate was 23% (32/140), even though most of these were small (less than 1cm in 25/36) and asymptomatic (24/32).(637) In comparison Meyer et al, who used the Prolift® mesh as well, on 48/208 patients with a mean follow-up of 7 years (range 5.8 to 8.1), the vaginal mesh exposure rate was 6% (3/48).(638)

3.2. Prevalence of vaginal mesh exposure after abdominal surgery

Vaginal mesh exposure rate following laparoscopic sacral colpopexy or hysteropexy is 2% (mean, range 1-7%) (Table 20) (Level 2). Vaginal mesh exposure rates were comparable regardless the surgical approach (open, laparoscopic, robot-assisted) (Level 2).(639,640) The risk of vaginal mesh exposure is significantly increased if hysterectomy is performed concomitantly (8.6%), in comparison to sacral colpopexy for post-hysterectomy prolapse (2.2%) (p<0.05) (641) (Level 2) or if permanent sutures are utilised (330,642). In contrast a recent RCT reported no difference in the rate of mesh exposure when comparing permanent and absorbable sutures at 12 months however the rate of mesh exposure was high at 6% in both groups and maybe explained by all undergoing concomitant hysterectomy.(643)

3.3. Risk factors of vaginal mesh exposure

Maher et al, have shown a non-significant increased rates of vaginal mesh exposure and reoperation for vaginal mesh exposure after vaginal mesh surgery in comparison to laparoscopic sacrocolpopexy (13% vs 2%, p=0.07 and 9% vs 2%, p=0.11, respectively). (324)(Level 2) However, that was not the primary endpoint of the study, and that study was underpowered for this parameter.

Younger age, higher parity, premenopausal status, diabetes mellitus, smoking, concomitant hysterectomy and surgery performed by a junior surgeon are significant risk factors for vaginal mesh exposure after female pelvic floor reconstructive surgery (Level 3).(644)

Concerning vaginal mesh surgery, obesity (BMI>30 kg/m², OR=10.1) has been shown by some authors to be an independent risk factor for vaginal mesh exposure.(645) However, others have reported no difference in the rate of mesh exposure related to BMI, in a study on 200 patients with advanced pelvic organ prolapse treated by vaginal sacrospinous ligament fixation with anterior mesh repair as primary surgery with an exposure rate of 4.1% at a mean follow-up of 36 months.(646) Furthermore, a recent paper on 201 patients with a mean mesh exposure rate of 8.5% at a mean follow-up of 14 months has reported that the BMI may negatively correlate with exposure rates (12.9% for BMI less than 25 kg/m, 9.5% for BMI of 25 to 29.9 kg/m, 3.1% for BMI of 30 to 34.9 kg/m, and 0% for BMI greater than or equal to 35 kg/m).(647)

Smoking has also been shown to be an independent risk factor for mesh exposure after vaginal mesh surgery [OR=3.1 to 3.7].(648-651) With regard to sacrocolpopexy, smoking [OR=5.2; 95%CI 1.7-16] is also an independent risk factor for vaginal mesh exposure. (253)

Current data on the impact of ageing on mesh complications are conflicting and no conclusion can be drawn.(253,257,645,652-654) In a recent study of 217 patients who underwent vaginal sacrospinous ligament fixation with anterior mesh repair for primary prolapse surgery, outcome measures were observed in cohorts of two age groups (<75 years and ≥75 years), with a mean follow-up of 34 and 36 months respectively. Although older women had significant-

ly more preoperative comorbidities, perioperative complications showed no difference between the two groups.(263) On the other hand, in a case-control study comparing mesh exposure requiring surgical revision (n=48) and controls who had no mesh exposures (n=48), the adjusted odds ratio of being one year older was 0.96 (95% CI 0.92-1.0) among women with mesh exposure.(650) Overall, it has been shown that although the absolute risk of death is low, elderly women have a higher risk of mortality and morbidity following urogynaecology surgery.(655) Among 264,340 women, increasing age was associated with a higher mortality risk per 1000 women (<60 years, 0.1; 60-69 years, 0.5 [OR 3.4; 95% CI 1.7-6.9]; 70-79 years, 0.9 [OR 4.9; 95% CI 2.2-10.9]; >80 years, 2.8 [OR 13.6; 95% CI 5.9-31.4]; P<.01) and a higher risk of complications per 1000 women (<60 years, 140; 60-69 years, 130; 70-79 years, 160; >80 years, 200 [OR 1.4; 95% CI 1.3-1.5]; P<.01). Furthermore, elderly women 80 years and over who underwent obliterative procedures had a lower risk of complications compared with those who underwent reconstructive procedures (17 vs 24.7%, P<.01).(655)

Sexual activity has been reported to be a risk factor for vaginal mesh exposure after vaginal mesh surgery(636,654)(Level 3). However, this could simply reflect that those who are sexually active are more likely to identify a mesh exposure than those who are not.

A bleeding complication at the time of mesh implantation (excessive bleeding >500, post-operative haematoma requiring drainage or embolisation) has also been shown to be an independent risk factor for mesh exposure requiring reoperation after vaginal mesh surgery [OR=7.25, 95% CI 1.47-35.66].(650)

Parity greater than two has also been shown to be an independent risk factor for mesh exposure after vaginal mesh surgery [OR=2.64, 95% CI 1.07-6.51].(649)

No study has shown that the following are significantly associated with mesh exposure: diabetes mellitus, corticosteroid use, immunosuppressive therapy, previous pelvic irradiation, history of previous mesh exposure, vaginal atrophy. However, many studies have shown that in other surgical specialties poorly controlled diabetes mellitus is a risk factor for post-operative infection. One study has reported that somatic inflammatory disease (mainly rheumatoid arthritis) is independent risk factor for mesh exposure after vaginal mesh surgery [25% (3/12) vs 7.6% (20/264), OR 5.11, 95% CI 1.17-22.23].(649) Somatic inflammatory disease (rheumatoid arthritis, Sjögren´s disease, lupus erythematosus) may by themselves influence wound healing but treatment is often accompanied by immunosuppressant medications which may prolong wound healing.

3.4. Treatment of vaginal mesh exposure after vaginal mesh surgery

Vaginal mesh exposure, both after vaginal mesh surgery or sacrocolpopexy is usually associated with vaginal discharge, and sometimes pain, dyspareunia, vaginal infection, and rarely abscess or cellulitis.(656,657)(Level 3). The choice of treatment has to take into account the type of mesh implanted (need to obtain previous surgical records), clinical symptoms, location and size of exposure. All cases with abscess or cellulitis need an immediate reoperation to remove the maximum (if possible, all) of the foreign material.

In cases of mesh exposure after vaginal mesh surgery, if there is no abscess or cellulitis, medical treatment is usually undertaken using local oestrogens and/or local antiseptic. However, medical treatment efficacy is low at 28% (Table 31) (Level 3).(234,651,657-662)

After failure of medical treatment, a reoperation under local or general anaesthesia is generally performed, in order to remove the exposed portion of the mesh and to close the vaginal epithelium. Although technically difficult in some cases, mesh excision was safe with resolution of almost all presenting symptoms.(140,665) Conversely, for others, recurrence was reported in up to 29% of patients with no change or worsening symptoms (recurrent discharge, persistent pelvic pain).(666) Furthermore, up to 62% of treated patients could require multiple surgical procedures.(667,668) Efficacy of surgical excision for vaginal mesh exposure after vaginal mesh surgery is 91% and summarised Table 32

A model to compare medical treatment and surgical excision has favoured surgical excision over conservative treatment in the initial management of mesh exposure following vaginal prolapse repair with synthetic mesh. However, in this model, the difference in Quality Adjusted Life Year (QALYs) between strategies was less than the Minimally Important Difference (MID). Therefore, the strategies are likely similar overall. Individual patient characteristics may ultimately drive clinical decision-making for this surgical complication. (670,671)

Furthermore, spontaneous evolution of asymptomatic (no vaginal discharge, no sexual problems) and small (≤1cm²) mesh exposure in the long-term could be without specific complications, allowing expectant management (Level 4).(672,673)

Table 31. Efficacy of medical treatment for vaginal mesh exposure after vaginal mesh surgery.

Author, Year	Mesh	Efficacy of medical treatment
Kato, 2021	PP	10/14
Cervigni Natale, 2011(659)	PP coated collagen (AVAULTA)	3/21
Withagen, 2011 (173)	PP (PROLIFT)	3/14
Long, 2011(663)	PP	3/14
Moore, 2010 (661)	PP (PERIGEE)	1/12
Feiner, 2010 (664)	PP (PROLIFT)	6/10
Collinet, 2006 (234)	PP	9/34
Deffieux, 2006 (657)	PP (GYNEMESH ou GYNEMESH Soft)	7/34
Achtari, 2005(658)	PP	4/14
Total		**46/163 (28%)**

Abbreviation: PP: polypropylene

Table 32. Efficacy of surgical excision for vaginal mesh exposure after vaginal mesh surgery.

Author, Year	Mesh	Efficacy of surgical treatment
Crosby, 2014(669)	Different mesh kits	53/56
Hansen,(666)	Different mesh kits	2/3
Wong, 2013 (668)	Different mesh kits	18/20
Firoozi, 2012 (140)	Different mesh kits (Prolift, Apogee/Perigee, Avaulta)	20/23
Total		**93/102 (91.2%)**

Abbreviation: PP: polypropylene, TVM: trans-vaginal mesh

In a study cohort consisting of 847 patients, Wong et al have reported 53 (6.2%) vaginal exposures after both vaginal (34/393, 8.7%) and abdominal surgery (19/454, 4%). Concerning treatment, permanent mesh exposures resolved most often after surgical excision (18/20, 90%) compared with office excision (6/14, 43%), vaginal oestrogen (6/33, 18%), or expectant management (1/3, 33%) (P<.001) (Level 3).(668)

According to AUGS/IUGA,(614) the different surgical procedures for mesh related complication should be classified as follow:

- Mesh Revision: Either no mesh is removed (e.g., dissecting and primarily closing vaginal epithelium), or a small edge of mesh is removed such that the structural integrity of the implant is left intact.
- Partial Vaginal Mesh Excision: A segment/component of the mesh is removed or transected, such that the structural integrity of the implant is altered.
- Complete Vaginal Mesh Excision: The entirety of the mesh that is in contact with the vagina is excised.
- Extra-vaginal Mesh Excision: Removal of segments or components of mesh beyond, or not in contact with, the vagina
- Total Mesh Excision: The surgical goal is the removal of 100% of the implant.

A new joint position statement on the management of mesh-related complications for both exposure and pain/dyspareunia has been published by AUGS and IUGA.(674)

3.5. Treatment of vaginal mesh exposure after abdominal surgery

In cases of vaginal mesh exposure after sacrocolpopexy, most authors report reoperation by the vaginal approach as first line, (262,330,616,675) because of the risk of spondylodiscitis and of the very low success rate of medical treatment (<15%). (253,262,676,677)

However, some authors reported good success rate (10/28 (35%) following vaginal oestrogen and/or antibiotics +/- trimming of the mesh in the office for vaginal mesh exposure after sacral colpopexy using polypropylene mesh.(678)(Level 4) Then if recurrence occurs after vaginal mesh excision, or in case of associated pelvic infection, total mesh removal by laparoscopy or laparotomy has been described. (679,680)(Level 4)

The success (resolution of vaginal mesh exposure) rate of partial mesh removal (resection of the exposed/extruded) portion of the mesh is high (80-90%) but additional surgical revision is sometimes required.(678)(Level 4) The outcome (improved or cured pelvic pain) following partial or complete removal of the mesh, ranged from 50 to 100% in observational series.(681)

4. VISCERAL (BLADDER, RECTUM) MESH EXPOSURE

There was no visceral mesh exposure reported in the randomised controlled trials after vaginal mesh surgeries, but follow-up was short. Late bladder or ureteric and rectal exposure have been reported after vaginal surgery (Level 4).(637,682,683)

In a large Japanese retrospective cohort study on 2648 patients who underwent transvaginal mesh prolapse surgery between 2006 and 2017, the rates of vaginal, bladder, ureter and rectal exposure were 0.68%, 0.38%, 0.08% and 0.15%, respectively.(684)

Visceral (bladder, rectum) mesh exposure have been reported rarely (< 0.1%) following sacral colpopexy or hysteropexy (OS, LS, RALS) (Level 4).(685,686)

Concerning non-mesh vaginal surgery, a recent study on 91 litigations in the US (687) has shown that the leading allegation of malpractice was negligence of surgery, whereas the most common complication was urinary tract injury (26%), followed by the need for additional surgery (24%), and new postoperative urinary symptoms (24%).

5. INFECTIOUS COMPLICATION

There is no clear definition of bacterial colonisation around a mesh or mesh infection. Consequently, the rate of infection is currently unknown.(685) Some studies have reported up to 80% bacterial mesh colonisation.(688,689) However, the rate of relevant clinical infection (abscess, cellulitis, spondylodiscitis) does not seem to be more than 1%, after both sacrocolpopexy (Level 4) (690-693), or vaginal mesh surgery (Level 4).(694-696)

In a cohort of 684 polypropylene mesh implanted vaginally (TVM procedure), the rates of pelvic abscess and cellulitis have been reported to occur in only 0.29% and 0.15%, respectively.(697) (Level 4).

One case of Actinomyces infection appearing five years after trocar-guided transvaginal mesh prolapse repair was recently reported.(698)

Severe pelvic infection has also been described after native tissue repair, including total colpocleisis.(699)

A recent study compared rates of perioperative complications of native tissue versus vaginal mesh repairs, using the National Surgical

Quality Improvement Program (NSQIP) database on 10 657 vaginal reconstructive procedures without mesh and 959 mesh-based repairs. Procedures with mesh had a higher rate of organ surgical site infection (SSI) (0.52% vs 0.17%, P = 0.02).(700)

More recently, Veit-Rubin et al. have shown that abnormal vaginal microbiome could be associated with vaginal mesh complications (701). They have shown that the presence of Veillonella spp. could be associated with mesh contraction, but they were not able to identify vaginal microbiotic dysbiosis as a factor associated with exposure.

Spondylitis had been reported rarely following laparoscopic sacral colpopexy or hysteropexy. The prevalence of this complication ranges from 0.1 to 0.2% (see Table 20). Cases of spondylodiscitis have been reported following laparoscopic sacral colpopexy with tacks, but also with sutures and it is impossible to determine with certainty whether it is the mesh material itself, the sacral colpopexy system, the vaginal fixation system or the exposure which was the cause of, or promoted, the spondylitis (probably multifactorial in origin).

Pelvic abscess has also been reported rarely following sacral colpo/hysteropexy.

A retrospective comparative series (Level 4) observed a very good agreement between MRI findings (loculated collection or tracking abscess or sinus tract or osteomyelitis) and surgical findings for mesh infection.(702,703) However, this series included only 11 cases of mesh infection.

6. PELVIC PAIN

6.1. Pelvic pain after vaginal surgery (with/without mesh, including mesh contraction)

The aetiology of chronic pelvic pain after vaginal mesh placement is variable, and the most significant causes include pelvic floor muscle spasm, pudendal neuralgia, and infection.(704) Obturator muscles laceration with consequent oedema provoked by the mesh arm could also explain pain. In such cases, Magnetic Resonance Imaging (MRI) will look for obturator muscle hyper-intensity consistent with muscular oedema and pain could be helped by oral corticosteroids.(705) The rate of polypropylene mesh-related pain reported ranges between 4 and 11% according to the definition used (Level 3) (119, 121, 173, 474, 606, 660, 661, 697). In the 2011 American FDA report regarding transvaginal mesh, vaginal pain and dyspareunia were the most common adverse events reported and vaginal pain and dyspareunia were also the most common indications for reoperation following transvaginal mesh in the report by Tijdink et al.(625) These reports contrast with the common perception in the literature that mesh exposure is the commonest complication associated with transvaginal meshes and requires ongoing evaluation.

Mesh contraction is also a possible aetiology. Feiner et al defined mesh contraction as an adverse outcome following armed polypropylene mesh repair in which patients experience vaginal pain with movement and dyspareunia and on examination have localised areas of prominent, tense and tender mesh under the vaginal epithelium.(706) Mesh contraction assessed on ultrasound examination after anterior vaginal mesh repair may correlate with de novo OAB symptoms and vaginal pain. Of 103 patients who underwent Prolift anterior™ implantation, after 6 months' follow-up, mesh contraction occurred in 19.4% of patients presenting with de novo OAB symptoms, and 22.3% of patients reporting post-operative vaginal pain (Level 4).(633)

Pain before surgery has been shown to be a predictive factor for pain after surgery, with an OR of 3.2 (95% CI 1.2-8.4), in a prospective observational cohort study on 284 patients with a post-operative pain rate of 13% (35/275) (Level 3).(651) Preoperative dyspareunia has also be shown by multivariable regression to be the only factor associated with postoperative dyspareunia (adjusted odds ratio 7.8, 95% CI 4.2–14.4.)(702)

Local pain around the mesh site could initially be treated conservatively with local injection using a combined steroid and local anaesthetic agent, as for groin pain after TVT,(707) but there is no evidence for vaginal mesh.

Although technically difficult in some cases, some authors have reported that purely transvaginal mesh excision appears to be safe with resolution of almost all presenting symptomatic, including pelvic pain(140), even if mesh removal was performed for painful mesh contraction, with a symptoms resolution rate of 77.9 to 93% (14/15) (Level 4).(708) Contrarily, others have reported unsatisfactory outcomes after mesh removal. On 58 women who underwent mesh excision for multiple complaints, including pelvic pain in 22%, re-excision of residual mesh was necessary in 27 women (29%), and only 14 women (24%) were treated successfully, with complete resolution of all presenting symptoms.(709)

6.2. Pelvic pain after abdominal surgery

Pelvic or back pain is a rare condition (ranging from 1 to 2%) following laparoscopic sacral colpopexy or hysteropexy (Level 2)(686) however, most did not assess lumbar/back pain before and after surgery and high rates of lower back pain are reported in the general population.(710) Maher et al have reported a reoperation rate for mesh contraction significantly greater after vaginal mesh surgery than after laparoscopic sacral colpopexy (7% vs 0%, p=0.05).(324) (Level 2). Other Complications

Other rare but severe complications have been described after pelvic organ prolapse surgery, such as massive haemorrhage after a trans-obturator mesh procedure, major vessel injury during sacral colpopexy, trocar hernia, bowel obstruction, urinary retention, ureteric complications and thrombo-embolism.

Post-operative haemorrhage or hematoma have been reported after native tissue repair, in 0.9% and 2.5% respectively.(711) In that study of 438 patients who underwent anterior and posterior colporrhaphy, associated with sacrospinous fixation for level I defects in 269 patients and hysterectomy in 255 cases, gluteal hematomas occurred more commonly after sacrospinous fixation (p = 0.019) (Level 3), while concomitant hysterectomy was not associated with more complications. A recent study has determined comparative rates of perioperative complications of native tissue versus vaginal mesh repairs, using the National Surgical Quality Improvement Program (NSQIP) database on 10 657 vaginal reconstructive procedures without mesh and 959 mesh-based repairs. Procedures with mesh had a higher rate of perioperative bleeding requiring transfusion than native tissue repair (2.3% vs 0.49%, P < 0.001).(700)

Post-operative urinary retention has been described after both native tissue repair and vaginal mesh surgery. Urinary retention could be defined as a post-void residual over 150 ml more than 48 h after catheter removal.(712) Posterior colporrhaphy has been shown to give more transient urinary retention than mid-urethral sling, in 32% vs 15% (P = 0.03), with longer bladder catheterisation (3.2±0.9 vs

1.8±0.4 days; P = 0.007), probably related to post-operative pain (Level 3).(713) Of 94 patients who underwent trans-obturator mesh (n=32) or anterior-apical mesh anchored to the sacrospinous ligament (n=62), with normal preoperative uroflowmetry and without concomitant mid-urethral sling, urinary retention occurred more frequently after the second technique [(17 (27 %) vs 2 (6.25 %), OR 5.7, 95% CI 1.2-26.3, p = 0.027] (Level 3), with a trend towards more frequent hospital discharge with self-catheterisation [8 % (5) vs 3 % (1)]. This phenomenon could be explained by more injury to pelvic splanchnic nerves during the dissection of the sacrospinous ligament.(712)

Post-operative ureteric complications have also been described after both native tissue repair and vaginal mesh surgery. In a retrospective chart review of 983 women who underwent uterosacral colpopexy for uterovaginal and post-hysterectomy vault prolapse, the overall adverse event rate was 31.2% (95%CI, 29.2-38.6), which included 4.5% (95%CI, 3.4-6.0) of ureteric kinking requiring suture removal (Level 3).(303) Ureteric kinking has also been reported with vaginal mesh surgery, and could be related to the traction of peri-ureteral tissue by the mesh arm.(154) In a study cohort consisted of 1,282 patients receiving 1,484 implants (847 synthetic mesh and 637 biologic grafts), Wong et al. have reported 59 (0.6%) ureteric injuries resulted from ureteric kinking during seven uterosacral ligament vaginal suspensions, one ureteric kinking during anterior implant placement, and one ureteric transection during sacrocolpopexy (Level 3).(668)

Concerning postoperative venous thrombo-embolism (within 30 days after surgery), in large POP surgery series (database), the prevalence ranged from 0.1% (on 13,023 women who have undergone reconstructive pelvic surgery (POP surgery or sling for USI) (714) to 0.4% (on 26,103 women who have undergone POP surgery).(715) Women with obesity, an increased length of stay, or ASA score of 3 or higher are at an increased risk for developing thrombo-embolism after undergoing surgery for POP (multivariate analysis) (Level 3).

Concerning laparoscopic sacral colpopexy, conversion to the open approach is rarely considered as a complication. However, conversion rates range from 0.7 to 11% (mean 3%), according to the surgeons' experience (Level 3).(341,686,716)

Mean bladder injury rate ranges from 0.6 to 2% during open or laparoscopic or robot-assisted sacral colpopexy or hysteropexy (Level 2).(685,686) Bladder injury may occur due to trocar placement, tissue dissection or suture placement. Injuries have been managed by immediate repair and extended duration of indwelling catheter. Mean bowel injury rate ranges from 0.07 to 1% (Level 2).(685,686)

Peri-operative blood loss is decreased using laparoscopic approach when compare to open approach (Level of evidence 2). However, blood losses amounts are limited (150-200ml) and the requirement of transfusion is rare (<1%), whatever the surgical route. Laparoscopic approach is associated with a decrease in the transfusion rate (multivariate analysis), when compared to open approach (Level 3). (717) Concomitant hysterectomy may increase blood loss.

Laparoscopic approach is associated with a decrease in the wound disruption, when compared to open approach (Level 3) (Linder et al, J Urol, 2018).

Obstructed defaecation is rarely reported (2-2.5%) following sacral colpopexy.(686) Small bowel obstruction (1.2%), and port site hernia (0.2%) have been reported following sacrocolpo/hysteropexy (Level 4).(686)

Vascular injuries are rare complications (<1%) of sacral colpopexy. (718) Some cases are due to anatomical variations of the internal iliac veins in the presacral area

Very rare complications (<0.1%) of sacral colpopexy include vascular injuries due to anatomical variations of the internal iliac veins in the presacral area.(719)

Corneal abrasions have been rarely reported during pelvic reconstructive surgery.(720) In this series, the prevalence of corneal abrasions was 2% following sacral colpopexy and 0.3% following vaginal surgery (p=0.04) (Level 3). However, the mean operative duration in the laparoscopic group was 312 min in this series. Furthermore, corneal abrasions did not occur in any patient with a total operating time less than 227 min. The amount of Trendelenburg was not recorded.

Fatalities occurred after vaginal surgery, open or laparoscopic sacrocolpopexy/hysteropexy. Concerning abdominal surgery, mortality rates ranged from 0.05 to 0.1 % (no difference between open and laparoscopic approach).(685)

7. METHODS OF PREVENTION

7.1. Methods of Prevention for both vaginal and abdominal approaches

Although there is no specific study in prolapse surgery, to demonstrate that cessation of smoking prior to surgery will decrease the post-operative complication rate (healing problems) in many other surgical specialties these data exist (Level 2). In a randomised controlled study on the effects of smoking cessation before surgery, including groin hernia repair using mesh, continued smoking up until the operation significantly increased the risk of acquiring post-operative complications compared to those who stopped smoking four weeks before the operation.(721)

Reducing bleeding during surgery is important as both excessive bleeding >500 ml and post-operative hematoma requiring drainage or embolisation are independent risk factors for mesh exposure requiring reoperation after vaginal mesh surgery [OR 7.25, 95% CI 1.47-35.66].(650)

Many studies have shown, in other surgical specialties, that poorly controlled diabetes mellitus is a risk factor for post-operative infection.

7.1.1. Oestrogen therapy

Vaginal oestrogen application before and/or after pelvic organ prolapse surgery has been shown to improve the vaginal maturation index and increased vaginal epithelial thickness. However, no study has shown that the use of pre and/or post-operative application of oestrogen was associated with a decrease in vaginal mesh exposure rates (Level 3).(722)

Furthermore, a retrospective cohort study conducted on 363 women who underwent sacral colpopexy, counter-intuitively observed that pre-menopausal women were at higher risk for mesh exposure than postmenopausal women (RR 4.5 95% CI 1.9-10.9 p=0.01). (678)

Two RCTs evaluated role of preoperative vaginal oestrogen in postmenopausal women undergoing POP surgery. The first trial confirmed RCT (LOTUS) (723) confirmed a larger trial was feasible and Marschalek reported a double blinded RCT and demonstrated that preoperative oestrogen reduced postoperative complications (p=0.045) and antibiotic use (p = 0.003). Surgeons blinded to treatment allocation, were unable to identify any difference in tissue perfusion, atrophy, consistency or dissection difficulty.(724)

7.1.2. Bowel preparation

One single-blind randomised trial has evaluated mechanical bowel preparation before reconstructive vaginal prolapse surgery (apical suspension and posterior colporrhaphy). Bowel preparation consisted of a clear liquid diet and two self-administered saline enemas the day before surgery (n=75). The patients in the control group are a normal diet (n=75). The bowel preparation group was less likely to report "complete" satisfaction compared with the control group (OR 0.11, 95% CI 0.04-0.35; P<.001) (Level 2). Abdominal fullness and cramping, fatigue, anal irritation, and hunger pains were greater in the bowel preparation group (all P<.01). Finally, preoperative bowel preparation conferred no benefit regarding surgeons' intraoperative assessment of the operative field (primary endpoint) (Level 2).(725)

Bowel preparation prior to sacral colpopexy is not routinely used in most series. One RCT assessed post-operative constipation (measured by the Patient Assessment of Constipation Symptoms (PAC-SYM)) following bowel preparation prior to sacral colpopexy. (726) In intervention group, the bowel preparation consisted of written and verbal instructions to be on a clear liquid diet the afternoon prior to surgery and i-to consume one bottle of magnesium citrate the day before surgery. No differences were noted on ITT (Level 2). Surgeons were more likely to rate the complexity of the case as "more difficult than average" (54.4% vs 40.1%, p =0.027) in those without a bowel preparation. However, the prevalence of peri-operative and postoperative complications was similar in both groups.

7.1.3. Antibiotic / Cranberries prophylaxis

There is no specific study on the use of antibiotic prophylaxis at the time of mesh reconstructive surgery for prolapse. However, most of studies report their use during pelvic organ prolapse surgery. (121,173) There are no data on the need to identify a urinary tract infection in the preoperative period nor to perform a vaginal bacteriological test or to use antiseptic or antibiotic meshes. Prolonged post-operative bladder catheterisation increases the risk of lower urinary tract infection (Level 3).(727)

One randomised double-blind placebo-controlled trial has been done to evaluate whether cranberries are able to prevent postoperative urinary bacteriuria in patients undergoing pelvic surgery and receiving transurethral catheterisation. 272 women were enrolled and have received 36 mg cranberry (proanthocyanidins, PAC) or placebo once daily for 10 days. Authors have shown that immediate postoperative prophylaxis with PAC does not reduce the risk of postoperative bacteriuria in patients receiving short-term transurethral catheterisation after pelvic surgery.(728)

7.1.4. Mesh implantation and visceral injury

Although there is no comparative study, most of authors would consider the use of mesh after a rectal injury during dissection as a contraindication to mesh insertion, due to a perceived higher risk of mesh infection and subsequent recto-vaginal fistula(729) (Level 4).

In the anterior compartment, a small series of five cases of recognised intra-operative bladder injury (out of 704 Trans-Vaginal Mesh procedures) has shown that mesh surgery was feasible without subsequent complications after appropriate bladder repair.(729) (Level 4) These data are limited and further evaluation is required.

7.1.5. Concomitant surgery for stress urinary incontinence

In a prospective longitudinal cohort study using a surgical registry on 1873 women in 13 French public hospitals, Fritel et al. have recently reported that the incidence of serious complications 6 months after the surgical procedure was higher when concomitant mid-urethral sling (MUS) was performed: 1.7% (0.0-3.8%) after vaginal native tissue repair, 2.8% (0.9-4.6%) after transvaginal mesh, 1.0% (0.1-1.9%) after laparoscopy with mesh, and 7.0% (2.8-11.3%) after prolapse surgery with MUS. (620)

7.1.6. Convalescence recommendations

There are substantial variations in activity restrictions placed on post-operative patients. In France, mean recommended time until recommencement of sexual intercourse is four weeks following pelvic organ surgery. Mean recommended lifting restrictions range from four to six weeks.(730)

In a RCT, 95 women were randomized. (n=45 liberal, n=50 restricted activity recommendations) Satisfaction and short-term anatomical outcomes were similar in both groups 3 months after prolapse surgery.(731) Post-operative complications were not reported in this RCT. "Restricted activity recommendations "was defined as follows " You should not lift anything heavier than 10 pounds for 12 weeks after surgery; you should avoid high impact activities such as running, aerobics, and sit-ups for 12 weeks after surgery". In both groups, it was advised to not have sexual intercourse for at least 6 weeks after surgery.

8. PREVENTION METHODS FOR VAGINAL MESH SURGERY

8.1. Learning curve

The data regarding the impact of the learning curve for transvaginal meshes on the incidence of post-operative complications is conflicting. Some authors have reported that learning has a significant effect on the complication rate(651,732-734) while others did not. (488,735) For de Tayrac et al, 113 patients underwent bilateral anterior sacrospinous ligament suspension associated with anterior mesh, the risk of major complications (ureteric complications, vaginal infections, sciatic pain) was reduced by approximately 30% every ten procedures (HR = 0.71, 95% CI: 0.53–0.95) (Level 3).(732) For Mowat et al, gynaecologists performing procedures approximately once a month or less were found to have higher rates of adverse outcomes in urogynaecology (RR 1.4, 95% CI 1.2-1.6), with higher rates of reoperation for mesh complications after mid-urethral sling procedures (RR 1.4, 95% CI 1.2-1.5).(734)

8.2. Concomitant hysterectomy

Although several studies did not find any differences,(233,657) most of the studies have shown an increased rate of vaginal mesh exposure with concomitant vaginal hysterectomy.(234,262,652,653,736-738) Meta-analysis demonstrates that the addition of hysterectomy to a transvaginal mesh surgery significantly (p<0.001) increases the risk of mesh exposure from 5.2% (43/824) without hysterectomy as compared to 18.9% (125/6620) with hysterectomy (P<.001) (Level 2) (Table 33).

8.3. Vaginal sutures

Three studies have evaluated the type of sutures used for closure of the vaginal skin. The first two studies have matched women under-

Table 33. Comparison mesh exposure rate at transvaginal polypropylene mesh surgery with and without hysterectomy.

Author	Year	Number	Review months	Surgical technique	"Mesh exposure hysterectomy n/N (%)"	"Mesh exposure no hysterectomy n/N (%)"	p value
Ganer Herman(739)	2019	70	18	Prolift, Avaulta, soft PP gynemesh	3/36 (8.3)	2/34 (5.8)	0.67
Huang(629)	2015	102	26-32	Prolift PP mesh	5/24 (20.8)	6/78 (7.7)	0.124
Stanford(740)	2015	142	24	Elevate PP mesh	4/29 (13.8)	4/112 (3.6)	0.094
El-Khawand (647)	2014	201	14	Prolift, Avaulta, Uphold and custom arcus-to-arcus polyform PP mesh	16/68 (23.5)	1/133 (0.8)	<0.001
Vu (741)	2012	77	29	Uphold PP mesh	2/24 (8%)	1/53 (2)	
Chu (736)	2011	91	9	Perigee & apogee PP mesh	5/39 (12.8)	2/52 (3.8)	
Guillilbert (737)	2009	208	36	PP mesh	24/77 (31.2)	7/40 (17.5)	
Ganj (653)	2009	127	18	PP mesh	6/21 (28.6)	7/106 (6.6)	
Neuman (738)	2007	79	29	Posterior IVS multifilament	6/44 (13.6)	4/35 (11.4)	
Deffieux (657)	**2007**	**138**	**32**	**Gynemesh PP mesh**	**20/103 (19.4)**	**7/35 (20)**	
de Tayrac (652)	**2007**	**143**	**10**	**Ugytex coated PP mesh**	**6/57 (10.5)**	**3/86 (3.5)**	**0.089**
Collinet (234)	**2006**	**277**	**2**	**Gynemesh Soft PP mesh**	**30/164 (18.3)**	**4/113 (3.5)**	
Total					**125/662 (18.9%)**	**43/824 (5.2%)**	**<0.001**

Abbreviation: PP: polypropylene, IVS: posterior intravaginal slingplasty

going POP surgery with vaginal closure with multi-filament sutures with a cohort in which 2.0 monofilament sutures were used. In the first study, the multifilament suture group had significantly higher rates of offensive discharge (p<0.001), vaginal bleeding (p<0.001) and vaginal pain (p=0.004) (Level 3). They were more likely to receive medical advice (0.007). However, patients in the multifilament group were no more likely to suffer from a UTI (p=1.000) or to be readmitted post-operatively (p=1.000).(742) In the second study, offensive vaginal discharge was also more common in the multifilament group (24% vs 12%; p=0.04) (Level 3). However, there was no increased requirement to seek advice from a health professional (33% vs. 25%; p = 0.27) or to require antibiotics. Vaginal bleeding (10% vs. 5%; p = 0.28) and urinary infection (2% vs. 5%; p = 0.44) were statistically no more common in the multifilament group (Level 3).(743) The third study has compared non-coated monofilament with triclosan-coated (antiseptic properties) monofilament sutures. Surgical site infections occurred in 3/78 (3.8%) in the first group versus 1/72 in the second group (1.4%), with no statistically significant difference (P=0.62) (Level 3).(744)

8.4. Vaginal packing

Only one double-blind randomised study of 190 women undergoing vaginal hysterectomy and/or pelvic floor repair has evaluated the effect of vaginal packing following pelvic floor surgery with regard to post-operative pain, bleeding and infection. No statistically significant differences in the post-operative pain scores or secondary outcome measures were demonstrated. Incidence of haematoma formation (14.8 % no pack, 7.3 % pack, p = 0.204) was not statistically significant (Level 2). There were three clinically significant complications in the no pack group and none in the pack group. There is no evidence to suggest that packing increases pain scores or post-operative morbidity. A trend towards increased haematoma and significant complications was seen in the no pack group. Unfortunately, duration of inpatient stay was not recorded in that study. As vaginal packing does no harm and may be of some benefit, authors argued that packing should be recommended as routine clinical practice for vaginal surgery.(745)

Another prospective study has been done on 63 consecutive women undergoing elective vaginal surgery for POP in whom vaginal packs were inserted after surgery, and weighed before insertion and at the time of removal the day after surgery. There was a statistically significant increase in pack weight of 6.7g (p<0.01). Five percent of the patients had a bleed of more than 25g into the pack. Removal of the pack was associated with minor discomfort. Complications in the post-operative period were low with 11% of patients seen in the first 6 weeks with bleeding or discharge. Authors have concluded that packs are probably not required for controlling post-operative blood loss in the majority of patients.(746)

9. PREVENTION METHODS FOR ABDOMINAL SACRAL COLPOPEXY

9.1. Learning curve

The prevalence of conversion to laparotomy, intra- and post-operative complications and early recurrence, seemed to be associated with the experience of the surgeon (learning curve). The surgical “proficiency” was achieved after 55-84 cases for laparoscopic or robot-assisted laparoscopic sacral-colpopexy/hysteropexy.(747-749) (Level 3) However, the incidence of severe complications does not seem to be related to the learning curve.(341,342)

In a comparative retrospective series, the rate of complications/re-intervention was not associated with the specialty of the surgeon (urologist or gynaecologist).(750) A recent RCT compared ETHIBOND (polyester) and absorbable VICRYL polyglactin) sutures for vaginal mesh attachment during sacral cervicopexy.(642) In this

study, 150 women were randomized. Primary outcome was the correction of POP; no difference was observed at 12 months follow-up (100% in both groups) however mesh exposure rate was non significantly higher at 4% following the permanent suture as compared to no exposures in the absorbable suture group.

9.2. Choice of surgical route for sacrocolpopexy

Most complications following sacral colpopexy occur irrespective of entry route. Most RCT's observed that laparoscopic sacral colpopexy is as effective as the open abdominal procedure, with a reduced rate of intraoperative bleeding, hospitalisation and wound complications.(337,338) Robotic sacral colpopexy (RSC) and laparoscopic procedure had similar operative times, short-term anatomic cure rates, and length of hospital stay (335,348) (Level 2) however the robotic approach had longer operating time, greater pain and higher costs than LSC.(348, 384, 639) The learning curve to reduce complications occurs around 55-70 procedures and is similar for laparoscopic and robotic approach are similar.(747-749)

Robot-assistance did not seem to be associated with a decrease risk in complications/reoperation rates when compared to the classical laparoscopic approach (751) especially concerning vaginal exposure rates and complications. (351)

The laparoscopic and robotic approaches are associated with a decrease in blood loss and shorter length of hospital stay, when compared to open route (Level 2).(639,685) However, overall complications rates are comparable in either approach.

9.3. Choose the right mesh for abdominal surgery

In a retrospective comparative study of open abdominal sacral colpopexy, Quiroz et al have shown that the short-term mesh-related complication rate was significantly higher with polypropylene than with porcine dermis [24/102 vs 12/134, p=0.003] (357)(Level 3), however the prolapse recurrence rate using porcine dermis was higher [7/93 vs 0/105, p = 0.004]. Another study comparing fascia lata and polypropylene meshes with five-year review, has shown a long-term increased recurrence rate, but with no differences in the rate of complication.(352)(Level 2) Concerning LSC, in a prospective comparative non randomised study, Deprest et al have shown that recurrences at the level of anterior and apical compartment occur significantly more often when using a biograft, in comparison to polypropylene, 21% vs 3%, p<0.01 and 36% vs 19%, p <0.05, respectively (Level 3).(358) Partially absorbable composite meshes (polyglactin + polypropylene) also seems to increase the risk of short-term recurrences (Level 4).(752)

The rate of mesh exposure 7-years following sacral colpopexy was high at 10% in the E-Care paper a finding that maybe related to graft and suture choice. More than 50% cases a multi-filament mesh was utilised, 50% used permanent sutures and 36% had concomitant hysterectomy all factors associated with high rate of mesh exposure.(327) Long-term rates of mesh exposure of 3% or less have been reported 5-years following laparoscopic sacrocolpopexy when monofilament microporous graft and delayed absorbable sutures are utilised.(331,640)

The risk of vaginal mesh exposure seems to be higher with the use of polytetrafluoroethylene than with polypropylene meshes at ASC (15% vs 0%, p=0.03) (Level 4) (619)[38] and 19% vs 5% (Level 2).(253) Similar results were observed with the use of silicon-coated polyester (19% vs 0%, p<0.05) (Level 4).(753)

A retrospective series (n=105) compared at 2 years follow-up, the outcomes of laparoscopic sacrocolpopexy either with polyvinylidene fluoride (PVDF) or hybrid polypropylene containing a resorbable polyglecaprone (PP+PG) mesh.(754) There were no differences in complications/reoperation rates, patient satisfaction and anatomical outcomes after LSCP either with PVDF or PP+PG mesh.

Another series (n=136) compared the surgical, anatomical, and functional outcomes of sacrocolpopexy using polyvinylidene fluoride (PVDF) mesh versus using the standard polypropylene mesh. (755) Postoperative anatomical correction was not significantly different between the two groups. The PVDF group showed superior results in term of storage symptoms (PVDF=0% versus PP=8.2%; p=0.02) and lower rate of sexual dysfunction (PVDF=0% versus PP=16,4%; p=0.001). Only 1 patient in PP group and 2 in PVDF group (p=0.47) presented a mesh exposure. There was no statistical difference in PGI-I scores (PP=1.5±1.0 vs PVDF=1.8±0.5; p=0.40).

Consensus Statement of the European Urology Association (EAU) and the European Urogynaecological Association on the Use of Implanted Materials for Treating Pelvic Organ Prolapse (756) and the European Commission's SCENIHR report on the use of surgical meshes (SCENIHR 2015) supported the use of polypropylene or polyester meshes for sacral colpopexy/hysteropexy.

For now, no comparative study was conducted on ultra-lightweight polypropylene mesh versus classical polypropylene meshes.

9.4. Choose the right fixation technique to the promontory, vaginal wall and levator ani

Most of authors perform a direct fixation to the vaginal wall using absorbable or non-absorbable sutures, and to the promontory using non-absorbable sutures (Level 3).(333,752,757,758)

Fewer authors use staples for the mesh fixation, both to the vaginal wall and to the levator ani muscle,(341) or tackers to the promontory.(66,324,337) Spondylitis has been reported after both tackers (759) and sutures (333,336,757) are utilised to secure the graft to the promontory. Whatever the fixation material use for the vaginal wall, the main method of preventing the occurrence of vaginal mesh exposure seems to avoid breaching the vaginal epithelium (Level 4).(760)

The rate of vaginal suture exposure was 7% in a long-term cohort series (when using polyester sutures). Use of permanent polyester (Ethibond) suture was strongly associated with an increased risk of vaginal suture erosion (OR 10.82 95%CI 2.54– 46.10 p =0.001; comparative use of PDS suture) when compared to slowly dissolvable, polydioxanone, monofilament sutures (PDS) (Level 3).(330)

This effect estimate was not changed by adjustment for other potentially relevant factors, including patient age and use of concomitant procedures. Furthermore a retrospective comparative series observed that the use of delayed-absorbable monofilament sutures for suturing the mesh to the vagina was not associated with an increased risk of failure in patients undergoing sacral colpopexy.(761)

In a RCT conducted in 204 patients undergoing sacrocolpopexy associated with total hysterectomy, absorbable (PDS) and non absorbable (GORE-TEX)) sutures were assessed for the polypropylene mesh attachment to the vagina; the primary outcome was vaginal mesh/suture exposure rate at 12 months-follow-up.(643) The vaginal mesh/permanent suture exposure was comparable in both groups (5%, vs 7%,RR 0.73; 95%CI 0.24-2.22) and much higher than the 2.1% reported in over 5000 trials reported above and may reflect the concomitant performance of hysterectomy in the cohort.

Composite success rate was comparable in both groups (93% vs 95%; p=0.43). Recently, a German group randomly compared absorbable vicryl (n=940 and non-absorbable ethibond sutures (n=96) at sacrocolpopexy for vault prolapse. At 6 months there were no mesh exposures and equivalent objective and subjective outcomes. There were three (3%) suture exposures in the permanent suture group and none in the vicryl sutures group.(762)

Alternative techniques of fixation may be anchors or glue, but limited data have been published concerning these techniques of suturing.

At short term follow-up, a limited sample sized RCT showed that the use of delayed absorbable anchors was associated with a decrease in the operative duration when compared to sutures for mesh vaginal attachment during robotic assisted sacral colpopexy (12 min vs 21 min, p<.001) (Level 2). However, the overall duration of the procedure, complication rates and PROs were comparable in the two groups (Level 3).(763)

At medium term follow-up (36 months), it was reported that the use of glue mesh fixation to the vagina was feasible and associated with good objective and subjective success rates following sacrocolpopexy.(Level 4)(764) However, one case of vaginal mesh exposure and 7 cases of “mesh shrinkage” have been reported in this series that involved 70 women.

9.5. Concomitant hysterectomy

The risk of vaginal mesh exposure is significantly increased in cases of sacrocolpopexy associated with concomitant total hysterectomy (8.6%), in comparison to 2.2% in those with previous hysterectomy , 1.5% at sacral hysteropexy and 1.7% subtotal hysterectomy. (641)(Level 4).

Previous hysterectomy was associated with an increased prevalence of serious complication when compared to concomitant hysterectomy, in a recent series conducted in more than 800 patients. (378)

9.6. Peritoneal closure

Reoperation rate related to the absence of peritoneal closure remains debated. Most of authors close the peritoneum after a sacrocolpopexy, both after open (262,675,765) and laparoscopic approach.(324,333,758) A recent review of 450 cases of laparoscopic and robotic sacrocolpopexy demonstrated a 1.8% rate of post-operative ileus or small bowel obstruction that were equally distributed between those with mesh that was and was not reperitionealised. (766)

In the largest series concerning sacral colpopexy/hysteropexy (n=178 with 35months review) without peritoneal closure,(767) a total of 77 complications were observed in 49 patients, ranging from one to six complications per patient. Five (3%) serious complications were unanimously or possibly thought to be possibly related to nonperitonealisation (ileus due to mesh adhesions or enterovaginal fistula requiring surgical intervention).

CONCLUSION

Pelvic organ prolapse reconstructive surgery is associated with rare but potentially severe complication, whatever the surgical approach and the use of mesh.

Preoperatively, patients should be informed that a mesh is considered a permanent implant; removal of mesh or correction of mesh-related complications may involve subsequent surgeries. Furthermore, complete removal of mesh may not be possible and additional surgeries may not fully correct some complications. Patients must also be informed of conservative and alternative surgical techniques.

Proposed Recommendations to Reduce the Rate of Complications

GoR A

Patients should be informed that transvaginal meshes have a higher reoperation rate than native tissue vaginal repairs.

GoR B

Concerning vaginal surgery:

Bowel preparation prior to surgery is not recommended.

If a synthetic mesh is placed by the vaginal route, it is recommended that a macroporous polypropylene monofilament mesh should be used.

The use of polyester mesh is not recommended.

Cranberies prophylaxis is not recommended.

***Concerning sacral colpopexy*:**

The use silicone-coated polyester, porcine dermis, fascia lata, and polytetrafluoroethylene meshes is not recommended.

It is recommended to avoid total hysterectomy.

GoR C

Whatever the surgical route:

The first cases should be undertaken with the guidance of an experienced surgeon in the relevant technique.

Pre-operative vaginal oestrogen therapy may reduce postoperative complications.

Concerning sacrocolpopexy:

Laparoscopic approach is recommended for sacral colpopexy

The use of polyester (without silicone coating) or monofilament polypropylene meshes is recommended.

Delayed absorbable sutures for securing mesh to vaginal recommended

Concomitant total hysterectomy associated increased risk mesh exposure

Expert Opinion

***Whatever the surgical route*:**

As with any surgery, cessation of smoking preoperatively is recommended.

It is recommended to comply with the prevention of nosocomial infections.

Antibiotic prophylaxis is recommended, regardless of the approach.

Thromboembolic prophylaxis is recommended, regardless of the approach.

It is recommended that preoperative urinary tract infections are identified and treated.

Concerning vaginal surgery:
It is recommended that a non-absorbable synthetic mesh should not be inserted into the rectovaginal septum when a rectal injury occurs.

The placement of a non-absorbable synthetic mesh into the vesicovaginal fascia may be considered after a bladder injury has been repaired if the repair is considered to be satisfactory.

It is possible to perform a hysterectomy in association with the introduction of a non-absorbable synthetic mesh inserted vaginally but this is not recommended routinely.

It is recommended to minimise the excision of vaginal tissue.

Concerning sacrocolpopexy:
It is recommended that the type and commercial name of mesh used in the operative report.

Peritoneal closure is recommended to cover the meshes.

X. RISK FACTORS RECURRENT PROLAPSE

While poor outcomes from prolapse surgery are difficult to succinctly define, knowledge of prognostic variables which could influence the outcome of surgery, along with incidences of failure and complications, are invaluable information for both patient and surgeon. While the remainder of the chapter concentrates on procedural safety and efficacy, in this section we seek to evaluate the impact of non-procedural factors such as patient and surgeon characteristics and peri-operative interventions on prolapse surgery outcomes.

1. PATIENT CHARACTERISTICS

Recurrent prolapse were most commonly reported in the anterior compartment(768,769) although in a10-year multivariate analysis of 374 American women by Denman et al this was not able to be confirmed.(108) They identified prior pelvic organ prolapse or urinary incontinence (POPUI) surgery conferred a hazard ratio of 1.9 (95% CI, 1.1-3.2; P .018) for recurrent prolapse surgery. The abdominal approach was protective against reoperation compared with the vaginal approach (hazard ratio, 0.37; 95% CI, 0.17-0.83; P .02). No association was observed for age, vaginal parity, previous hysterectomy, body mass index, prolapse severity, ethnicity, chronic lung disease, smoking, oestrogen status, surgical indication, or anatomic compartment.

Vergeldt et al completed a comprehensive systematic review evaluating 28 pre-determined risk factors for recurrent prolapse(770) and after screening 7,500 relevant articles only 5 trials fulfilled predefined inclusion criteria(768,771-774) (POP recurrence defined as stage 2 or greater, at least 1 year review, native tissue repairs only and a multivariate analysis reported. The only predictive factor for recurrent prolapse in all five papers was preoperative POP-Q stages III or IV prolapse although in Tegerstedt et al(774) only preoperative stage III, and not IV was a risk factor. Briefly, Weemhoff et al(772) prospectively evaluated 156 women having repair of vaginal repair cystocele. Risk factors for anatomical recurrence were complete avulsion of puborectalis muscle (OR, 2.4; 95% CI, 1.3, 4.7), advanced preoperative stage (OR, 2.0; 95% CI, 1.0, 4.1), family history of prolapse (OR, 2.4; 95% CI, 1.2, 4.9), and sacrospinous ligament fixation (SSLF) (OR, 6.5; 95% CI, 2.0, 21.2). Salvatore identified 36 of an original 360 women who had undergone vaginal prolapse surgery and the only predictive factor for recurrence was initial stage III or IV prolapse (OR 2.4, 1.1–5.1 95% CI).(771)

Diez-Itza et al (768) reported on a retrospective cohort of 134 women five years after prolapse surgery and while 42 (31.3%) had anatomical recurrence of the prolapse (grade≥II), only 10 (7.4%) had prolapse related symptoms. Advanced preoperative prolapse (grade III–IV) of any compartment was associated with anatomical failure but not with symptomatic recurrence, (OR 3.93; 95% CI, 1.19–12.97). This study also suggested age under 60 years and weight over 65kg were additional prognostic factors for recurrence. Poor levator muscle contraction strength was not a risk factor for recurrent prolapse.

In a prospective observational study of 389 patients, age less than 60 years (OR 3.2; 95% CI, 1.6-6.4) and POP-Q stages III and IV, (OR 2.7; 95% CI, 1.3-5.3) were associated with greater risk for recurrent prolapse at 1 year.(773) No other prognostic variables were identified in this prospective observational study. Specifically, there was no difference in outcomes between the four surgeons, all described as Urogynaecologist. Concomitant Burch or sling for stress incontinence protected against recurrent anterior wall prolapse, but increased the risk of a posterior wall prolapse.

Diminished levator strength and wide genital hiatus are possible risk factors for recurrent prolapse. The data on levator muscle strength is conflicting. Diez-Itza et al (768) demonstrated in multivariate analysis that decreased levator strength was not predictive of recurrent prolapse. However, in univariate analysis of 358 women 5 months after prolapse surgery, Vakili et al demonstrated diminished levator strength was associated with recurrent prolapse (35.8% versus 0%; P = .017) as was a genital hiatus 5 cm or greater (44.2% vs 27.8%; P = .034). Increasing levator contraction strength was associated with a decreased reoperation rate for pelvic floor disorders.(775) The theory of an enlarged genital hiatus being a risk factor for recurrent prolapse is supported by the retrospective univariate analysis by Medina et al (776) which demonstrated a correlation for recurrent anterior compartment prolapse and genital hiatus measurement greater than 5cm. The rate of post-operative anterior vaginal wall prolapse was greater in patients with a wide genital hiatus compared with those with a normal genital hiatus (34.3% vs 10% respectively; OR 4.7 95% CI 1.0– 24.1).

As noted above Weemhoff confirmed after multivariate analysis that complete avulsion of the puborectalis muscle (USS confirmed) was a risk factor for objective recurrence of cystocele (OR, 2.3; 95% CI, 1.1, 4.8).(772)

Diez-Itza 2020 prospectively evaluated 455 women one year after undergoing anterior colporrhaphy surgery for anterior compartment prolapse and after multivariate analysis determined that levator ani defects (OR 1.96), levator hiatal area >25cm^2 (OR 2.51) stage 3 (OR 2.34) and stage 4 prolapse (OR 4.47) were independent risk factors for recurrence.

Alternatively, a variety of authors evaluating women with cystoceles did not identify LAM defects as being predictive of failure after multivariate analysis.

Wong et al 2013 evaluated 209 women, 2.2 years (range 3 months to 5.6 years) after a variety of anterior transvaginal mesh procedures. Levator avulsion was not a risk factor for symptomatic prolapse, POP-Q stage 2 prolapse, descent of Point Ba on examination, or mean bladder descent on ultrasound. (777) Vergeldt et al , in an evaluation of 287 women undergoing anterior colporrhaphy, after multivariate analysis levator defects were not an independent risk factor for recurrent prolapse OR 1.37 (0.8 to 2.34).(778)

Wong et al 2020 reported on 154 Chinese women with Stage 3-4 prolapse 2-years following native tissue repair and 5-years after vaginal and abdominal mesh procedures and found LAM defect was not a risk factor for recurrent prolapse after multivariate analysis.(779)

A South American group retrospectively evaluated 134 women 16 months after laparoscopic sacral colpopexy and reported LAM defect (OR 0.99 95% CI 0.098-10.1) or ballooning on pelvic floor USS (OR 1.1 95% CI 0.99-1.2) were not risk factors for recurrent prolapse after multivariate analysis.(780)

Similarly, Norwegian group reported only preoperative stage 3 or greater POP (OR 2.8 95% CI 1.4-5.3) was an independent risk factor for recurrent prolapse 1-year after Manchester repair (n=189) performed for anterior compartment prolapse. LAM defect was not an independent risk factor (OR 1.7 95% CI 0.9-3.2).(200)

The data from multivariate analysis is inconsistent in determining if pre-operative levator ani defects are a risk factor for recurrent prolapse.

While women with a positive family history are two to three times more likely to develop prolapse than women without a positive family history,(781,782) the evidence from multivariate analysis is conflicting in regard to recurrent prolapse.(768,772) It has also been demonstrated that women with reduced type 1 collagen and increased collagenolytic activity in vaginal tissue are predisposed to prolapse.(783,784) In a preliminary study, Khaja et al was not able to demonstrate a relationship between quality or type of collagen and outcome of anterior colporrhaphy.(785) Further evaluation of these risk factors is warranted.

2. SURGEON CHARACTERISTICS

2.1. Surgeon experience

The experience of the surgeon was not identified as an increased risk of vaginal prolapse recurrence following prolapse surgery in a multivariate analysis undertaken by Diez-Itza et al.(768) A systematic review by Mowat et al of low versus high volume surgery (low defined as < than 12 procedures/year) found a higher rates of complications for of all gynaecology procedures for low versus high volume surgeons. In the urogynaecology group, a single study reported that the LVS group had a higher rate of any complication (RR 1.4 95% CI 1.2-1.6). The evidence is of moderate to very low quality.(734)

Surgeon surgical volume was assessed in a retrospective analysis of all 5,488 vaginal mesh POP procedures performed by 368 surgeons in Ontario Canada, from 2002 to 2013. At 10-year review, the hazard of reoperation for complications was lower for patients of high-volume (>14 cases per annum) surgeons (3.0%, 145/3,001] compared with non- high-volume surgeons (4.8%, 73/2,447), adjusted hazards ratio 0.59, 95% CI 0.40–0.86). In multivariable modelling, younger age, concomitant hysterectomy, blood transfusion, and increased medical comorbidity were all also associated with reoperation. Patients of high-volume surgeons were less likely to have a concurrent hysterectomy (32.5% versus 37.7%) and had a shorter post-operative stay in the hospital (median 2.0 versus 3 days).(786) Overall, 1 in 20 women required a second surgery for a transvaginal mesh complication, after 10 years of follow-up and this risk was reduced by 41% for patients of high volume surgeons.

2.2. Surgeon learning curve

For total vaginal mesh (TVM) repair for POP, a significant surgeon learning curve was demonstrated in a multivariate analysis by Long et al.(787) Women operated on during the surgeons first 50 cases were 11.93 times (95% CI: 1.79–240.1) more likely than subsequent women to develop a stage 2 POP-Q recurrence. A further retrospective study of 138 SSLF procedures also identified lower surgeon experience (< 20 cases) as a significant risk factor for recurrence (OR 2.7 95% CI 1.1 to 6.8) as compared to surgeon having performed > 20 cases.(788)

LSC requires the attaining of laparoscopic suturing and knot tying skills. Claerhout et al observed that LSC operative duration decreased rapidly during the first 30 procedures and reached steady state after 90 cases. However, complication rates remained unchanged throughout this learning curve series. Using a cumulative sum approach, they hypothesized that adequate learning occurred after 60 cases (Level 4).(341) Akladios et al also observed that LSC operation duration decreased after 25 procedures.(342) The complication rates were also low throughout this series and were not affected by learning curve. However, this study analysed the learning curve of a senior urogynaecology surgeon who was initiated into this technique, and not the learning curve of a trainee. Kantartzis et al analysed the learning curves of the first 180 LSC done by 4 attending Urogynaecologist and observed that there was no significant difference in the rate of overall complications regardless of the number of prior procedures performed (Level 4).(789) Mustafa et al (2012) observed that LSC operative time decreased considerably following the first 15 cases (Level 4).(343)

However, since complication rates associated with LSC are low, the published series cannot assess the effect of under-experience since the number of cases is few in each series. Furthermore, the complication rates are probably limited because of the supervision by a ‘senior surgeon’ during this learning curve. Prior training in laparoscopic suturing coincided with a short learning process for the phases requiring suturing.(747) The most time-consuming step is the dissection of the vault, for which it took the trainee 31 procedures to achieve an operation time comparable to that of the teacher.(747)

Protagonist of robotic approach to sacral colpopexy often cite quicker learning compared to laparoscopic approach as a significant advantage to robotic technique. Recent reviews do not support this view with reduction in operating time and complications very similar to that reported above for laparoscopic approach. An American group reported operating time of RSC plateaued after 60 cases and peri-operative complications stabilized after 84 cases.(748) Almost identically a Dutch group reported operating time reduction of

25% was achieved after 28 cases and perioperative complications stabilised at 78 cases.(749)

Similarly, Morgan et al (790) used multivariate analysis to look at the effect of surgeon case volume on use of apical colpopexy and cystoscopy and in the rate of intraoperative complications during hysterectomy for prolapse. Vaginal hysterectomy was undertaken for 78% of cases. Low (≤10 cases), intermediate (1 1–49 cases)-, and high (≥50 cases)-volume surgeon groups over a 4-year period were established a priori. High-volume (OR, 0.42; 95% CI, 0.30-0.61) and low-volume (OR, 0.32; 95% CI, 0.15-0.66) surgeons were less likely than intermediate-volume surgeons to have intraoperative complications during vaginal hysterectomy for prolapse. The difference between high- and low-volume surgeons was not statistically significant (OR, 0.77; 95% CI, 0.5-1.2). The finding that intermediate-volume surgeons have the highest rates of intraoperative complications suggests a nonlinear relationship between surgeon volume and avoidance of injury. The low volume surgeons however were far more likely to have a second experienced surgeon present for the case which could account for this. High volume surgeons were more likely to perform concomitant colpopexy and cystoscopy than intermediate or low volume surgeons.

A retrospective surgical database study by Sung et al(791) demonstrated that for urogynaecological procedures low volume (<8 case per year) and intermediate volume (8-18 cases per year) had significantly higher rates of intraoperative complications (RR 1.36 and 1.24 respectively) than high volume surgeons (>18 cases per year). This was from the Nationwide Inpatient sample in the USA which represents a 20% stratified sample of US hospitals between 1998 and 2003.

2.3. Physiotherapy

Pelvic floor muscle training (PFMT) is often recommended for women undergoing surgery for pelvic organ prolapse despite little evidence in the literature to support its routine use.

Jarvis et al(792) randomised 60 women undergoing surgery for prolapse or incontinence and reported an improvement in urinary symptoms and quality of life in the women who received pre and post-operative pelvic floor muscle training (Jarvis et al). Follow up was only to 3 months post operatively and the differences in outcomes could be explained by the fact that the treatment group underwent continence surgery (10/23, 44%) twice as frequently as the control group (6/27 22%).

In another Australian RCT by Frawley et al, (793) 51 women were allocated prolapse or continence surgery with and without supervised pre and post-operative pelvic floor exercises. No differences were detected at 1 year between the groups in Urogenital Distress Inventory (UDI) and the Incontinence Impact Questionnaire (IIQ) scores. Neither of the above trials reported effect on prolapse symptoms or need for retreatment.

Pauls reported no benefit in a recent RCT (n=25 each group) comparing native tissue prolapse surgery with and without structured PFMT (1 preoperative and 5 post-operative visits with expert pelvic floor therapist) at 6-month review on a variety of outcomes including validated pelvic floor questionnaires and POP-Q staging. Quality of life and prolapsed, urinary and sexual function scores were improved equally in both groups reflecting the effect of the surgery and not the addition of a PFMT program.

In a slightly larger (n=28 in each group) multi-centre RCT, McClurg et al (794) compared prolapse surgery with and without structured PFMT (1 preoperative, one phone call in week one and five post-operative visits with a dedicated pelvic floor physiotherapist over a 12-week period). At 6-month review of the whole available cohort no differences were detected between the two groups. Participant retention was problematic with less than 50% completing questionnaires and less than 20% completed examination at 12 months. At 12-month review at a single study site the treatment group had improved outcomes on the POP-SS and SF-12 scores. Unfortunately,

Table 34. Risk factors for recurrent prolapse

Outcomes	Multivariate evidence	Risk quantification	GoE
Patient factors			
Age	<60 yrs.	OR 3.2-4.1(768, 773)	GoE B
BMI/Weight (Kgs)	Conflicting		
Family history	Conflicting		
Stage 3-4 prolapse	Yes		GoE A
Prior Pelvic floor Surgery	Conflicting	RR 2.0-3.9(768, 771, 772)	
Levator defect			
Size Genital Hiatus	Conflicting data		
Poor levator strength	Not risk factor		GoE C
Levator defects	Conflicting data		
Type collagen	Not risk factor		
Perioperative Factors			
Surgeon factors			
Less experienced			
Recurrent prolapse	↑ LVS	2.7-11.9(787, 788)	GoE C
Complications	No evidence		
HVS vs LVS			
Recurrent prolapse	No evidence		
Complications	↑LVS	RR 1.4 to 2.4(734, 790, 791)	GoE B
Perioperative Physio	Not protective		GoE A

Abbreviation: PP: polypropylene, IVS: posterior intravaginal slingplasty

the 12-month results do not include eligible participants from other sites which detracts from the validity of the trial.

In the largest randomised trial to date by Barber et al,(297) 374 women undergoing surgery to treat both apical vaginal prolapse and stress urinary incontinence were recruited and two-year follow-up rate was 84.5%. The intervention group underwent pelvic floor assessment and taught PFMT 2 to 4 weeks pre-op and were re-assessed four times post operatively up to 12 weeks. Importantly this trial did include prolapse specific follow up assessment as well as urinary symptoms using UDI. No difference was found between behavioural therapy and pelvic floor muscle training and control group for urinary scores at 6 months [treatment difference −6.7 (95% CI −19.7, 6.2)], or prolapse scores at 24 months [treatment difference −8.0(95% CI −22.1, 6.1)] or anatomic success at 24 months. This trial differs from those by Frawley and Jarvis in that those supervising and teaching the behavioral package and PFMT were not interventional physiotherapists, but trained and certified clinicians.

Durate et al most recently randomised 95 women undergoing prolapse surgery to surgery with perioperative structured PFE (4 preoperative and 7 postoperative physiotherapy visits) and without PFE. At 90 days there was no discernible benefit in prolapse symptoms, quality of life, sexual function or pelvic floor muscle strength. (795)

These findings do not support the routine use of PFMT programs for women undergoing repair for pelvic organ prolapse. Table 34 summarises data relating to possible risk factors for recurrent prolapse and the Grade of evidence supporting the finding

XI. ECONOMICS OF PROLAPSE SURGERY

Despite the high prevalence and frequency of surgery for pelvic organ prolapse (POP), there is insufficient information on the costs of medical care for this condition. POP is a common pathology in middle-aged women, affecting approximately 50% of women over 50,(7) with an estimated global prevalence of 2.9% in women older than 20 in USA.(796) A study in USA estimated that the direct costs of POP surgery were substantial, amounting to $1,012 million (95% confidence interval $755, 1,251 million) for a total of 226,000 patient surgical procedures during 1997.(797) A European study showed that the number (rate) of admissions for POP surgery was 36,679 (1.14 per 1,000 women) in France and 28,959 (1.13 per 1,000 women) in England in the year 2005. The total costs were €144,236,557, €83,067,825 and €81,030,907 in German, France and England respectively, which were considered to be substantial, and required more attention in order to decrease the burden on the countries studied.(798) In addition, direct costs must be added to the indirect costs resulting from the loss of productivity and wages as well as the intangible costs arising from the deterioration of the quality of life. Mestre et al (799) reviewed that 50% women who consulted for urogynaecological problems are still active in the society and 60% of them reported some type of sexual dysfunction.

In the current situation of progressive aging population, a significant increase in the prevalence of POP is to be expected. In USA, a study estimated that there will be an increase in the number of women with symptomatic POP between 2010 and 2050 from 46% (3.2 to 4.9 million women) to 200% (from 3.3 to 9.2 million women). (800) This will lead to an increase in demand for treatment as well as the need for economic resources.

Traditionally, Gynaecologists have based their decisions regarding treatment options upon the success rate, patient satisfaction, peri-operative morbidities and complications. With rising health care costs and in a setting of finite resources, it is now imperative that clinicians should include the financial costs of surgical interventions as a vital part of their decision-making process. Hullfish et al designed a study to compare the relative cost-effectiveness of treatment decision alternatives for post-hysterectomy POP.(801) The authors used a Markov decision analysis model to assess and compare the relative cost-effectiveness of expectant management, use of a ring pessary and vaginal reconstructive surgery (VRS) and open or robotic sacral colpopexy to obtain months of quality adjusted life (OALY) over 1 year. Laparoscopy for prolapse surgery and vaginal mesh kits were excluded as the authors do not utilise those two procedures at their institutions and colpocleisis was also excluded as the baseline cases desired preservation of coital function. Only two decision alternatives were found to be cost-effective: pessary use and VRS. Pessary use achieved 10.4 OALY at a cost of $10,000 per patient. This cost included all events for patients initially assigned to pessary use including costs for those patients who eventually underwent surgeries within the 12-month time frame. The VRS alternative obtained 11.4 QALY at $15,000 per patient. Each of the other alternatives achieved fewer OALY at greater cost. National Institute for Health and Case Excellence (NICE) had updated guidelines on management of POP in 2019, commenting that a time horizon of at least 5 years would be required to capture all important differences in costs and outcomes between surgery and pessary.(802) Even though pessary has lower intervention costs when compared with surgery, when taking into account the whole sequelae of events the cost differential will be reduced. At the same time, even though surgery has a high risk of complications that may require intensive care and may incur high costs, the women's individual choices and quality of life should be the main outcome of interest. In the analysis "Vaginal Pessaries for Pelvic Organ Prolapse or Stress Urinary Incontinence: A Health Technology Assessment",(803) the authors did the first known analysis estimating the cost-effectiveness of treatment sequences for POP (Pessary -> PFMT -> Surgery, PFMT -> pessary -> surgery, PFMT-> surgery, Pessary -> surgery, surgery), accounting for the complexities of treating these chronic conditions through a stepped care approach (a sequence of interventions followed after the current treatment proves ineffective). The time horizon was 10 years, which is useful when evaluating conservative treatments as they have a large discontinuations rate over time. They concluded that there was high degree of certainty that pessaries were cost-effective in a population with POP. When the treatment sequence of pessaries and surgery was compared with surgery alone, the pessaries treatment sequence dominated surgery alone in the cohort with POP, and in the cohort with SUI pessaries had an incremental cost-effectiveness ratio (ICER) of $1,033 per QALY gained.

There are several surgical techniques and materials used in the treatment of POP. For anterior, the cost-effectiveness of surgical management options (including mesh and non-mesh procedures) were evaluated. Over the last decade both clinical efficacy and cost-efficiency of the mid-urethral sling in incontinence surgery has been demonstrated. Transvaginal mesh kits have been introduced to prolapse surgery in an attempt to replicate this benefit for the community. A study on the analysis of the cost-effectiveness of traditional anterior colporrhaphy (AC), non-kit mesh and commercial mesh kits for anterior vaginal prolapse repair showed that commercial mesh-kits are not cost-effective.(804) The authors included the

estimated cost of managing recurrent prolapse and extrusions in the analytic model after performing a meta-analysis of 18 papers relating to anterior compartment repair to determine operating and admission time, recurrence rate and mesh extrusion rate for the three groups. The cost of non-kit mesh was $3,380, AC was $3,461 and mesh kits $4,678. Non-kit mesh repair is cost-effective, compared with AC, if extrusion rates remain below 25%. One-way cost sensitivity analysis demonstrates that when the reoperation rate for AC reached 28%, the commercial mesh kits became cost-effective. The balance of the costs of AC and non-mesh kits depends significantly on recurrence and extrusion rates could be erosion or exposure. Two-way cost sensitivity analysis demonstrated that if the re-operation rate of AC is below 20%, AC is more cost-effective even if the extrusion rate is 0%. When the reoperation rate of AC is 30% the non-mesh kit repair is the most effective operation if the extrusion rate is less than 25%.

At the same time Jacklin et al also used a decision-analytic Markov model to compare the cost effectiveness of anterior repair augmented with synthetic mesh against non-mesh anterior repair (805) and concluded that anterior augmented repair with mesh was relatively less cost-effective. Under base case assumption at five years, the incremental cost-effectiveness ratio (ICER) for mesh-augmented anterior repairs was £15 million per OALY. This was mostly due to the extra costs associated with the price of the mesh and treatment of mesh erosion. Glazener et al (587) evaluated the cost-effectiveness of surgical options for the management of anterior and / or posterior vaginal wall prolapse in the United Kingdom. The economic analysis was conducted alongside RCTs and supplemented with modelling. The first analysis was conducted alongside an RCT in women who were having their first (primary) anterior or posterior prolapse repair (n= 1,348). The interventions included standard repair, synthetic mesh, and biological graft. The secondary analysis was conducted alongside an RCT in women who were having their secondary anterior or posterior prolapse repair (n= 154). The analysis was conducted from NHS perspective and included a range of direct cost including intervention procedure costs (mesh cost, staff time in theatre, cost of drugs in theatre, cost of catheterisation, cost of vaginal packing, theatre overheads), inpatient and follow up secondary care costs (including new prolapse and incontinence procedures, other related readmissions, further prolapse related surgery, outpatient visits) and costs of primary care services relating to the index prolapse surgery (including physiotherapy, GP nurse, GP doctor, shelf pessary, ring pessary, incontinence drugs, oestrogen, intermittent catheter, absorbent pads, other drug treatments). For the outcome of primary anterior and / or posterior repair, incremental costs were £363 (95% CI, £32 to £758) and £565 (95% CI, £180 to £950) for synthetic mesh and biological graft Vs standard respectively. Incremental OALY were 0.071 (95% CI, 0.004 to 0.145) and 0.039 (95% CI, 0.041 to 0.120) for mesh and graft Vs standard respectively. A Markov decision model extrapolating trial results over 5 years showed standard repair had the highest probability of cost-effectiveness, but results were surrounded by considerable uncertainty. For secondary repair, there were no statistically significant differences between the randomised groups in any outcome measures, but the sample size was too small to be conclusive. The conclusions made were: in women who were having primary repairs, there was evidence of no benefit from the use of synthetic mesh or biological graft compared with standard repair. The secondary trials were two small to provide conclusive results. The NICE guidelines (802) committee acknowledged the existing UK-based economic evidence which showed that mesh was potentially cost-ineffective when compared with a non-mesh procedure in women with primary anterior POP. The guideline economic analysis with a 15-year time horizon demonstrated that anterior colporrhaphy (without mesh) was the dominant procedure (that is, it resulted in lower costs and higher OALYs) when compared with anterior colporrhaphy with biological graft / synthetic partially absorbable mesh / non absorbable mesh. The cost ineffectiveness of mesh was attributed to a higher rate of mesh complications including mesh extrusion / erosion and pain, and high costs associated with managing mesh complications. The probability of anterior colporrhaphy (without mesh) being cost effective was 0.69 at a NICE's lower cost-effectiveness threshold of £20,000 per OALY. Sensitivity analysis indicated the risk of mesh complications including mesh extrusion and pain would need to be very low for the mesh to be considered cost-effective. The committee also suggested that for women with a recurrent anterior POP with adequate apical support or when an abdominal approach is contraindicated, synthetic polypropylene or biological mesh placement could be considered as an option. In such cases, the benefits of synthetic or biological mesh placement will potentially outweigh the costs associated with the higher risk of mesh complications.

It is now recognised that women with advanced prolapse require adequate apical support to ensure durability of a simultaneous anterior and / or posterior correction.(806) Options for correcting apical prolapse include: sacral colpopexy (ASC) which can be performed via a laparotomy or laparoscopically including robotically assisted laparoscopy, sacrospinous ligament fixation (SSLF), uterosacral ligament suspension, McCall's culdoplasty and levator myorrhaphy. A Cochrane meta-analysis of level 1 data comparing abdominal sacrocolpopexy (ASC) with sacrospinous fixation (SSLF) showed that ASC was superior in terms of recurrent vault prolapse, post-operative stress urinary incontinence (SUI) and post-operative dyspareunia. However, the downside of ASC includes longer operating time, longer recovery time, and increased inpatient cost. Ohno et al used a decision analytic model to compare ASC to SSLF using TreeAge Pro (2013). Results showed that ASC is more expensive than SSLF ($13,988 vs $11,950) but is more effective (QALY 1.53 vs 1.45) and is cost-effective (ICER $24,574 / OALY) at 2 years (807). The additional costs incurred with ASC are justifiable owing to the improved outcome associated with ASC. However, if the cost of SSLF further decreases, or if the post-operative outcomes after SSLF improve, then ASC is no longer cost-effective. Limitations of the study include the lack of incorporation of the peri-operative complications like mesh erosion, wound complications etc. Evaluations extending the analysis to longer than two years are required.

Lua (808) also assessed the costs of sacrospinous ligament fixation (SSF), abdominal sacrocolpopexy (ASC), laparoscopic sacrocolpopexy (LSC), in women with apical prolapse in USA. The resource use estimates were based on the retrospective observational cohort study, commercial claims and encounter database (SSF, n=17,459); (ASC, n=6,126); (LSC, n=10,708). The mean total costs per women were $13,916 for SSF, $15,716 for ASC, and $16,838 for LSC. SSF was found to be more cost saving when compared with both ASC and LSC. Two cost-minimisation studies have evaluated the relative inpatient cost of robotic sacral colpopexy (RCS), laparoscopic sacral colpopexy (LSC) and ASC (809,810) with both findings that the ASC was the least costly inpatient option. Patel reviewed 15 cases, 5 each of ASC, LSC, RSC performed in USA in 2008 (Patel et al, 2009). Results showed that ASC was the least expensive at $13,419, LSC at $19,308 and RSC the most expensive at $24,161. Importantly, in this model there were no differences in length of stay and all procedures had long operating times, with the robotic procedure being over 2hr quicker than the laparoscopic procedures, which does not reflect common practice in the literature. Judd et al., using a decision model, estimated the hospital cost of ASC at $5,792, LSC at $7,353 and RSC at $8,508 (ex-

cluding the cost of the robotic system). In this model, RSC and LSC became cost equivalent only when the robotic operating time was reduced to 149 min, robotic disposables were reduced to $2,132 or laparoscopic disposables were increased to $3,413. Both models of analysis only included inpatient care and may not reflect other benefits of the minimally invasive approach such as quicker recovery and possibly faster return to work. Paraiso et al. performed an RCT comparing RSC (38) and LSC (40) for vault prolapse and reported the robotic group incurred significantly greater costs than the laparoscopic group (mean differences +$1,936; 95% CI $417-$3,454; P=0.008).(384) Importantly, in this study the authors were experienced laparoscopic surgeons who had also completed the learning phase of the RSC. At that same time; Anger et al (811) also randomised 78 women into laparoscopic and robotic group. The RSC group had higher initial hospital costs ($19,616 compared with $11,573, p<0.001) and over six weeks, hospital costs remained higher for RSC ($20,898 compared with $12,170, p<0.001). When costs of robot purchase and maintenance had been excluded, the difference would not be significant. Therefore, primary cost difference between RSC and LSC resulted from robot maintenance and purchase costs.

Maher and Connelly reported a cost minimisation analysis of an RCT comparing total vaginal mesh (TVM n=55) and LSC (n=53) in the management of vault prolapse at two years.(812) Opportunity costs, defined as the economic costs to the women associated with recovery time were added to define the total economic cost. Mean total economic costs were significantly lower in the LSC group compared with the TVM ($4,013.07, 95% CI 3,107.77-4,918.37). Labour costs were significantly greater for the LSC, reflecting that the operating time was twice as long as that of the TVM procedure. These higher labour costs were offset by lower consumable, inpatient, opportunity and reoperation costs for the LSC compared with the TVM. One-way cost analysis for the LSC and TVM demonstrates that cost equivalence would be achieved once the consumable cost reduced to zero, or the reoperation rate was zero in the TVM group or the operating time of the LSC was 130 min longer than that of the TVM. By using similar decision analysis model, Richardson et al compared the cost-effectiveness of three strategies for the use of a mid-urethral sling to prevent occult urinary incontinence in patients under-going abdominal sacral colpopexy.(813) They concluded that universal concomitant mid-urethral sling is the most cost-effective prophylaxis strategy for occult stress urinary incontinence undergoing ASC. Corracedo (814) compared the cost-effectiveness of laparoscopic sacrocolpopexy (LS) and transvaginal mesh (TVM) in women with POP in Spain. He made the conclusion that the mean total costs per woman were €5,985.7 (95% CI, €5,613.1 to €6,358.3) for LS and €6,534.3 (95% CI, €6,290.4 to €6778.3) for TVM. Based on the above costs, LS is cost saving when compared with TVM. Ehlert (815) assessed the costs associated with robotic sacrocolpopexy (RSC) when compared with transvaginal mesh repair (TVM) in women (n=226) the required surgical repair of POP in USA. In women who were also undergoing concomitant hysterectomy, the mean total costs per women were $12,483 for RSC and $9,676 for RSC and $6,719 for TVM. Based on the above costs, TVM is cost saving procedure. This was mainly due to lower surgical supplies costs and also shorter operating time. Husby (816) assessed the costs associated with Manchester-Fothergill procedure against uterosacral ligament suspension (with vaginal hysterectomy) in Denmark when considering only the primary operation, the mean total costs per woman over 20 months were €3,514 for uterosacral ligament suspension (with hysterectomy) and €2,318 for Manchster-Fothergill procedure is less expensive when compared with uterosacral ligament suspension (with hysterectomy) in women with apical POP. This was due to greater reoperations costs post uterosacral ligament suspension. The NICE committee (802) commented that the existing economic evidence for apical POP was non UK based and was too heterogenous. As a result, the committee could not draw any conclusion from it. Although, it was noted that laparoscopic procedure is less invasive, quicker to perform, and is associated with a shorter recovery, not all surgeons are trained in its use and it is not available in all centres.

According to NICE guidelines,(802) the existing economic evidence pertaining to posterior surgery was limited to one UK study (587) with the study population comprised of women with anterior and / or posterior POP. The probability of standard repair being cost-effective was 0.5 at any willingness-to-pay value per OALY. This supports that non-mesh repair is more favourable cost-effectiveness when compared with mesh repair.

An interesting retrospective study in 2016 studied the trends and factors influencing inpatient prolapse surgical cost and length of stay in United States.(817) This retrospective cross-sectional study along with longitudinal trend analysis from 2001 to 2011 National Inpatient Sample (NIS) included 116,474 subjects who underwent inpatient POP repairs. The NIS is the largest all-payer inpatient care database that is publicly available in USA and provides reliable estimates of average LOS and costs. Unadjusted analysis revealed increase LOS with age of 80 years or older. African American race, uninsured status, lower income and lower surgical volume hospitals (≤75%) all increased cost in the West and public hospitals. African Americans had 1.09 (95% CI, 1.05-1.13, p<0.001) times longer LOS compared with Caucasians, and the uninsured had 1.15 (95% CI, 1.01-1.30, p=0.032) times longer LOS compared with those privately insured. Comorbidities associated with 20% increase in LOS and causes were pulmonary circulation disorders, metastatic cancer, weight loss, coagulopathy, and electrolyte/ fluid imbalance (p<0.001). Congestive heart failure and blood loss / deficiency anaemia lead to 20% longer LOS (p<0.001). In 2001-2011, mean LOS declined from 2.42 days (95% CI, 2.37-2.47) to 1.79 days (95% CI, 1.71-1.87, p<0.001) whereas mean total cost increased from $6,233 (95% CI, $5,859-$6,607) to $9,035 (95% CI, $8,632 -$9,438, p<0.001). The authors concluded that some patient and hospital characteristics are associated with increased inpatient LOS and cost and modifiable factors could be addressed to reduce cost. If medical comorbidity is not modifiable, non-surgical treatment should be considered as an alternative. In addition, some modifiable factors such as pre-operative planning, peri-operative management of medical conditions and high-volume surgical programs will lead to decreased LOS and costs which allow the physicians and hospitals to advocate and plan for necessary health care resources allocation.

Conclusions

- Native tissue vaginal repairs are more cost effective than transvaginal mesh repairs. (GoR B)
- ASC is more expensive than SSLF ($13,988 vs $11,950) but is more effective (QALY 1.53 vs 1.45) and is cost-effective (ICER $24,574 / OALY) at 2 years. (GoR C)
- Mean total economic costs were significantly lower in the LSC group compared with the TVM ($4,013.07, 95% CI 3,107.77-4,918.37). (GoR B)
- Based on inpatient cost alone Robotic approach is more expensive than laparoscopic approach which is more expensive than open approach to sacrocolpopexy. (GoR C)

Future research recommendations

- The surgical management of uterine prolapse needs significant further clarification.
- The surgical management of anterior compartment prolapse including recurrent prolapse needs further clarification.
- The role of potential risk factors for recurrent prolapse needs clarification to aid in informed individual decision making.
- New biomaterials for reconstructive surgery are required.

Summary of Findings

While the above text is significant in the evaluation of the surgical management of POP, the reader should note that no trial to date has reported a single intervention that has demonstrated superior outcomes to any other intervention using validated quality of life pelvic floor questionnaires for vaginal prolapse, bladder or bowel function. This indicates that either the interventions are not significantly different for the patients or that the questionnaires are not sensitive enough to detect change. Notwithstanding this problem, our committee has developed a treatment algorithm for the surgical management of prolapse (Figure 10). The committee recognises the algorithm is a guideline for both patients and clinicians and that patient's treatment is best individualised and recorded in open and transparent consultation and consent. The decisions that informed the algorithm are based on the findings in the report and the recommendations are summarised in Table 28.

The committee notes that prolapse surgery has undergone significant changes over the last four years with the removal of many commercial transvaginal mesh products from the market. Despite extensive criticism and concern raised by the general community regarding our unguarded optimism with the introduction of new surgical techniques and changes to regulatory pathways for new devices, as a group we continue to perform surgeries with little evidence as to their safety and efficacy. For example, many of the newer light weight mesh devices that are currently available have little supportive data and these products require significant further evaluation prior to being introduced into treatment pathways for the surgical management of prolapse.

A second example relates to the anecdotal perception that the performance of sacral colpopexy for uterine prolapse, that includes sacrohysteropexy, or supracervical or total hysterectomy and sacral colpopexy, is increasingly common. The confidence in surgical outcomes relating to sacral colpopexy is largely derived from post hysterectomy prolapse data and there is a paucity of data relating to these interventions. An interesting contradiction is emerging that while there is increasing data to support the performance of sacral colpopexy for post-hysterectomy prolapse, the limited early data available in this review suggest that neither sacrohysteropexy, nor supracervical or total hysterectomy and sacral colpopexy are superior to a variety of vaginal based interventions. The current evidence based algorithm points towards vaginal based native tissue interventions for primary uterine prolapse and reserving sacral colpopexy for post-hysterectomy and recurrent prolapse.

Innovation in the surgical management of pelvic organ prolapse remains vital to improving the outcomes of the women we are privileged to treat. There remains a simple obligation for clinicians and industry to work collaboratively and within the confines of appropriate national and local regulatory oversight to ensure that these new interventions are adequately evaluated prior to the wider introduction to the general market. These simple measures will help ensure that we are able to recapture the confidence of the community we serve.

Table 35 Summarises key finding and relevant GoR for the surgical treatment of pelvic organ prolapse

Table 35 summarises key findings and GoR summary for the POP surgery chapter

Treatment	GoR
Obliterative Surgery	
• Effective low morbidity surgery for women not wishing to retain coital activity	C
• Partial Colpocleisis is preferred over vaginal hysterectomy and total colpocleisis when there is no specific indication for hysterectomy and no interest in preserving coital function.	C
Reconstructive Surgery	
Isolated cystocele:	
• Anterior Colporrhaphy (AC) is generally recommended however permanent synthetic mesh could be considered for recurrent prolapse if women understand the risk/benefit profile	A
• Biological grafts offer no significant advantage over AC	B
Isolated rectocele:	
• Posterior Colporrhaphy (PC) is the procedure of choice	B
• Fascial plication superior to site specific posterior vaginal repair	C
• Levatorplasty associated with high rate of dyspareunia	C
• No evidence demonstrating benefit for synthetic or biological graft	C
• PC reduced prolapse with equal functional outcome compared to transanal approach	B
• No data demonstrates ventral rectopexy ± vaginal graft is effective for rectocele.	D
• Those with combined rectal and vaginal prolapse benefit from colorectal & gynaecologist collaboration	C
Apical prolapse	
• Apical suspension at AC or PC significantly reduces the need for subsequent prolapse surgery	B

Treatment	GoR
Vault prolapse (post hysterectomy)	
• Sacrocolpopexy has significant anatomical and functional advantages when compared with a broad group of vaginal surgery (±mesh)	A
• Vaginal apical suspensions appropriate those not suitable for SC (Delphi)	C
• Transvaginal apical mesh confers no advantage when compared to native tissue repairs	A
• Uterosacral & sacrospinous colpopexy have similar efficacy for apical prolapse	B
• Laparoscopic sacrocolpopexy has advantages over both robotic and open approach however the learning curve with both laparoscopic and robotic approach is significant.	B
Uterine prolapse	
• Relative contraindications to uterine preservation are listed in the Table 6.	C
• Salpingectomy ↓risk of ovarian Ca in women retaining ovaries at the time of hysterectomy	B
• Vaginal hysteropexy is equally effective as vaginal hysterectomy with apical suspension and is associated with reduced blood loss and operating time	B
• Opportunistic salpingectomy which is not able to be performed at vaginal hysteropexy should be included in the shared decision making process (Delphi)	C
• Large database studies demonstrated lower reoperation rates for recurrent prolapse and slightly higher complication rates in the hysterectomy group compared to hysteropexy.	C
• Vaginal hysterectomy with apical suspension has a lower reoperation rate for prolapse than abdominal sacr-hysteropexy	B
• Sacrohysteropexy (SHP) has a similar success rate and reoperation for prolapse when compared to vaginal hysterectomy and USLS, however lower success rates than sacrocolpopexy with total or supracervical hysterectomy.	C
• Sacrocolpoexy with hysterectomy is associated with a high rate of mesh exposure	B
• Supracervical hysterectomy has a lower rate of mesh exposure than hysterectomy & SC	B
• Supracervical hysterectomy has ↑ rate of recurrent POP compared to SC & hysterectomy	C
Prolapse surgery and lower urinary tract functions	
• POP + SUI consider POP and continence surgery	A
• POP + occult SUI consider POP & continence surgery (consider staged procedure)	B
• POP without occult SUI does not require concomitant continence surgery.	B
• Preoperative OAB resolves in approximately 50% post prolapse surgery although the impact of concomitant non- surgical treatment on this date has not been clarified.	D
• The rate of reported denovo OAB varies widely 2-32% with further clarification required.	C
• Rates of Urinary retention following POP surgery varies from 0-34% and is nearly always temporary.	C
• Pre-operative urinary retention resolves in as many as 90% post prolapse surgery	C
Risk factors for recurrent prolapse	
• Age < 60 years	C
• Stage 3 or Stage 4 prolapse	B
• Preoperative widened genital hiatus or levator defects on USS: data are inconclusive	D
• Less experienced surgeons have higher rates of recurrent prolapse after transvaginal surgery	C
• Low volume surgeons have ↑ rate of complications compared to high volume surgeons	B
• Peri-operative physiotheraphy does not reduce rate of recurrent prolapse	A
Prolapse surgery Complications	
• Vaginal mesh repairs have a higher rate of complications than native tissue repairs	A
Concerning vaginal surgery	
• If a synthetic mesh is utilised it is recommended that it be macroporous monofilament polypropylene and hysterectomy avoided	B
• Bowel preparation prior to surgery is not recommended	B
• It is recommended to avoid excessive excision of vaginal skin	C
Concerning sacrocolpopexy	
• A macroporous monofilament polypropylene mesh recommended	B
• Concomitant hysterectomy not recommended	B
• Laparoscopy preferred approach	B
• Delayed absorbable sutures preferenced in securing mesh to vagina	C
• Closure peritoneum recommended (Delphi)	C
Expert Opinion Recommendations	
• Cessation smoking pre-operatively	C
• Comply with prevention of nosocomial infections	C
• Antibiotic and thromboembolic prophylaxis	C
• Treat UTIs preoperatively	C

Treatment	GoR
Prolapse surgery and sexual function	
• Sexual function generally improves or remains unchanged following prolapse surgery	B
• Sexual satisfaction measured with validated PISQ is lower after transvaginal mesh than native tissue vaginal repair while the rates of denovo dyspareunia and total dyspareunia are similar	B
• Synthetic transvaginal mesh has a higher rate of dyspareunia compared to sacrocolpopexy	C
• When comparing vaginal biologic grafts to vaginal native tissue repairs, there are similar decreases in postoperative dyspareunia and similar changes in sexual function	C
• When reporting prolapse surgery outcomes pre and postoperative sexual activity, dyspareunia and use of validated sexual function questionnaire and rate denovo dyspareunia preferrable	C
Cost prolapse surgery	
• Native tissue vaginal repair is more cost effective than transvaginal mesh repairs	B
• ASC is more expensive than SSLF ($13,988 vs $11,950) but is more effective (QALY 1.53 vs 1.45) and is cost-effective (ICER $24,574 / OALY) at 2 years	B
• Inpatient cost and total cost are higher for robotic than laparoscopic sacrocolpopexy	B
• Inpatient cost are higher for laparoscopic than open sacrocolpopexy.	B
Prolapse surgery Rates and Outcomes	
• Significant variation exist in reporting rates and types of surgery performed worldwide	B
• Early evidence of declining Rates of prolapse surgery worldwide requires further evaluation s	B
• Evidence based pathways for surgical treatment of prolapse may reduce variability in surgical interventions (Delphi)	C
Reporting outcomes	
• Anatomical outcomes should include all POP-Q points and staging utilising traditional definition of success. Assessment should be prospective blinded and without any conflict of interest related to intervention	C
• Subjective assessment should be absence of vaginal bulge	C
• Functional outcomes are best reported using valid, reliable and responsive symptom questionnaires and condition specific HRQOL instruments	C
• Prolapse surgery should be defined as primary surgery, and repeat surgery subclassified as primary surgery different site, repeat surgery, complications related to surgery and surgery for non-related conditions.	C

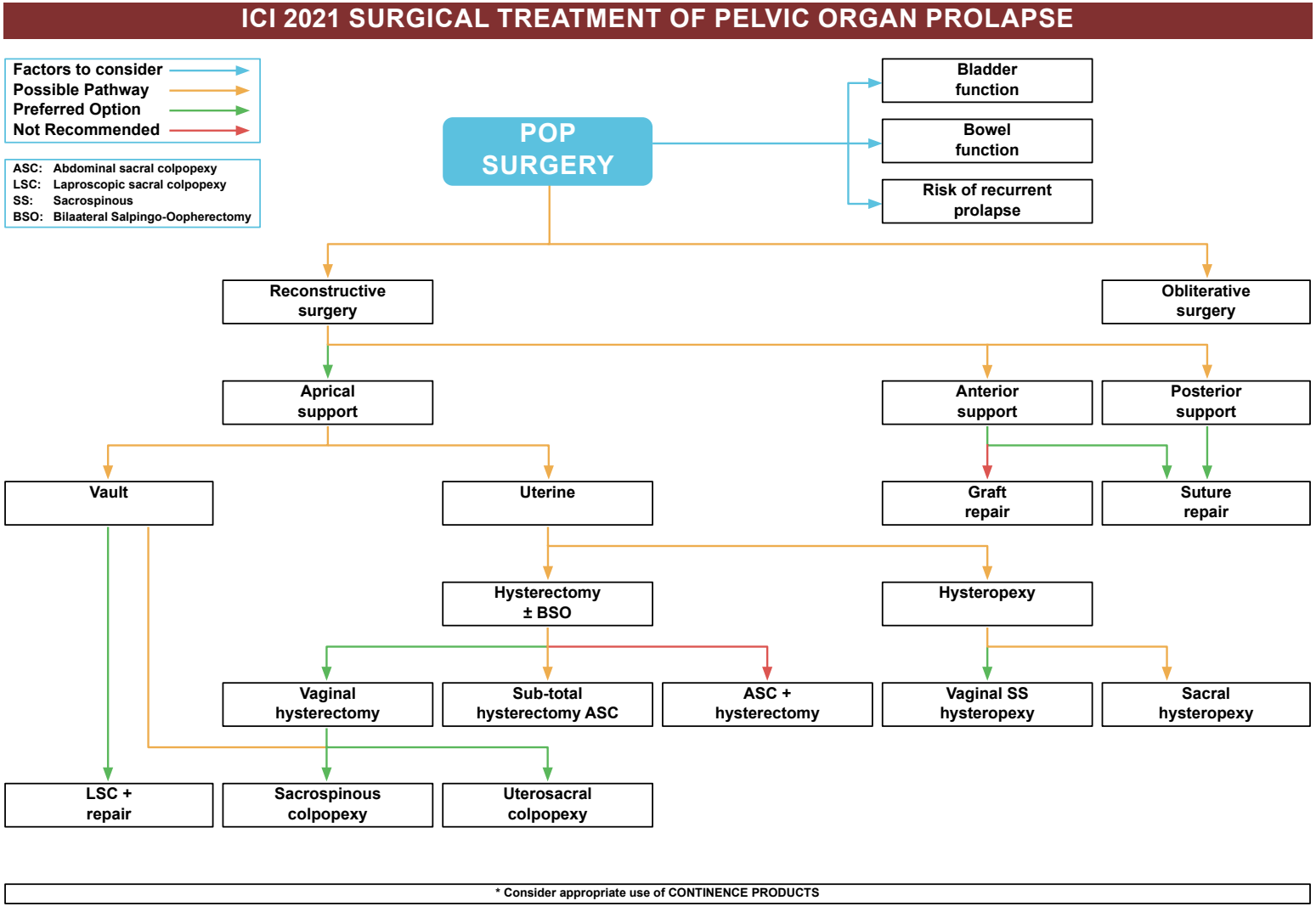

Figure 10 flow diagram summarises findings 2022 POP surgery.

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COMMITTEE 18

INTERSTITIAL CYSTITIS / BLADDER PAIN SYNDROME

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Gold , Daniela (Austria)
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Meijlink, Jane (Netherlands)
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INTERSTITIAL CYSTITIS / BLADDER PAIN SYNDROME

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ABBREVIATIONS

AHRP	Association of Reproductive Health Professionals (United States)
AL	alkalinized lidocaine
APF	antiproliferative factor
ATP	adenosine triphosphate
BACH	Boston Area Community Health Survey
BBDQ	bladder and bowel dysfunction questionnaire
BCG	Bacillus Calmette-Guerin
BPI	Brief Pain Inventory
BPIC-SS	bladder pain interstitial cystitis symptom score
BPS	bladder pain syndrome
BTX	botulinum toxin
CFS	chronic fatigue syndrome
CL	confidence limit
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
CPP	chronic pelvic pain
CPP	chronic pelvic pain
CS	chondroitin sulfate
DMSO	dimethyl sulfoxide
DO	detrusor overactivity
DRE	digital rectal examination
EAU	European Association of Urology
EBMP	education and behavioral modification program
ECS	endogenous cannabinoid system
EMDA	electromotive drug administration
EMG	electromyographic
ESSIC	European Society for the Study of Bladder Pain Syndrome
FDA	Food and Drug Administration (United States)
FM	fibromyalgia
FSD	female sexual dysfunction
FSS	functional somatic syndrome
GAG	glyocosaminoglycan
GIBS	Global Interstitial Cystitis/Bladder Pain Syndrome Society (India)
GRA	global response assessment
GUPI	genitourinary pain index
HA	hyaluronic acid
HB-EGF	heparin-binding epidermal growth factor-like growth factor
HIF	hypoxia-inducible factor
HLD	Hunner lesion disease
HPFD	hypertonic pelvic floor dysfunction
HSB	hypersensitive bladder
IASP	International Association for the Study of Pain
IBS	irritable bowel syndrome
IC	interstitial cystitis
IC/BPS	interstitial cystitis/bladder pain syndrome
ICA	Interstitial Cystitis Association
ICDB	Interstitial cystitis database
ICI	International Consultation on Incontinence
ICICJ	International Conference on Interstitial Cystitis Japan
ICPI	interstitial cystitis problem index
ICS	International Continence Society
ICSI	interstitial cystitis symptom index
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
ISSVD	International Society for the Study of Vulvovaginal Disease
KC	ketamine cystitis
KCl	potassium chloride
LPFD	hypotonic pelvic floor dysfunction
MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
NBS	nonbladder syndrome
NHANES	National Health and Nutrition Examination Survey
NHS	Nurses' Health Study
NIDDK	National Institutes of Diabetes and Digestive and Kidney Diseases
NMDA	N-methyl-D-aspartate
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drugs
OAB	overactive bladder
OLS	O'Leary Sant
OR	odds ration
PBS	painful bladder syndrome
PBS/IC	painful bladder syndrome/interstitial cystitis
PD-EDGF	platelet derived endothelial growth factor
PDE5	phosphodiesterace type 5
PEA	palmitoylethanolamide
PFD	pelvic floor dysfunction
PNS	pudendal nerve stimulation
PPS	pentosanpolysulfate
PST	potassium sensitivity test
PTNS	percutaneous tibial nerve stimulation
PUF	Pelvic Pain and Urgency/Frequency
PVD	provocative vulvodynia
RICE	Rand Interstitial Cystitis Epidemiology
SNS	sacral nerve stimulation
TENS	transcutaneous electrical nerve stimulation
TLR	toll-like receptor
TNF	tumor necrosis factor
TRPV1	transient receptor potential V1
UCPPS	Urologic chronic pelvic pain syndrome
UCPPS	urologic chronic pelvic pain syndrome
UPOINT	urinary, psychosocial, organ-specific, infection, neurological/systemic and tenderness phenotype system
VAS	visual analog scale
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
WAS	water avoidance test

I. INTRODUCTION

1. EVIDENCE ACQUISITION

The unrestricted, fully exploded Medical Subject Heading (MeSH) "interstitial cystitis" (including all related terms as "painful bladder syndrome", "bladder pain syndrome", or different terms such as "chronic interstitial cystitis", etc.) were used to thoroughly search the Pub Med database (https://www.ncbi.nlm.nih.gov/pubmed/) of the United States National Library of Medicine of the National Institutes of Health from the years 2017-2021. Seven hundred fifty-five publications in English or with English abstracts were reviewed.

Focus was on clinical trials, randomized controlled trials, meta-analyses, scientific guidelines, and core clinical journals. The literature update this achieved was added to the previously existing database reflected in the 2017 publication that was established according to a similar protocol. (1)

Rating of the level of evidence and grade of recommendation was performed according to the Oxford Scale. The committee believes that the Oxford system for categorizing levels of evidence is primarily relevant only for the sections on treatment which follow. While the committee's opinions will be expressed where applicable regarding evidence and conclusions for other areas including diagnoses, aetiology, and pathophysiology, use of the Oxford system in this context is more open to interpretation.

2. DEFINITION AND TAXONOMY

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". (2) **table 1** Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a clinical diagnosis that relies on symptoms of pain in the bladder and or pelvis and other urinary symptoms like urgency and frequency. It is a physical disorder that is often associated with pervasive and severe psychosocial impacts (3). Therapeutic regimens and clinical trials can be difficult to interpret as up to half of patients tend to improve with time with or without regular follow-up and seemingly unrelated to treatment (4,5).

Based on the evolving consensus that IC/BPS is strongly related to other pain syndromes like Irritable Bowel Syndrome, Fibromyalgia and Chronic Fatigue Syndrome in some patients, the European Society for the Study of Bladder Pain Syndrome (ESSIC) published a comprehensive paper on definition and diagnosis of IC/BPS. (6) IC/BPS was defined as chronic (>6 months) pelvic pain, pressure, or discomfort *perceived to be* related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies. **table 2** The presence of other organ symptoms as well as cognitive, behavioural, emotional, and sexual symptoms should be addressed.

This definition has been broadly accepted although actual wording differs somewhat (7). Because omitting the name "Interstitial Cystitis" might cause serious problems in different health systems by affecting reimbursement and disability determinations, and because worldwide in 2022 the terms interstitial cystitis and bladder pain syndrome are used interchangeably in the world-wide literature, the name "interstitial cystitis/bladder pain syndrome" "IC/BPS" will be the preferred terminology in this updated Consultation. **Interstitial cystitis and bladder pain syndrome are essentially interchangeable as there is no accepted definition that clearly delineates the interstitial cystitis syndrome from bladder pain syndrome. Many studies referred to in this document will denote the syndrome as BPS, IC, or painful bladder syndrome, but are understood to represent the same collection of symptoms.**

Table 1. *2020 International Association for the study of Pain (IASP) Revised Definition of Pain explanatory notes. From Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised international association for the study of pain definition of pain. Pain 2020, May 23;Publish Ahead of Print(9)*

Pain
An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.

Notes
- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- A person's report of an experience as pain should be respected.*
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

Etymology
Middle English, from Anglo-French peine (pain, suffering), from Latin poena (penalty, punishment), in tum from Greek poinē (payment, penalty, recompense). *The Declaration of Montréal, a document developed during the First International Pain Summit on September 3, 2010, states that "Access to pain management is a fundamental human right."

Table 2. ESSIC Classification of Bladder Pain Syndrome. *From van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: An ESSIC proposal. Eur Urol 2008, Jan;53(1):60-7.*

		cystoscopy with hydrodistension			
		not done	normal	glomerulations[1]	Hunner's lesion[2]
biopsy	not done	XX	1X	2X	3X
	normal	XA	1A	2A	3A
	inconclusive	XB	1B	2B	3B
	positive[3]	XC	1C	2C	3C

[1] cystoscopy: glomerulations grade II-III
[2] with or without glomerulations
[3] histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis

Historically, definitions of IC have moved from a severe inflammatory bladder disease to a syndrome described primarily by symptoms (7) **table 3**

Table 3. Historical definitions of IC/BPS. *Hanno P, Nordling J, van OA. What is new in bladder pain syndrome/interstitial cystitis? Curr Opin Urol 2008, Jul;18(4):353-8.*

1887 Skene {Skene 1887}: An inflammation that has destroyed the mucous membrane partly or wholly and extended to the muscular parietes.
1915 Hunner: {Hunner 1915}: A peculiar form of bladder ulceration whose diagnosis depends ultimately on its resistance to all ordinary forms of treatment in patients with frequency and bladder symptoms (spasms).
1951 Bourque {Bourque 1951} : Patients who suffer chronically from their bladder; and we mean the ones who are distressed, not only periodically but constantly, having to urinate at all moments of the dav and of the night suffering pains every time they void.
1978 Messing and Stamey {Messing 1978} : Nonspecific and highly subjective symptoms of around-the-clock frequency, urgency, and pain somewhat relieved by voiding when associated with glomerulations upon bladder distention under anesthesia.
1990 Revised NIDDK Criteria: Pain associated with the bladder or urinary urgency, and, glomerulations or Hunner's ulcer on cystoscopy under anesthesia in patients with 9 months or more of symptoms, at least 8 voids per day, 1 void per night, and cystometric bladder capacity less than 350cc. {Gillenwater 1988} {Hanno 1990a}
1997 NIDDK Interstitial Cystitis Database Entry Criteria {Simon 1997a}: Unexplained urgency or frequency (7 or more voids per day), OR pelvic pain of at least 6 months duration in the absence of other definable aetiologies.
2008 European Society for the Study of Bladder Pain Syndrome (ESSIC) {VanDeMerwe 2008a}: Chronic (>6 months) pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded.
2014 Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) {Landis 2014}, National Institutes of Health: Chronic unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms, in the absence of infection or other identifiable causes.
2009/2016 East Asian Guideline {Homma 2009} {Homma 2016}: A disease of the urinary bladder diagnosed by 3 conditions: lower urinary tract symptoms, Hunner lesion or mucosal bleeding after distention, and exclusion of confusable diseases. The characteristic symptom complex (hypersensitive bladder syndrome) includes bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain.
2011/2015 American Urological Association {Hanno 2011} {Hanno 2015}: An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes.
2015 Spanish Urological Association: {Esteban 2015} The unpleasant sensation (pain, pressure, discomfort) perceived in relation to the filling of the bladder and accompanied by at least another symptom of the lower urinary tract, either daytime or nightime, such as increased urinary frequency and in the absence of infection or another identifiable cause.
2016 Canadian Urological Association: {Cox 2016} See American Urological Association guideline
2019 German Guideline: {Bschleipfer 2019} Bladder pain syndrome is a symptom complex in which, in the absence of an infection or another underlying disease, the sufferer experiences chronic bladder-associated pelvic pain, pressure or discomfort, and at least one other specific symptom (e.g., a frequent or persistent urge to urinate. Hunner type, in which Hunner's lesions are clearly visible on cystoscopy. Non-Hunner type, in which no Hunner's lesions are observed during/after bladder filling.
2019 European Association of Urology: {Engeler} Bladder pain syndrome is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. There is no proven infection or other obvious local pathology.
2020 East Asian Guideline {Homma 2020} IC/BPS is the condition with chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by other urinary symptoms, such as persistent urge to void or urinary frequency in the absence of confusable diseases. HIC is IC/BPS with Hunner lesions. BPS is IC/BPS without Hunner lesions.

The International Continence Society (8) (ICS) used the term Painful Bladder Syndrome (PBS) defined as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology". ICS reserved the diagnosis Interstitial Cystitis (IC) to patients with "typical cystoscopic and histological features", without further specifying these. It has however been shown that only a fraction of patients believed by experts to have IC/BPS fulfil this definition (9).

In the remainder of this chapter the condition will be referred to as interstitial cystitis/bladder pain syndrome (IC/BPS). Some of the older literature may be discussed using the original terminology in the interests of clarity. Logically "interstitial cystitis" should include some form of demonstrable inflammation in the bladder wall, while "bladder pain syndrome" should include pain in the region of the bladder (10). The diagnosis is based on exclusion of other diseases in the bladder, urethra, and other pelvic organs including the musculoskeletal system. As with other disorders without clear objective diagnostic criteria or pathophysiological explanation, countless theories have been put forward without adding much to the delineation or understanding of the disease.

In practice, patients with symptoms of IC/BPS are screened to exclude other relevant diagnoses or confusable diseases (6), and a focused evaluation is performed at the discretion of the physician or centre. This evaluation might include cystoscopy under local or general anaesthesia, bladder distension with registration of bladder capacity and/or the presence of glomerulations and Hunner lesion. Bladder wall biopsies might be obtained and evaluated for inflammation, ulcer, fibrosis, mast cells etc. The evaluation might also include urodynamics with registration of awake bladder capacity,

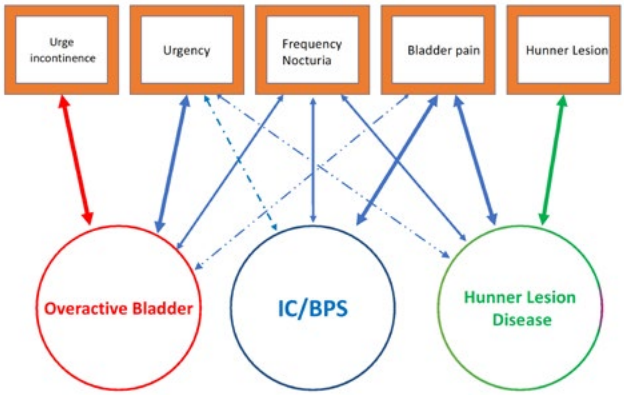

Figure 1. Overactive bladder and its relationship to IC/BPS and HLD. *Adapted from Abrams P, Hanno P, Wein A. Overactive bladder and painful bladder syndrome: There need not be confusion. Neurourol Urodyn 2005;24(2):149-50.*

compliance, and bladder stability (11). The potential symptom overlap of IC/BPS with overactive bladder (OAB) is graphically depicted in **figure 1** (12). The 14% incidence of urodynamic detrusor overactivity in the IC/BPS (13) patients is probably close to what one might expect in the general population if studied urodynamically (14). More recent publications suggest that the distinction with the confounding diagnosis of OAB is not quite as clear or easy to make as we had thought in the past. (15-18) Current thinking is illustrated in **Figure 2.** This is loosely adapted from the excellent work of Homma and the East Asian group studying the disorder. (19,20)

In the end, many of these investigations might prove to be normal and the patients are identified as having IC/BPS as a diagnosis of exclusion. The relevance of urodynamic, cystoscopic and histological findings is limited by a lack of consistency in technique, and it is therefore recommended to use the standardisations described by ESSIC (21) when comparing different cohorts of patients.

Coincident with this 2021 Consultation, there is much discussion in the world-wide literature with regard to the place of Hunner lesion patients in the IC/BPS spectrum (22-29) . This impacts directly on the issue of definition. The Consultation was one of the early leaders in calling for Hunner lesion patients to be classified as having a *disease* and no longer be considered as a part of the interstitial cystitis/bladder pain *syndrome.* (30) This puts Hunner lesion more in the spectrum of patients with an identifiable cause of their bladder pain and frequency such as radiation cystitis, urinary tract infection, ketamine cystitis, etc. This idea is not new and was originally proposed by Magnus Fall in 1987, but largely ignored (31). Fall, Nordling and the ESSIC group have reviewed this literature (32) and conclude that the Hunner lesion patient which first defined the patient group with “interstitial cystitis” should indeed be looked at as a disease unto itself in the absence of contrary data. A similar consensus has developed in Asia. (20) The large group of patients who meet the definition of IC/BPS as a diagnosis of exclusion are best served when viewed apart from those with specific disorders. As we learn more in the future, the IC/BPS group will by necessity diminish in size, but now makes up well over 60% of the combined Hunner lesion/IC/BPS population (33). The new classification of pain as either primary (a disease in its own right) or secondary (pain as a symptom of an underlying identifiable problem) that is proposed by the International Association for the Study of Pain would easily mesh with this concept. (34,35)

For now, FDA continues to look at IC/BPS as one disorder (36) and pharmaceutical companies are not obliged to study Hunner lesion and non Hunner lesion patients in individual trials. This may be subject to change in the future. In this chapter we will try to differentiate these groups as best as possible given previous publication and study parameters.

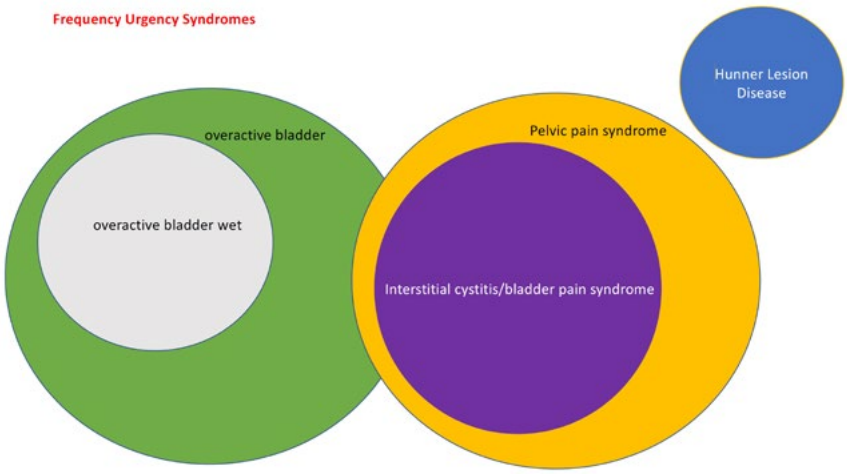

Figure 2. Relationship of Hunner Lesion Disease to frequency/urgency syndromes. *Adapted From Homma Y. Lower urinary tract symptomatology: Its definition and confusion. Int J Urol 2008, Jan;15(1):35-43. Homma Y, Akiyama Y, Tomoe H, Furuta A, Ueda T, Maeda D, et al. Clinical guidelines for interstitial cystitis/bladder pain syndrome. Int J Urol 2020, Apr 14;27(7):578-89.*
OAB: overactive bladder
IC/BPS: interstitial cystitis/bladder pain syndrome
HLD: Hunner lesion disease
Hunner lesion is considered a disease rather than a part of a syndrome and depends on characteristic findings on endoscopy and pathology. Hunner lesion in this diagram is separated from the purely symptomatic diagnoses though indistinguishable from BPS/IC based on symptoms alone.

II. HISTORICAL NOTES

Recent historical reviews confirm that interstitial cystitis was recognized as a pathologic entity during the 19th century. (37,38) In his textbook Practical Observations on Strangulated Hernia and Some Diseases of the Urinary Organs, Joseph Parrish, a Philadelphia surgeon, described 3 problematic cases of recurrent, severe lower urinary tract symptoms in which he made repeated attempts to locate a bladder stone, which was the most common source for these symptoms in early 19th century America. (39) As Teichman et al have convincingly argued, these patients displayed all the clinical hallmarks of IC including chronic frequency, urgency, dysuria and pelvic pain in the absence of demonstrable pathology. (40) Although he used the term repeatedly in his manuscript, Parrish did not elaborate upon the clinical definition of "tic douloureux," likely because contemporaneous physicians would have been familiar with the then popular neuralgia concept. Parrish attributed the term tic douloureux to his mentor, Dr. Phillip Syng Physick, who had applied it to patients with severe lower urinary tract symptoms with no discernible etiology. The most common etiology for these symptoms during the 19th century would be bladder calculi.

By 1808 Physick had developed a concept of bladder inflammation, a "bladder ulcer," that produced lower urinary tract symptoms in the absence of bladder stone. (38) Tic douloureux at the time represented a neurological irritation, most often associated with the trigeminal nerve but applicable to other sensory distributions as well, which produced pain and discomfort in the absence of injury or other specific physical findings. In applying the concept of tic douloureux to bladder sensation, Parrish was ascribing the paroxysmal lower urinary tract symptoms occurring in patients to an idiopathic process affecting the nerves of the bladder. Furthermore, tic douloureux allowed him to formulate a diagnosis for those patients who chronically manifested the symptoms caused by a stone (severe frequency, urgency, dysuria and pelvic pain) but had no stone that could be detected. That is, he considered a neuralgic aetiology in the absence of any other tangible causes of bladder pain.

By 1876, the 3rd edition of the book by Samuel D. Gross, revised and updated by his son Samuel W. Gross, reported that "When all the coats are implicated, it is termed interstitial or parenchymatous cystitis". (41)

Two years later, Skene used the term interstitial cystitis to describe an inflammation that has "destroyed the mucous membrane partly or wholly and extended to the muscular parietes". (42) Early in the 20th century, at a New England Section meeting of the American Urological Association, Guy Hunner reported on 8 women with a history of suprapubic pain, frequency, nocturia, and urgency lasting an average of 17 years. (43,44) He drew attention to the disease which he himself described as "elusive ulcer". However, the red, bleeding areas Hunner described on the bladder wall soon acquired the pseudonym "Hunner's ulcer". As Walsh observed, this has proven to be unfortunate. (45) In the early part of the 20th century, the very best cystoscopes available gave a poorly defined and ill-lit view of the fundus of the bladder. It is not surprising that when Hunner saw red and bleeding areas high on the bladder wall, he thought they were ulcers. For the next 60 years, urologists would look for actual ulcers and fail to make a diagnosis in their absence. The disease was thought to be a focal, rather than a pancystitis.

Hand authored the first comprehensive review about the disease, reporting 223 cases. "I have frequently observed that what appeared to be a normal mucosa before and during the first bladder distention showed typical interstitial cystitis on subsequent distension" he notes, further adding "small, discrete, submucosal haemorrhages, showing variations in form…dot-like bleeding points… little or no restriction to bladder capacity." (46) He describes three grades of disease, with grade 3 matching the small-capacity, scarred bladder described by Hunner. Sixty-nine percent of patients were grade 1 and only 13% were grade 3. Walsh later coined the term "glomerulations" to describe the petechial haemorrhages that Hand had described. (45) But it was not until Messing and Stamey discussed the "early diagnosis" of IC that attention turned from looking for ulcers to the concepts that 1) symptoms and glomerulations at the time of bladder distention under anaesthesia were the disease hallmarks, and 2) the diagnosis was primarily one of exclusion. (47) However, this description proved unsuitable for defining this disease in a manner that would help physicians make the diagnosis and set up research protocols.

The National Institute of Diabetes, Digestive, and Kidney Disorders (NIDDK) held a key meeting in 1987 with researchers and clinicians from around the world. (48) This ultimately resulted in the 1990 Revised NIDDK Criteria: Pain associated with the bladder or urinary urgency, and glomerulations or Hunner's ulcer on cystoscopy under anaesthesia in patients with 9 months or more of symptoms, at least 8 voids per day, 1 void per night, and cystometric bladder capacity less than 350cc. (49)

To validate the criteria, which were designed not for clinical diagnosis, but rather to ensure that patients enrolled in research trials could be agreed upon to have the disease, a database with broad entry criteria was created. The 1997 NIDDK Interstitial Cystitis Database Entry Criteria: Unexplained urgency or frequency (7 or more voids per day), OR pelvic pain of at least 6 months duration in the absence of other definable etiologies . (50) Urgency was not defined in the protocol. Participants were given a 10 point scale, and those who scored 2 or higher on self-report satisfied the urgency criteria.

A comparison of the NIDDK revised criteria with the database entry criteria revealed that up to 60% of patients clinically believed to have IC by experienced clinicians were being missed when the NIDDK research criteria were used as a definition of the disease. (51) With the demise of the NIDDK criteria as an appropriate clinical definition of the disorder, the controversial issues of nomenclature, taxonomy and diagnosis were actively debated internationally over the next 2 decades with no consensus reached. The numerous different names, definitions and criteria resulted in a great deal of confusion worldwide. (52) By 2002, the newly designated "overactive bladder syndrome" was dominating attention in urology to such an extent that IC/BPS was increasingly relegated to the field of pain and psychology, ultimately bringing any real progress in research and treatment to a virtual standstill. (53)

The history has been nicely summarized in a 2014 review by Meijlink. (54)

Over the last several decades, along with numerous attempts to improve therapies, nomenclature and taxonomy have taken center stage to improve methodology to enhance research in aetiology and treatment.

III. MODERN HISTORY

The literature over the past 200 years has seen numerous changes in the description and nomenclature of the bladder disease variously referred to as tic douloureux or neuralgia of the bladder, (chronic)

interstitial cystitis, parenchymatous cystitis, elusive ulcer, Hunner's ulcer, panmural ulcerative cystitis, urethral syndrome, painful bladder syndrome and bladder pain syndrome. (37,40,42,44,55-57)

From the nineteen seventies to the end of the 20th century, the name stabilized as interstitial cystitis, even though it was by now being used for patients with both lesion and non-lesion disease. However, publication of the formal definition of the term ''painful bladder syndrome'' by the ICS in 2000 (8) led to a move in the first decade of the new millennium to change the name from what some then felt to be a too restrictive term (interstitial cystitis) to a broader umbrella term (bladder pain syndrome) in line with an 'organ-pain-syndrome' classification system first conceived by the International Association for the Study of Pain (IASP). It first appeared in a European Association of Urology (EAU) guideline on chronic pelvic pain in 2004 (58) and was then adopted by ESSIC. (6) The place of IC/BPS in the complete taxonomy of chronic pelvic pain syndromes has been published by the International Association for the Study of Pain. (35)

The lack of consensus among stakeholders about nomenclature is not merely a theoretical problem. Table 4 It has hampered international harmonization in the field and may be impacting progress on identifying aetiologies, epidemiologic studies, and implementation of effective therapies. The failure to discover important phenotypes within the syndrome has affected treatment trials and produced conflicting data. As a result, health and regulatory authorities approve and reimburse treatments vastly differently throughout the world.

Table 4.Nomenclature currently in use. *Meijlink J. Interstitial cystitis/bladder pain syndrome/hypersensitive bladder: Worldwide confusion! What has gone wrong and how can we put it right for the sake of the patients? Int J Urol 2019, Jun;26 Suppl 1:41-5.*

Interstitial Cystitis
Chronic Interstitial Cystitis
Bladder Pain Syndrome
Painful Bladder Syndrome
Hypersensitive Bladder
Non-Hunner type interstitial cystitis
Non-Hunner Lesion interstitial cystitis/bladder pain syndrome
Urologic chronic pelvic pain syndrome
Nomenclature Referring to Hunner Lesion Disease
Classic Interstitial Cystitis
Hunner ('s) Lesion
Hunner Lesion Disease
Hunner-type interstitial cystitis
Hunner Lesion Interstitial Cystitis
Hunner('s) Ulcer
Hunner Cystitis
Hunner's Patches
Ulcerative (Interstitial) Cystitis

1. LANDMARKS IN THE NEW MILLENNIUM

2002: In its Standardization of Terminology of Lower Urinary Tract Function document, the International Continence Society (ICS) introduced the term "painful bladder syndrome", defining it as: "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology", reserving "interstitial cystitis" for a specific diagnosis requiring confirmation by typical cystoscopic and histological features. The fact that it did not exactly describe these features caused some confusion and the disorder subsequently came to be known as PBS/IC or IC/PBS. (53)

2003: At the 1st meeting of the International Consultation on Interstitial Cystitis, Japan (ICICJ) in Kyoto, it was agreed that the term ''interstitial cystitis'' should be expanded to ''interstitial cystitis/chronic pelvic pain syndrome'' when pelvic pain is at least of 3 months duration and associated with no obvious treatable condition/pathology. (59)

2003: At a meeting of the NIDDK entitled ''Research Insights into Interstitial Cystitis'', it was concluded that ''interstitial cystitis'' will inexorably be replaced as a sole name for this syndrome. It will be a gradual process over several years. At the meeting it was referred to as ''interstitial cystitis/painful bladder syndrome'' in keeping with ICS nomenclature. (60)

2004: The International Consultation on Incontinence (ICI) included the syndrome as a part of its consultation. The chapter in the report was titled, ''painful bladder syndrome (including interstitial cystitis),'' suggesting that IC formed an identifiable subset within the broader syndrome. Because such a distinction is difficult to define, within the body of the chapter it was referred to as PBS/ IC (one inclusive entity). (60)

2004: The European Association of Urology (EAU) published a guideline on chronic pelvic pain, based on the 1994 IASP taxonomy of chronic pain, and opted for bladder pain syndrome. "Since symptoms invariably define the clinical condition the term ''Painful bladder syndrome'' or ''Bladder pain syndrome'' is more apposite." (58)

2006: Abrams et al published an editorial focusing on the nomenclature problem. (61). They noted that: "It is an advantage if the medical term has clear diagnostic features that translate to a known pathophysiologic process so that effective treatment may be given. …These organ-based diagnoses are mysterious, misleading and unhelpful, and can lead to therapies that are misguided or even dangerous." The editorial went on to say that a single pathologic descriptive term (interstitial cystitis) for a spectrum of symptom combinations ill serves patients. The umbrella term ''painful bladder syndrome'' was proposed, with a goal to define and investigate subsets of patients who could be clearly identified within the spectrum of PBS.

2006: At the IC research conference, held by the National Institute of Diabetes, Digestive, and Kidney Disorders (NIDDK), the ESSIC group suggested that Painful Bladder Syndrome be redesignated as Bladder Pain Syndrome (BPS), followed by a type designation. This was because PBS did not fit into the taxonomy of other pelvic pain syndromes such as urethral or vulvar pain syndromes, and because IC is open to different interpretations. (6)

2008 (-2021) The NIDDK decided a completely new approach needed to be taken and set up the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) project with a broader, multidisciplinary input and included researchers with clinical, epidemiological, and basic research expertise, all working collaboratively. Urologic Chronic Pelvic Pain Syndrome (UCPPS) is the term adopted by the network to encompass any urologic chronic pelvic pain syndrome, including IC/BPS and chronic prostatitis/chronic pelvic

pain syndrome in men. These syndromes were hypothesized to be similar until proven otherwise by MAPP research, thus receiving the similar designation of UCPPS. In creating yet a new diagnosis, the data generated became difficult to assess with regard to any previously defined syndromes. It has made the mountains of data generated by the MAPP difficult to interpret.

2009: The Japanese Interstitial Cystitis guideline committee re-introduced an earlier concept of hypersensitive bladder, originally defined in an ICS Standardization Document in 1988 as increased bladder sensation on filling. (62) This Japanese guideline suggested the term "hypersensitive bladder syndrome" for the symptom syndrome associated with IC or IC-like conditions. (63)

2012: The IASP Classification of Chronic Pain was updated in 2012. Bladder pain syndrome was defined as "the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and daytime and/or night-time urinary frequency. There is no proven infection or other obvious local pathology." It further notes that "other terms that have been used include "interstitial cystitis", "painful bladder syndrome", and "PBS/IC" or "BPS/IC"; these terms are no longer recommended." (64)

2013: At the joint meeting of the 3rd International Consultation on Interstitial Cystitis, Japan and ESSIC in Kyoto, it was agreed to limit the use of the term "interstitial cystitis" to patients with bladder pain syndrome with a Hunner lesion. (65) This was supported by findings that suggest that Hunner lesions or what was classically referred to as "interstitial cystitis" denote a truly different disorder than "bladder pain syndrome" and can either be considered a distinct phenotype lying within the IC/BPS framework or a separate disease entirely. (25)

2013: In an editorial, Homma pointed out that IC is a disease name long used in medical and patient societies, but that it lacks clear definition. Furthermore, PBS and BPS both include the word "pain", creating the impression that patients must have pain, although a substantial number *do not interpret discomfort or pressure as being pain*. Homma noted that the urgency and frequency experienced by these patients are suggestive of increased sensation of the bladder or urothelium and therefore proposed the term "hypersensitive bladder (HSB)". (66)

2014: In a review article, Homma described taxonomy or nomenclature concerning interstitial cystitis and its related symptom syndromes as being in a state of confusion. In Japan, "interstitial cystitis is defined by three requirements: (i) hypersensitive bladder symptoms; (ii) bladder pathology; and (iii) no other diseases, where bladder pathology should be clearly stated either as Hunner's lesion or glomerulations after hydrodistention. Hypersensitive bladder can be used for the condition with hypersensitive bladder symptoms, but no obvious disease explaining hypersensitive bladder symptoms identified." (67)

2018: 4th ICICJ Conference, Kyoto, with an International Discussion Meeting. The theme was Hunner lesion and non-Hunner lesion. The meeting underlined the global confusion and lack of consensus and the damage that this was doing to the patients. While most of the delegates had been recommending splitting off Hunner lesion from non-lesion disease as a matter of urgency for clinical trials, it was reported that the FDA (USA Food & Drug Administration) Advisory Committee had inexplicably voted unanimously in favour of combining patients with and without Hunner lesions in clinical trials! (68)

2019: At the ESSIC Annual Scientific Meeting in Amsterdam, JJ Wyndaele noted that it is very concerning that there are multiple national and international guidelines in use, with differences in nomenclature, definitions, and recommended diagnostic investigations. Philip Hanno emphasized that we need a new international guideline sensitive to different healthcare systems and sensibilities. This should be a guideline that embraces new ideas from the past 5 years, and which is easily updated in accordance with new developments and insights. Many speakers emphasized the absolute importance of cystoscopy to differentiate between lesion and non-lesion, stressing that it is now urgent to separate the two. It was also noted by meeting chair Dick Janssen that it is important to incorporate patients and their organizations in research and listen to them to improve our healthcare.

2020: Global Interstitial Cystitis/Bladder Pain Syndrome Society (GIBS), INDIA, Virtual Annual Meeting September 2020.

By now meetings had gone virtual due to the COVID-19 crisis. Here too it was stressed that Hunner lesion disease should not be evaluated with non-Hunner disease in clinical studies. The only proven phenotype in 2020 is the Hunner lesion. The Hunner lesion patient population seems to be different to non-Hunner lesion patients. Its histology is also quite different. Gynaecologist Dr Tanvir Singh noted that cystoscopy should be mandatory to exclude other conditions and to diagnose Hunner lesion. Speakers emphasized the need for mandatory cystoscopy to distinguish Hunner lesion and exclude other disorders and this has now been incorporated an an Indian guideline.

2020: Being unable to hold an annual meeting, ESSIC organized a virtual Masterclass series.

There was much discussion of phenotyping and Hunner Lesion, with Philip Hanno quoting Magnus Fall:

"We have to, bit by bit, identify various causes of the IC/BPS syndrome (like CNS diseases, peripheral nerve damage, pelvic floor dysfunctions, inflammatory conditions, etc.). Diseases so identified have to be given proper denominations and have to be included in the diagnostic algorithms. The ultimate goal is to be able to administer the proper and best treatment for each condition. In oncology, various phenotypes are identified all the time and more intelligent and target-oriented treatments can be offered. To ignore identification of diverse clinical subgroups of IC/BPS with essentially different aetiology and pathogenesis in upcoming drug studies would be an historical mistake."

2. THE URGENCY DEBATE

An urgent need to void has always been one of the hallmark symptoms of IC/BPS and was perhaps most vividly described in 1918 by Guy Hunner, writing that "the patient often had such extreme urgency that she had to leave a street-car in order to enter the nearest house and ask for permission to void." (44)

This "sensory" (or hypersensitive) type of urgency, due to increasingly overwhelming, intolerable pain or unpleasant sensation as typically experienced by IC/BPS patients has always been the cause of immense stress and anxiety for these patients who may be afraid to leave their home in case they cannot find a toilet when they need it. It was described in the 1988 summary of the 1987 meeting of the National Institute of Diabetes and Digestive and Kidney Dis-

eases (NIDDK) on Interstitial Cystitis which stated that an automatic exclusion was an “absence of sensory urgency”. (48)

The 1988 International Continence Society (ICS) Standardization of Terminology of Lower Urinary Tract Function document noted under point 3 Procedures Related to the Evaluation of Urine Storage: “Urgency (this is defined as a strong desire to void accompanied by fear of leakage or fear of pain)”. [It should be noted here that “fear of pain” was never really appropriate and it would have been more accurate to describe this as “due to pain”]. This document also subdivided urgency into “motor urgency” and “sensory urgency” stating in sub-section 6.1.3 that: “Urgency may be associated with two types of dysfunction: a. Overactive detrusor function (motor urgency), and b. Hypersensitivity (sensory urgency)”. (62)

However, this all changed following the launch of the term Overactive Bladder Syndrome (OAB), when the term urgency was redefined in 2002 in the Standardization of Lower Urinary Tract Function Report from the Standardization Sub-committee of the International Continence Society as: “a sudden compelling desire to void” with no mention of sensory urgency. Addition of the word “sudden” made it exclusively applicable to OAB and urge(ncy) incontinence and urgency from this moment on was consequently only applicable to OAB patients. On paper, IC/BPS patients no longer had urgency. (8)

In 2007, the US Association of Reproductive Health Professionals (ARHP) and the Interstitial Cystitis Association (ICA) attempted to replace the term urgency in the IC patient with “persistent urge”, the stated purpose being to distinguish the symptoms of IC/painful bladder syndrome from those of overactive bladder. This was an attempt to harmonize with ICS but keep the symptoms described by many IC patients. They defined IC/PBS as follows: Pelvic pain, pressure, or discomfort related to the bladder, typically associated with persistent urge to void or urinary frequency, in the absence of infection or other pathology. However, persistent urge is not the same as an urgent need to find a toilet and misrepresents IC/BPS symptoms. Sensory or painful urgency needs to be reconsidered in official definitions for the sake of meaningful research and treatment of the patients in the future. (69)

IV. RECOMMENDATIONS FOR TERMINOLOGY

The Consultation has opted to use the term interstitial/cystitis/bladder pain syndrome (IC/BPS). Hunner lesion disease (HLD) will be used for patients with discrete inflammatory areas in the bladder that meet the definition of Hunner lesion and are diagnosed by cystoscopy. Further ongoing efforts at phenotyping will no doubt require changes and be reflected in future iterations of the Consultation.

V. PATIENT PERSPECTIVE

IC/BPS is a distressing bladder condition with far-reaching psycho-social consequences for the patient and can change not just a patient’s whole life but even their whole character. The problems they may have experienced in getting a diagnosis – in simply being believed – may have completely taken away their self-confidence and their confidence in the medical profession.

Bladder pain is a particularly stressful type of pain, while the frequent need to urinate both day and night means that many patients never get a proper night’s sleep and this sleep deprivation can have many detrimental consequences, both physical and psychological. In the daytime, the constant, urgent need to find toilets is a source of immense stress and anxiety, resulting in many patients hardly ever leaving their home, and becoming socially isolated.

While every patient is different, and the severity of their IC/BPS can vary from very mild to totally debilitating, IC/BPS can have a hugely detrimental impact on a patient’s quality of life, ability to function in society, and on their family life as a whole. IC/BPS can have a negative impact on intimate relationships since sexual intercourse may be painful or even impossible for both male and female patients. Since patients may find it difficult to raise this intimate and embarrassing subject with their doctor, it is important for the healthcare provider to raise this aspect. Furthermore, bladder issues are still taboo today. Patients find it embarrassing to talk about their bladder condition, while family and friends certainly don’t want to hear about it. This makes IC/BPS a very lonely disease.

The psycho-social impact on patients means that they need a great deal of empathy, support, time and patience from their healthcare providers. This might also go some way towards helping to restore the self-confidence of the patients and helping them to cope. Treating these patients requires specialized training and, ideally, specialized IC/BPS clinics.

IC/BPS also has a negative financial impact on patients and their families since work in some jobs becomes impossible when you need to keep running to the toilet, are suffering from chronic fatigue or even dangerously drowsy from pain medication. This financial aspect is exacerbated by the fact that in many countries effective treatment is not reimbursed, making it unaffordable for many desperate patients who then must make do with less effective treatment or none at all.

Despite years of research, treatment is still an art rather than a science, and patients increasingly have the feeling that the medical world has failed them. The past two decades have been disappointing and frustrating for the IC/BPS patients and their support groups who feel that no real progress has been made either in finding the right treatment for the right patient or in identifying the cause(s) of their pain, urgency and frequency which have such a devastating impact on their lives.

New patients are astonished to discover that this condition has so many different names and definitions and have difficulty in comprehending how this has happened. There are now a number of new patient support groups around the world and their leaders are experiencing great difficulty in persuading a) physicians in their country to take this nebulous, multi-named condition seriously and b) health and insurance authorities to approve and reimburse treatment.

An additional reason behind this lack of official approval is the repeated failure of studies and trials to produce convincing evidence of efficacy. A significant factor in this regard is that patients with every kind of bladder/pelvic pain disorder, with and without lesions and with or without bladder-centric symptoms, have been bundled together instead of being separated into subtypes and phenotypes. How did this happen? Or rather, why is it still happening?

It is clear that a different approach is now urgently needed. Hunner lesion must now be separated from non-lesion disease at least for research and treatment, while both Hunner lesion and non-lesion

types urgently need meaningful phenotyping so as to enable the best possible treatment and improvement in the patient's quality of life. Research must be able to move forward for the sake of the patients. (70)

VI. EPIDEMIOLOGY

In this 2021 Consultation, the nomenclature has been updated and is now referred to IC/ BPS and/ or HLD. Since the clinical diagnosis of IC/BPS is controversial, epidemiology studies of IC/BPS have been problematic and have randomly used BPS/ IC/ HLD. (71) The previous lack of an accepted definition, the absence of a validated diagnostic marker, and questions regarding etiology and pathophysiology, as well as overlapping causes of bladder pain, lower urinary tract symptoms and pelvic pain present challenges for clinical practice and research. (72) The other major difficulty in evaluating various prevalence research is that some is based on unverified self- report, others by physician diagnoses (with or without some type of verification) or by identification of IC/BPS symptoms (with or without exclusion of other confusable conditions) , each of which gives a different figure. This confusion becomes apparent when one looks at the variation in prevalence reports in the United States and around the world. These range from 3.5 per 100,000 population in Japan (73), to a questionnaire based study that suggests a figure of 20,000 per 100,000 in US women. (74) Studies, however, have consistently shown that bladder pain symptoms are more common than suggested by coded physician diagnoses. (75) In the following section, the terms BPS/ IC/ HLD are used as previously described in the original publication. Prevalence studies are difficult given the overlapping nature and taxonomy of chronic pelvic pain syndromes. (**Figure 3**)

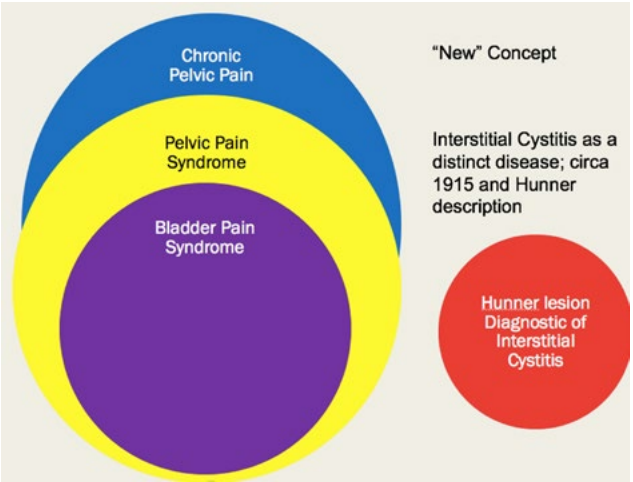

Figure 3. International Consultation Conception of bladder pain syndrome and interstitial cystitis.

2.1. Early epidemiological studies:

One of the first population-based studies (76) included "almost all the patients with interstitial cystitis in the city of Helsinki". This superb, brief report from Finland surveyed all diagnosed cases in a population approaching 1 million. The prevalence of the disease in women was 18.1 per 100,000. The joint prevalence in both sexes was 10.6 cases per 100,000. Ten per cent of cases were in men.

Another early population study, this in the United States, first demonstrated the potential extent of what had been previously considered a very rare disease. (4) The following population groups were surveyed: 1) random survey of 127 board-certified urologists 2) 64 IC patients selected by the surveyed urologists and divided among the last patient with IC seen, and the last patient with IC diagnosed 3) 904 female patients belonging to the Interstitial Cystitis Association and 4) random phone survey of 119 persons from the US population. This 1987 study reached the following conclusions (interestingly, most of these conclusions have stood the test of time and many further epidemiological studies described later in this section):

1. 43,500 to 90,000 diagnosed cases of IC in the USA (twice the Finnish prevalence)
2. Up to a five-fold increase in IC prevalence if all patients with painful bladder and sterile urine had been given the diagnosis, yielding up to half million possible cases in the USA
3. Median age of onset 40 years
4. Late deterioration in symptoms unusual
5. 50% temporary spontaneous remission rate, mean duration 8 months
6. 10 times higher incidence of childhood bladder problems in IC patients vs controls
7. 2 times the incidence of a history of urinary tract infection vs. controls
8. Lower quality of life than dialysis patients
9. Costs including lost economic production in 1987 of $427 million ($988 million in 2021 dollars)

2.2. Patient Self report surveys:

As mentioned earlier, the prevalence of IC/BPS can be estimated from patient self-reports, physician diagnoses and/or symptom based surveys. Jones and Nyberg (77) obtained their data from unverified self-report of a previous diagnosis of IC in the 1989 National Household Interview Survey. The survey estimated an overall prevalence of 500 per 100,00 populations (0.5% of the population), or >1,000,000 people in the United States with a self-reported diagnosis of IC. For women this prevalence figure was 865 per 100,000. As part of the third National Health and Nutrition Examination Survey (NHANES III), patients who answered yes to two questions (pain in the bladder/frequent urination and a diagnosis of IC or PBS) resulted in a remarkably similar estimated prevalence of 470 per 100,000 (850 per 100,000 women). (78) Ibrahim et al. analysed the prevalence of self-reported IC diagnosis and IC-like symptoms among 823 community-dwelling women. Depending on the questions used, the authors estimated a prevalence of 3.7% to 4.4%. If the survey was expanded by including women who reported pelvic pain only it increased to 17.3% giving an estimated number of 422,803 to 21,454,813 women with IC in the US. (79) These numbers must be viewed with caution because of inaccurate patient recall or confusion with other pain or bladder related conditions. However, these patient-reported diagnoses figures certainly suggest that IC/BPS is a common occurrence.

2.3. Physician Diagnoses Studies

Estimations of prevalence based on physicians' diagnoses may be thought to produce more accurate estimates, and while they do provide different figures, these are in part based on the local or geographic diagnostic criteria employed. Bade et al (80) used a physician questionnaire-based survey in the Netherlands yielding an overall prevalence of 8-16 per 100,000 females, with diagnosis heavily dependent on pathology and presence of mast cells. The Nurses Health Study I and II (81) showed a prevalence of IC between 52 and 67 per 100,000 in the USA. This report was based on self-reports with validation using data from medical records. The prevalence of a physician-based diagnosis of IC/BPS in men and

women in a managed care population in the US Northwest was 197 per 100,00 women and 41 per 100,000 men. (78) However, these rates decreased to 99 per 100,000 women and 19 per 100,000 men if the definition of the condition was limited to individuals who had undergone cystoscopy. Nickel, et al performed a prospective practice audit in outpatient urology practice populations of 65 urologists and noted that the prevalence of IC and IC diagnosis in urology outpatient practice, confirmed by both investigation and symptom scoring, was determined to be 2.8%. (82) Significantly lower was the estimated incidence in a study from Roberts et al. based on a population of around 150.000 in Olmsted county, USA, all patients who had received a physician-assigned diagnosis of IC/ BPS between 1976 and 1996 were identified through the resources of the Rochester Epidemiology Project. The age-adjusted incidence rates were 1.6 per 100000 in women and 0.6 per 100000 in me. (83) This of course does not represent in any way the burden of this condition in the general population, but rather reflects the national referral and practice traditions. There are other limitations using physician diagnoses to determine prevalence. Studies that utilize physician diagnoses to define the presence of IC/BPS will likely underestimate the true prevalence, primarily because they do not identify patients with undiagnosed disease, or they may not assign a diagnosis when the symptoms are present (reluctance to label a patient with the condition or alternatively are not familiar with diagnosing it).

2.4. Symptom based surveys

Another and possibly more sensitive method to examine prevalence and incidence of IC/BPS is to assess the presence of symptoms that suggest IC/BPS. A follow-up study utilizing the Nurses' Health Study (NHS) cohort) (84) used a mailed questionnaire followed by a detailed supplementary questionnaire if the participant responded "yes" to a bladder or pelvic pain question. They observed that the prevalence of IC/BPS symptoms was 1.7% in women younger than 65 years and increased progressively to 4.0% in women aged 80 years or older. This study suggested that the prevalence of IC/BPS increases with age. Warren, et al (85) combined a mail-in survey with randomly selected telephone surveys to determine the prevalence of IC/BPS amongst first degree relatives in comparison to that of the general population. They concluded that adult female first degree relatives of patients with IC/BPS may have a prevalence 17 times that found in the general population. This suggests but does not prove a genetic susceptibility to IC/BPS. The Boston Area Community Health (BACH) Survey (75), a population based cross-sectional survey of individuals in the Boston area which included an in person interview, determined the prevalence of painful bladder symptoms to be 0.83% to 2.71% in women and 0.25% to 1.22% in men depending of the definition used.

The O'Leary Sant (OLS) and the Pelvic Pain and Urgency/Frequency (PUF) questionnaires were compared by Rosenberg and Hazard (86) in the same general practice population of 1218 patients. The prevalence of IC/BPS with the OLS was determined to be 0.57%, with the PUF the prevalence was determined to be 12.6%. Leppilahti and colleagues estimated the prevalence in the general Population of Finland using a rather robust definition based on the OLS to be 0.68%. (87,88) However, when a sample of those women was examined by one of the urologists, the more accurate prevalence was 0.3%.

Clements et al employed 3 different definitions of IC/BPS related symptoms. The first included only self- reported pelvic pain with voiding symptoms. (78) The second included increasing pain with bladder filling and relief with urination. The third included a score of 12 or more on the OLS, including 2 episodes of nocturia and a pain score of 2 or greater. The prevalence estimates based on these definitions were 11,200 per 100,00 women and 6,200 per 100,000 men for definition 1; 3,300 per 100,00 women and 1,400 per 100,00 men for definition 2; and 6,200 per 100,000 women and 2,300 per 100,00 men for definition 3. Using a similar methodology, (89) it was concluded that the prevalence of IC/BPS-like symptoms in South Korean women appear to be lower than in Europe (90) and the United States, similar to Japan and higher than in China. (91) It is conceivable that the acknowledgement by individual patients of these specific IC/BPS symptoms may be influenced by cultural differences.

The most comprehensive and perhaps most accurate estimation of the prevalence of IC/BPS symptoms involved population-based symptom prevalence estimate using 2 validated case definitions to identify bladder pain syndrome/interstitial cystitis in 131,691 adult females. (92) Based on a high sensitivity definition, 6.5% (6,500 per 100,000) of women met the symptoms criteria, while 2.7% (2,700 per 100,000) of women met the criteria for a high specificity definition. These percentages translated into 3.3 to 7.9 million US women over 18 years of age with symptoms of bladder pain and/or interstitial cystitis. But only 9.7% of these identified women reported being assigned a bladder pain syndrome or interstitial cystitis diagnosis. A further study compared 3,397 women identified in this RAND Interstitial Cystitis Epidemiology (RICE) survey (71) with urinary symptoms consistent with a diagnosis of IC/BPS to 277 women with an actual IC/BPS diagnosis recruited from specialist practices in the USA. (93) The two cohorts showed remarkably similar demographics, symptoms and quality of life measures, confirming that IC/BPS is a very prevalent condition that is very likely under diagnosed and under-treated in the USA.

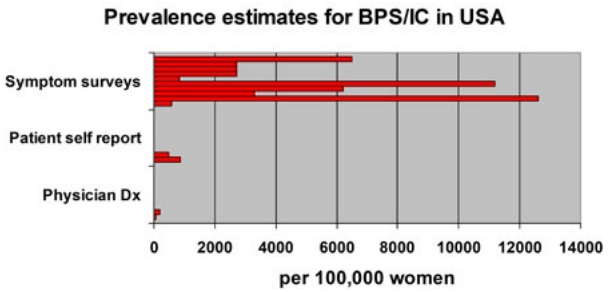

Figure 4. BPS Prevalence Varies by Methodology.

Conclusion: Based on these studies, it is impossible to determine an accurate estimation of the prevalence of IC/BPS or HLD, but a review of studies suggests that this is a very prevalent medical condition (Figure 4). The lowest prevalence figures are derived from physician diagnosis, while the prevalence of IC/BPS symptom complexes are more common than those based on patient self-report diagnoses. It is apparent that there has been no standardized method of determining the prevalence of IC/BPS, with wide variation of estimates in the same study employing different definitions or criteria for identifying the condition. Many factors including bias, cultural differences, methodology, geographic variations in diagnostic criteria and/or possibly real differences in different populations lead to further variations between countries.

Recommendation: A reasonable prevalence estimation for world-wide patients diagnosed with IC/ BPS would be about 300 per 100,000 women. This is based on O'leary Sant symptom surveys which yield comparable data in the United States, Finland, Austria, and Korea. (86,88-90) The male prevalence is 10% to 20% of the female estimate but potentially up to 60% of

the female number based on Rand data. (94) The prevalence of women and men *with symptoms suggestive of BPS* could be as much as 10 times more. (95)

Level of Evidence: 1 Grade of Recommendation: A

1. INCIDENCE

Only a few estimates of incidence have been reported. The annual incidence of new female cases in Oravisto et al, 1975 study was 1.2 per 100,000. (76) The overall age- and sex-adjusted incidence rate of physician assigned diagnoses of IC/BPS in Olmstead county (75) was 1.1 per 100,00 per year (1.6 per 100,00 per year for women and 0.6 per 100,000 for men. (96) Another review of physicians' diagnoses identified a much higher yearly incidence of 21 per 100,000 women and 4 per 100,000 men. (78) A physician-coded diagnosis supplemented with chart review of the Kaiser Permanente database suggested an IC/BPS incidence rate of 15 per 100,000 women per year. (97) The mean average age of patients was 51 years. Lower numbers were observed in a comparative study using a US claims database. 0.06% of 3,973,000 subjects from the general population developed IC within 2 years. Of the 249,200 individuals with depression, 320 (0.13%) developed IC suggesting that depression increases the risk of developing IC. (98) Similarly in a nationwide population-based cohort study where data were gathered from the National Health Insurance Research Database of Taiwan women with systemic lupus erythematosus showed an increased incidence of IC rate ratio of 2.26 (95% confidence interval 1.57-3.27, P < 0.0001). (99) With such a wide variation between two similar studies in the same country, it is evident that we really do not have an accurate estimation of IC/BPS incidence.

Recommendation:
The available data suggests that the incidence of IC/BPS diagnoses is somewhere between 1 and 15 per 100,000 per year. This does not include the women who have developed symptoms but have not been diagnosed with the condition.

Level of Evidence: 2 Grade of Recommendation: B

2. OTHER CONSIDERATIONS

2.1. Children

Geist and Antolak (100) reviewed and added to reports of disease occurring in childhood. A childhood presentation of IC/BPS is extremely rare and must be differentiated from the much more common and benign-behaving condition variously called the *urinary frequency syndrome of childhood or dysfunctional elimination syndrome*, a self-limited condition of unknown etiology. Nevertheless, there is a small cohort of children with chronic symptoms of bladder pain, urinary frequency, and sensory urgency in the absence of infection who have been evaluated with urodynamics, cystoscopy, and bladder distention and have findings consistent with the diagnosis of IC/BPS. In Close and colleagues' review of 20 such children (101), the median age of onset was younger than 5 years, and the vast majority of patients had long-term remissions with bladder distention. Rackow et al assessed 28 women aged 13 to 25 with chronic pelvic pain syndrome and confirmed that 39% had a diagnosis of IC while a further 25% had both IC and endometriosis. (102) The relationship between dysfunctional voiding and bowel symptoms in early life was suggested in a mail based questionnaire study in 215 IC/BPS patients and 823 controls. (101) Doiron et al. analyzed 190 women with IC/ BPS stratified by irritable bowel syndrome (IBS) (103). Women with IBS were more likely to recall painful urination in childhood assessed by a modified form of a clinical bladder and bowel dysfunction (BBD) questionnaire (BBDQ), as well as Interstitial Cystitis Symptoms Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Pelvic Pain and Urgency/Frequency (PUF) questionnaires and UPOINT categorization. Another study examining early childhood events (102) showed that early childhood trauma, in particular sexual trauma was more common in IC/BPS patients than asymptomatic control subjects. While not proven in these studies, it may be possible to link early childhood events to the eventual development of IC/BPS symptoms in some patients.

Recommendation:
The diagnosis of IC/BPS, while extremely rare, should be considered in children and adolescents with typical symptoms with no other explanation.

Level of Evidence: 3 Grade of Recommendation: A

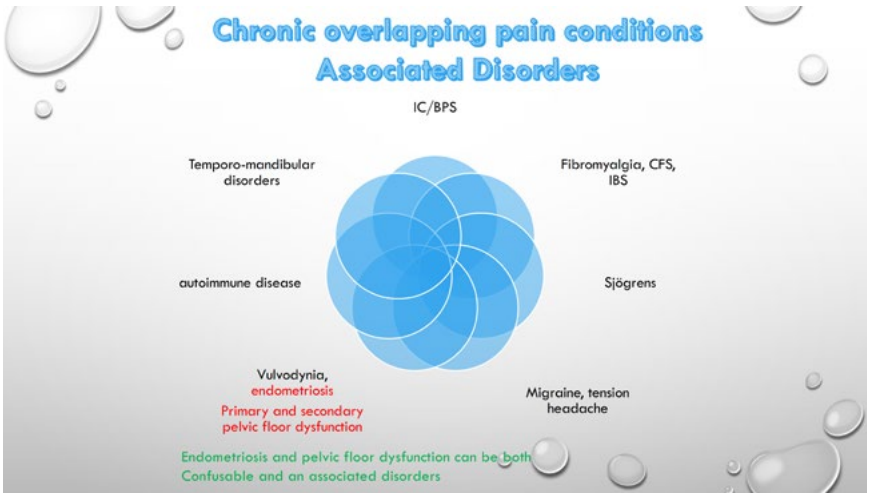

Figure 5. Associated and confusable disorders commonly diagnosed in patients with IC/BPS.

2.2. Men

Most studies show a female to male preponderance of 5:1 or greater. (60,78,104) In the absence of a validated marker, it is often difficult to distinguish IC/BPS from the chronic pelvic pain syndrome (nonbacterial prostatitis, prostatodynia) that affects males (105,106), and the percentage of men with IC/BPS may actually be higher. (107,108) Men tend to be diagnosed at an older age and have a higher percentage of Hunner lesion in the case series reported. In the Rand NIH epidemiology prevalence study the male to female ratio approached one to one. (94)

Recommendation:
The Male to Female ratio of IC/BPS cases is approximately 1:5. IC/BPS in men may be underdiagnosed and overlooked due to confusable disorders including chronic pelvic pain syndrome/ nonbacterial prostatitis, overactive bladder, and outlet obstruction.

Level of Evidence: 2 Grade of Recommendation: B

2.3. Overlapping Comorbidities

While the obvious clinical pain site associated with the diagnosis of IC/BPS is the bladder (pelvic pain only), it has become quite evident that many women with IC/BPS have multiple pain sites outside the bladder and pelvis area, with over 75% of women with a clinical diagnosis of IC/BPS reporting pain outside the pelvis (pelvic pain and beyond). (109)

Multiple observations have shown that IC/BPS patients are more likely than controls to have pain related syndromes manifesting symptoms beyond the bladder and even the pelvis. In 1997, Clauw, et al (110) reported on the symptom overlap between two cohorts of patients, one with fibromyalgia and one with IC/BPS. In the same year an analysis of a survey by Alagiri, et al (111) of over 6,700 persons who had a physician diagnosis of Interstitial Cystitis reported that individuals with IC/BPS were 100 times more likely to have inflammatory bowel disease, and that allergies, irritable bowel syndrome, sensitive skin, and fibromyalgia also have an increased association with IC/BPS. The presence of non-bladder syndromes (NBSs) and IC/BPS has further complicated the interpretation of epidemiological studies. Investigators have subsequently compared IC/BPS patients to controls on multiple NBSs. Wu et al. (112) compared 749 cases with IC/BPS to 1498 randomly selected and matched controls. Significantly more cases had FM, IBS, chronic pelvic pain (CPP), endometriosis, depression, anxiety, and vulvodynia. Overholt et al. analyzed 431 women with IC/BPS; out of those 82 (19%) had co-occurring endometriosis. These women were more likely to carry several comorbid, systemic pain diagnoses ($p<=.05$). (113) Clemens et al. (114) compared 239 women with ICD-coded IC/BPS to 717 matched controls and showed that cases significantly exceeded controls in myalgias, gastrointestinal symptoms, gynecologic pain, headache, back disorders, depression, and anxiety. Similarly, Chung et al. also found a higher incidence of anxiety disorder in women with IC/BPS compared to randomly selected female controls. Chung 2013c} This finding was still significant after adjusting for chronic pelvic pain, irritable bowel syndrome, fibromyalgia, migraines, sicca syndrome, allergies, asthma, and an overactive bladder (OR 4.37 (95% CI = 2.16-8.85, $P < 0.001$). Warren et al. (115) demonstrated that significantly more IC/BPS cases than matched controls had 11 antecedent syndromes: FM, CFS, IBS, sicca syndrome, Chronic pelvic pain, migraine, allergies, asthma, depression, panic disorder, and vulvodynia. Nickel et al. found significantly higher prevalence of self-reported FM, CFS, IBS, migraine and tension headaches, vulvodynia, temporomandibular disorder and low back pain in 207 female IC/BPS cases than in 117 controls as well as significantly more with depression and anxiety in a study in several urology practices in 3 continents. (116) A review confirmed that fibromyalgia (FM), chronic fatigue syndrome (CFS), and irritable bowel syndrome (IBS) were associated with IC/BPS. (117) In a study from Cheng et al., in 150 women with chronic pelvic pain undergoing laparoscopy glomerulations were identified in 48/150 (32%) individuals, and 80/150 (53%) had symptoms of IC/BPS. (118) The etiological and epidemiological questions that remain unanswered is how are these NBSs associated with IC/BPS; do these NBSs precede or follow IC/BPS and do multiple NBSs increase the risk of IC/BPS. Irritable bowel syndrome was shown to increase the subsequent risk of IC/BPS in a 12 year cohort study conducted in Taiwan (119). Warren and colleagues (120) have introduced a number of hypotheses, however the studies to validate these await data analysis from the NIDDK MAPP research effort. Relatives of IC/BPS patients appear to have an increased risk of associated conditions including myalgia and fibromyalgia as well as constipation, suggesting shared underlying genetic factors. (121) Women with IC/ BPS might have a higher rate of previous primary dysmenorrhea as has been assessed by Chung et al through a population-based data study (OR 1.86 (95% CI 1.37-2.52, $p < 0.001$. (122) Similarly, women with pelvic inflammatory disease seem to have a higher risk for suffering from IC/BPS according to Chung et al. ($p<0.001$). (123) There might also be an association with rheumatoid arthritis according to Keller et al. (124) based on an analysis of the Taiwan National Health Insurance Database, with significantly higher rate of previous rheumatoid arthritis in women with IC/BPS compared to controls. A similar study design revealed a possible correlation with a higher incidence of succeeding coronary heart disease during a 3-year follow-up period. (125)

One other comorbidity that is sometime neglected or forgotten in these epidemiological associations is the association of IC/BPS with sexual dysfunction. Multiple studies have shown that women with IC/BPS diagnoses or symptoms experience very high levels of sexual dysfunction. (126-129) This is likely related to deep dyspareunia (pain with deep vaginal penetration) associated with anterior vaginal wall pain from a hypersensitive bladder but can also be related to vulvodynia, a common NBS seen in female IC/BPS patients. (130)

Recommendation:
Overlapping comorbidities are common in patients with a diagnosis of IC/BPS.

Level of Evidence: 1 Grade of Recommendation: A

2.4. Progression:

The disease onset is generally described as subacute rather than insidious, and full development of the classic symptom complex occurs over a relatively short time. It appears that IC/BPS does progress initially, but usually reaches its final stage rapidly (within 5 years) and then continues without significant change in symptomatology. (131) Subsequent major deterioration is unusual. (76) The duration of symptoms before diagnosis was 3-5 years in the Finnish study (76) while a very early American study quoted 7-12 years. (46) Time to diagnosis has likely diminished in the internet era. The Interstitial Cystitis Database Cohort (ICDB) of patients has been carefully studied, and the findings seem to bear out those of other epidemiologic surveys. (132) Patterns of change in symptoms with time suggest regression to the mean and an intervention effect associated with the increased follow-up and care of cohort participants. Although all symptoms fluctuated, there was no evidence of significant long-term change in overall disease severity. In an interesting Canadian study, chronic pelvic pain severity was

shown to decrease in the year after entry into the cohort, but higher pain catastrophizing scores at baseline were associated with greater chronic pelvic pain severity at 1 year. (133) MAPP study indicates that longer symptom duration is generally not associated with more severe symptoms in the majority of patients, nor is disease duration associated with risk for chronic overlapping pain conditions or mental health comorbidities. (134) The data suggest that IC/BPS is a chronic disease, and no current treatments have a significant impact on symptoms over time in the majority of patients. In a large series in Taiwan on patients with 5 or more years of consecutive medical records since diagnosis, about half of the patients with IC/BPS exhibited symptom improvement with time, with or without regular follow-up and receiving a new treatment. (5) Whether some patients undergo a phenotypic progression over time from a purely organ specific (eg. bladder) condition to a regional pain syndrome (eg. IBS, vulvodynia) to a more generalized pain syndrome (eg. FM, CFS) (135) is controversial. Long term longitudinal studies examining progression issues in IC/BPS are lacking.

Recommendation:
Epidemiological data required to describe progression patterns of IC/BPS is lacking.

Level of Evidence: 1 Grade of Recommendation: A

VII. ETIOLOGY

The etiology of IC/BPS remains a wide-open field for investigation. Etiology is still an enigma and often the proposed causes for IC/BPS cannot be mirrored to the suggested treatment. Hence, a possible pathophysiological pathway leading to clinical manifestation of IC/BPS cannot absolutely lead to the analogue treatment. Symptoms like urinary frequency and bladder pain may be indicative of bladder injury, but they are rather heterogenous, causing more diffusion when investigation tries to locate the origin of this situation. Moreover, research findings in animal and human models do not always match, challenging more studies even in novel pathophysiological pathways including adverse childhood experiences as a potential etiologic factor. (136)

1. IMMUNE CELL ACTIVATION

Immune response in IC/BPS could be provoked by the activation of specific series of immune cells, the mast cells. Mast cells are multifunctional immune cells that can secrete highly potent inflammatory mediators such as histamine, leukotrienes, serotonins and mainly cytokines (137). Actually, the pathway involving the inflammatory process could provide an adequate explanation for the clinical manifestation of IC/BPS and its microscopic findings, such as frequency, oedema, angiogenesis in lamina propria and fibrosis. Pathogenesis involving mast cells suggest their interference with other inflammatory cells and the nervous system, keeping their role in pathogen-

Figure 6. The complex potential etiologies of IC/BPS. See text for compete description.

esis of high importance (138). Moreover, mast cell concentration seems to be higher in those patients with Hunner lesion, comparing to those with non-Hunner lesion IC/BPS or those with overactive bladder (139,140). Researching the pathway of bladder insult, a study on a murine model demonstrated an inflammatory and pain axis implicating IL-33 and mast cell activation, suggesting a potent way of propagation for pain and inflammation (141). Activated mast cells release proinflammatory cytokines, such as TNF and the overexpression of TNF by urothelial cells in vivo caused significant pelvic pain behavior, voiding dysfunction, and urothelial lesions, which supports the potential role of TNF in the pathogenesis of IC (142). Recently, a potent role of microRNA in mast cells activation has been investigated, demonstrating that over-expression of microRNA-132 increased inflammatory cell infiltration, collagens I and III expressions and mast cell growth (143).

However, in contrast to all above, a digital quantitative analysis of mast cell infiltration in interstitial cystitis has shown that mast cell density is not significantly different between IC/BPS specimens and non-IC/BPS control specimens with a similar degree of background inflammation (144).

Apart from mast cells, an implication of another type of immune cell, the plasma cell, has been proposed, proving that CXCR3-positive plasma cells may play a role in Hunner lesion disease, but not in IC/BPS, activating the CXCR3 inflammation pathway (145).

The role of immune cell activation on the pathogenesis of IC/BPS seems to be crucial and future research may provide more information and evidence.

Level of Evidence: 1

2. INCREASED PERMEABILITY OF THE UROTHELIUM

The key barrier that inhibits the transit of low and high molecular weight solutes from urine to bladder interstitium, is bladder urothelium. This barrier consists of a dense layer of glycosaminoglycans and variable intercellular junctions. Hence, any damage at this level of inhibition could be the beginning of bladder insult, contributing to the development of IC/BPS. Decreased expression of the tight junction proteins ZO-1 and occludin, as well as increased expression of the adhesion protein E-cadherin, in patients with IC/BPS, could be associated with higher permeability of the urothelium, due to loosen intercellular junctions (146). Additionally, lower expression of E-cadherin could contribute to higher apoptosis in IC/BPS patients' urothelium (147).

MicroRNA is presented, also, as an important regulator of intercellular junctions in patients with IC/BPS. More specifically, microRNA miR-199a-5p has been identified as overexpressed in IC/BPS patients' urothelium, combined with incorrect tight junctions and increased urothelial permeability (148,149). However, currently, there are a variety of microRNA expressions under investigation demonstrating possible involvement in IC/BPS development. Upregulated microRNAs such as miR-21, miR-4435-2HG, and miR-155HG and downregulated miR-205HG were identified as key microRNAs in Hunner lesion disease (150). In another study of postmenopausal women with IC/BPS, the suppression of miR-214 expression has been found to promote the epithelial transition and contribute to bladder wall fibrosis (151).

The damage of the glycosaminoglycan (GAG) layer contributes, also, to a higher permeability of the urothelium with the sub-mucosal nerve filaments becoming more accessible to noxious substances of the urine. (152,153). However, Grundy et.al. demonstrated in an experimental model that while induced changes in bladder permeability are able to induce transient bladder afferent hypersensitivity in the absence of inflammation, highly regulated homeostatic mechanisms exist to rapidly repair the urothelial barrier and normalize bladder afferent mechanosensitivity, suggesting that additional pathophysiology is required to induce chronic bladder dysfunction. (154)

Level of Evidence: 2

3. INHIBITION OF BLADDER UROTHELIAL CELL PROLIFERATION

Explanted urothelial cells from patients with IC/BPS seem to differ from the controls in the rate of proliferation and the production of an antiproliferative factor (APF). This has been shown in a study over gene expression patterns in normal bladder urothelial cells treated with APF and with mock APF as compared to patterns expressed by IC/BPS urothelial cells (155). More specifically, this theory may involve both down-regulation of genes that stimulate cell proliferation along with up-regulation of genes that inhibit cell growth. Interestingly, APF seems to be specifically elevated in the urine of patients with IC/BPS but not in healthy or patients with confusable diseases (156,157). APF testing is done through a bioassay and initial studies have not been confirmed by subsequent investigators.

Recently, a novel function of p53 and p21 proteins, in regulating ZO-1 and E-cadherin gene expression in bladder epithelial cell explanted from IC/BPS patients, has been investigated and suggested a possible suppression in cell proliferation (158).

Level of Evidence:2

4. AUTOIMMUNE MECHANISMS

The role of autoantibodies and their association with the presence of IC/BPS has long been a research objective, but their precise identity has yet to be determined (159-162). Actually, the autoimmune disturbances of the most common autoimmune diseases do not differ significantly from those of IC/BPS, with the presence of antinuclear antibodies and histopathological characteristics quite similar to the autoantibody profiles of some systemic diseases, like Sjögren syndrome (163-165). However, only a portion of IC/BPS patients have autoantibodies and those seem to be related to more severe symptoms (166).

The involvement of the immune system in the development and expression of IC/BPS has been recently investigated at the level of toll-like receptors (TLR), showing TLR7-gene expression and TLR7 immuno-reactive cells in the bladder biopsy specimens of patients with Hunner lesion disease compared with the controls. It is already known that TLR7 contributes to the development of several autoimmune diseases, such as Systemic Lupus Erythematosus and Sjögren (167).

Vascular immunopathology with immune deposits in the bladder wall, as well as activation of complement are additional findings of several studies, enhancing the association of IC/BPS with autoimmune responses (168,169). It is, also, an interesting observation that T-cell infiltrates and B-cell nodules were seen in Hunner lesion disease patients and not in non-lesion IC/BPS (170). Additionally, in a mouse autoimmune model, the antigenic T2 peptide activated T cells and interacted with TRPM8 receptor in the bladder tissue resulting in an autoimmune reaction leading to IC/BPS (171).

Autoimmune mechanisms may have a key role in the etiology of IC/BPS (172) , but even recent studies are quite heterogenous and difficult to compare, in order to allow for any conclusions.

Level of Evidence: 2

5. INFECTION

The role of micro-organisms as a key factor causing IC/BPS has been widely investigated. No Gram-positive or Gram-negative bacteria have been implicated in IC/BPS, nor has an increase of IgG or IgM been detected in the urine of IC/BPS patients (164,173) . In another study including women with IC/BPS, there was no significant correlation of the onset of symptoms with the appearance of UTI (174). With the absence of acute bacterial infection as a direct etiology for IC/BPS, attention has now turned to possible involvement of nano-bacteria and microbiota as potentially important. Hence, in the study of Zhang et al, nano-bacteria has been found in women's urine with IC/BPS and interestingly the anti-nano-bacteria treatment was also effective in improving symptoms (175). Nickel's study on microbiota role in women with IC/BPS revealed that those women with a flare of symptoms had a higher prevalence of fungi compared to those without flare. All patients had a persistent negative urine culture for common micro-organisms (176).
Additionally, another type of bacteria known as L-form bacteria could be cultured with specific materials and methodology and a role in pathogenesis has not been ruled out (177). Urinary microbiome and cytokine levels in women with IC/BPS have been investigated in another study, trying to find measurable differences in the urinary microbiota and cytokine levels. Authors suggested a role of Lactobacillus species, specifically L acidophilus. Their presence was associated with improved symptom scores when compared with IC/BPC women with deficiency of Lactobacillus species. Jacobs et.al. found the presence of Lactobacillus did not differ between cohorts of IC/BPS patients and controls and did not impact symptom severity. Bacteria were not isolated by expanded quantitative culture techniques. (178) In another study, the urinary microbiome of patients with IC/BPS was less diverse, less likely to contain Lactobacillus species, and associated with higher levels of proinflammatory cytokines than a control group. (179).
At this time there is no reason to believe that IC/BPS is a manifestation of an infectious disease.

Level of Evidence: 1

6. NEUROBIOLOGY

The effect of changes in the nervous system as related to IC/BPS symptoms is a field of wide research with a variety of etiologic hypothesis. Some studies on the S-100 family of proteins presence in Schwann cells, have shown lower levels of those proteins in patients with non-Hunner lesion IC/BPS, consistent with a decreased nerve content in these patients (180). On the other hand, the use of PGP9.5 antibody revealed increased nerve content in patients with IC/BPS compared to patients with overactive bladder and controls (181,182) . Also, the hypothesis of neurogenic inflammation as the origin of the pathophysiological sequence of IC/BPS has been proposed in the study of Elbadawi and Light (183).
A more complicated, but also challenging pathway implicating in the etiology of IC/BPS could involve the connection of neurobiology with the immune cell system, through the activity of intravesical substance P. In animal models, intravesical substance P has been found to induce remarkable referred hyperalgesia accompanying slight bladder mucosal swelling, without the presence of ulcerous surfaces (184). The fact of the co-interference of immune and neurogenic pathways in the etiology of IC/BPS could also be supported by the significant increase of tyrosine hydroxylase immunoreactivity in bladder tissue of IC/BPS patients, as compared to controls (185).
In a mouse model, a correlation of Toll-like receptor 4 (TLR4) with the development of IC/BPS has been studied. TLR4 is expressed in numerous cell types including neuronal and non-neuronal glial cells in the central nervous system, as well as immune and non-immune somatic cells including bladder epithelial cells. The activation of TLR4 leads to a consecutive inflammatory process through the production of cytokines. The investigators found an independent role of TLR4 especially in the expression of IC/BPS pain and inflammation, possibly through the production of IL-1β and IL-6 (186).
The implication of dysfunctional C-fibers might be another explanation of lower pain resistance in patients with chronic pelvic pain syndrome and specifically bladder hyperalgesia. Actually, the water avoidance test (WAS) assessed by cystometrogram has shown that stress-induced bladder dysfunction may derive from the increased sensitivity of C-fibers and mechanoreceptors. However, the role of C-fiber activation in WAS-induced bladder hyperalgesia has to be further investigated in IC/BPS patients (187).
Clinical observations over brain MRIs in IC/BPS women have shown increase in gray matter volume in several regions of the brain probably associated with lower pain tolerance and higher anxiety. This may imply cortical tissue in the neurobiological component of IC/BPS (188).

Level of Evidence: 2

7. PELVIC ORGAN CROSS-TALK

A bidirectional neural cross-sensitization of the colon and lower urinary tract has been demonstrated by few studies, showing that colon disease may be associated with bladder hypersensitivity and hyperalgesia in animal models (189-193). A central induced cross-organ sensitization of visceral nociception between the colon and urinary bladder has been demonstrated in cases of acute colitis and this may support a substantial overlap of IC/BPS with inflammatory bowel diseases, apart from the neurogenic etiology (106). Certainly, another reason of a crosstalk between bladder and colon in the era of IC/BPS is the observation in rat models that intravesical protamine sulfate increased permeability of bladder urothelium and the permeability of colon, as well (194).

Level of Evidence: 3

8. URINARY TOXIC AGENTS

Some investigators have suggested that some toxic substances may be a potent causative factor for the development of IC/BPS. Interestingly, the more cationic urine content seems to be harmful to the GAG layer of the bladder resulting to a cytotoxic effect on urothelial cells (195). Also, abnormal glycosylation of Tamm-Horsfall protein, produced in kidneys, has been found in patients with IC/BPS, while defective constituent cytokine production may decrease mucosal defense to toxic agents promoting bladder insult in IC/BPS patients (196,197) .

Level of Evidence: 3

9. HYPOXIA

The question as to whether an IC/BPS bladder may be hypoxic is still without a well evidenced answer. Lee et al have found that hypoxia-inducible factor-1alpha (HIF-1a) is over-expressed in the bladder tissue of IC/BPS patients (198). Other investigators have proposed disturbances in bladder microvascular density and deficiency in bladder perfusion (199-201). In another study, internal iliac artery blood flow has been found significantly lower in patients with IC/BPS compared with the control group and this is in accordance with atherosclerosis-induced chronic bladder ischemia and lower urinary tract dysfunction, already known by the research in animal models (202).

Level of Evidence: 4

10. THE ROLE OF GENETICS

The potent role of heredity in IC/BPC patients has also been researched and the first demonstration was a greater concordance among monozygotic than among dizygotic twins and certainly female first-degree relatives of patients with IC/BPS may have a prevalence of IC/BPS 17 time higher than found in the general population (85,203). In another study on more than 25,000 female twins, genetic factors have been found to contribute in less than one-third of the total variation in susceptibility to IC/BPS, suggesting the environment is an add-on factor for the development of the disease (204).

Patients and their first-degree relatives with panic and anxiety disorders have been suggested as susceptible to IC/BPS through chromosome 13 (205,206) . A recent investigation has provided significant evidence for genetic linkage on 3p13-p12.3 for IC/BPS. More specifically, genetic variants on chromosome 3 and possibly chromosomes 1, 4, 9, and 14 may contribute to IC/BPS predisposition (207).

Alternations on the regulation of several families of micro-RNA and mRNA have also been suggested as a genetic factor for the etiology of Hunner lesion disease through the disturbances on the expression of specific genes. (207,208)

Level of Evidence: 1

11. OTHER SUGGESTED FACTORS

A variety of independent etiological mechanisms has been proposed adding some evidence in the labyrinth of IC/BPS. Hence, endometriosis increased the risk of the disease, but this is provided only as epidemiological evidence (209). Infection with Epstein-Barr virus might be a causative factor of persistent inflammation in a subset of patients with IC/BPS (210).

12. CONCLUSION

The etiology of IC/BPS includes a lot of factors with a variation in their influence on the development and the physical history of the disease. Certainly, some of them seem to interact with others making the etiological labyrinth even more complex. Classifying IC/BPS among generalized somatic disorders could open new horizons for research, as it may open new pathophysiological pathways for investigation. Current evidence seems to guide novel research to neuroscience, immunology, infection, and genetics as potent major etiological factors for IC/BPS. Figure 6 summarizes the etiology for IC/BPS with respect to separate factors for each category. Study of Hunner lesion disease etiology awaits its recognition as a specific entity apart from IC/BPS.

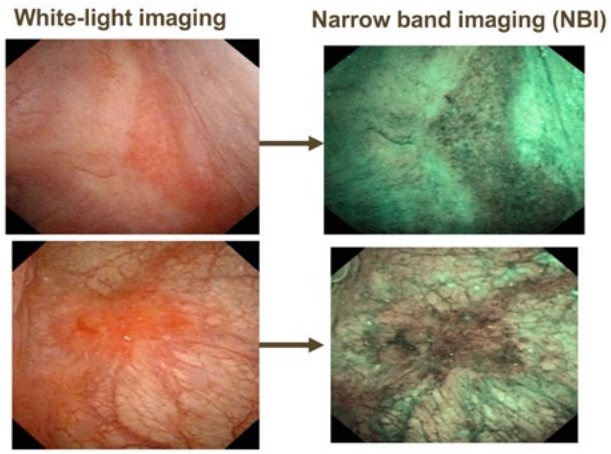

Figure 7. Hunner lesions: white-light imaging (left) and narrow-band imaging (NBI) (right) in 2 patients with IC/BPS. The entire erythematous area should be included in local treatment.

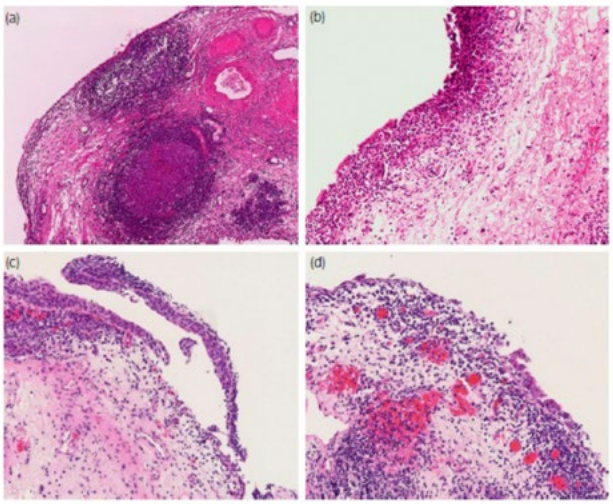

Figure 8. Histopathology of Hunner lesion disease. Dense inflammatory cell infiltration is observed in the subepithelial region. (a) Lymphoid follicles are frequently present. (b) Linear inflammatory cell infiltration is present in the subepithelial region. (c) Epithelial denudation is often observed. Numerous plasma cells are present along with lymphocytes in HIC bladder. Microvessels are increased. The superficial layer of the epithelium is lost. (d) The epithelial cells in the basal layers show degenerative changes. Homma Y, Akiyama Y, Tomoe H, Furuta A, Ueda T, Maeda D, et al. Clinical guidelines for interstitial cystitis/bladder pain syndrome. Int J Urol 2020, Apr 14;27(7):578-89.

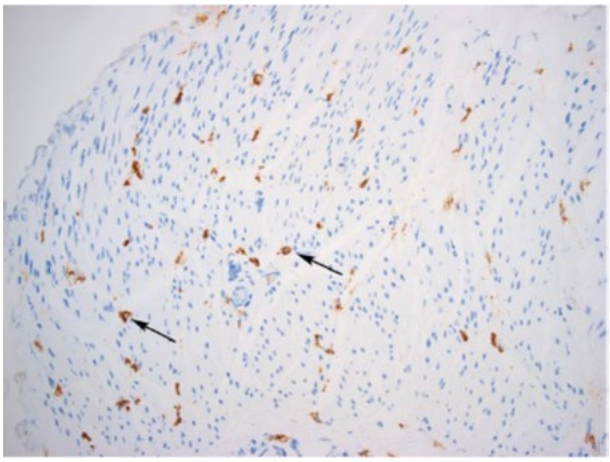

Figure 9. The detrusor muscle with mastocytosis showing mast cells positive with Mast Cell Tryptase (arrows). Magnification 200. Fall M, Nordling J, Cervigni M, Dinis Oliveira P, Fariello J, Hanno P, et al. Hunner lesion disease differs in diagnosis, treatment and outcome from bladder pain syndrome: An ESSIC working group report. Scand J Urol 2020, Apr;54(2):91-8.

VIII. PATHOLOGY

(special thanks to Naoki Yoshimura)

The previous ICI chapter in 2017 summarized that bladder histopathology plays a supportive diagnostic role at best (30), and that the exclusion of other pathologically identifiable diseases is the primary utility of bladder biopsy (211,212) . However, recent studies have shown that Hunner-lesion disease (HLD) (**FIGURE 7)** not only is different clinically from IC/BPS (213,214), but also exhibits histological differences such as significant inflammation and denudation in the bladder, which are clinically and pathologically distinct from non-Hunner IC/BPS and may be categorized as a separate disease entity termed "Hunner lesion disease (HLD)". (24,28,32) .

1. HUNNER LESION DISEASE

Inflammation: Chronic inflammation in the lamina propria is a major characteristic of HLD **(FiGURE 8),** which is not only confined to the Hunner lesion areas, but also found in the region outside Hunner lesions. Infiltration of the inflammatory cells in the lamina propria, mostly consisting of lymphocytes and plasma cells, is a predominant histological feature of HLD bladders. Also, lymphoid germinal center formation is observed in approximately 40% of patients. While a small number of macrophages and neutrophils. can be present, eosinophils are generally absent.

Epithelial denudation: Another important histological finding of HLD is bladder epithelial denudation, partially or entirely of the epithelial layer in the Hunner lesion as well as in the surrounded area of Hunner lesions (**FIGURE 8)** (24).

Mast cells: The role of the mast cell in HLD has been described (137,215,216) . Proteinase immune staining with mast cell tryptase (**FIGURE 9**) yields higher numbers of mast cells in HLD mucosal stroma and detrusor muscle layers compared to counts in non-HLD and normal bladders. However, it has been suggested that mast cells may not play a pivotal role in HLD pathogenesis because mast cell infiltration is less dense compared to other infiltrating inflammatory cells in the lamina propria (20). Furthermore, mast cells, which are seen at a lesser degree, have been implicated in afferent hypersensitivity and neurogenic inflammation in non-Hunner IC/BPS (217).

Fibrosis: Fibrosis is also found in the deeper layer of bladder mucosa showing detrusor bundles separated by fibrotic tissues (32).

Proteomic analysis: Significant differences in protein expression have been found between HLD bladder tissue biopsies and IC/BPS tissue. HLD tissue had increases in inflammatory and endoplasmic

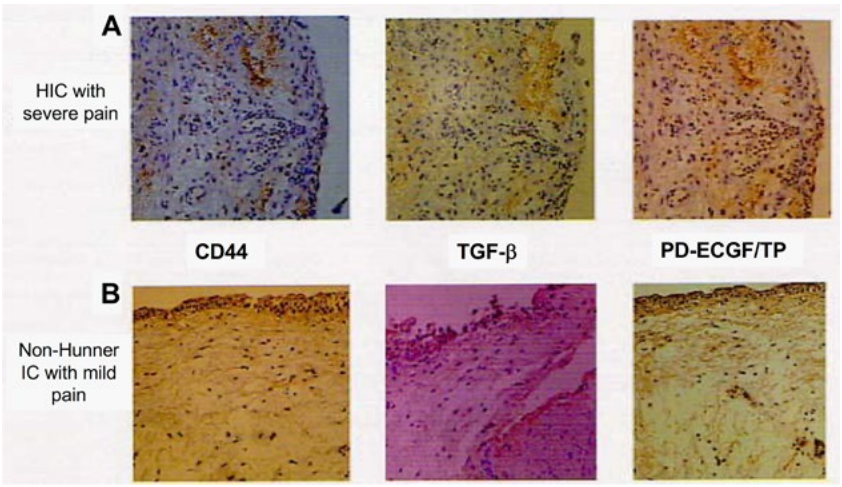

Figure 10. Overexpression of angiogenic factors in the bladder of IC/BPS patients.
The images show the results of immunohistochemical staining for epithelial and submucosal CD 44, transforming growth factor (TGF)-β, and PD-ECGF/TP in bladder tissue sections from patients with IC/BPS. A; Positive staining in the severe IC type (Hunner-type IC [HIC] patients with severe pain) is seen in the deeper part of the submucosal layer. B: Positive staining in the mild IC type (non-Hunner-type patients with relatively mild pain) is present along the basement membrane of the bladder epithelium; 200x magnification.

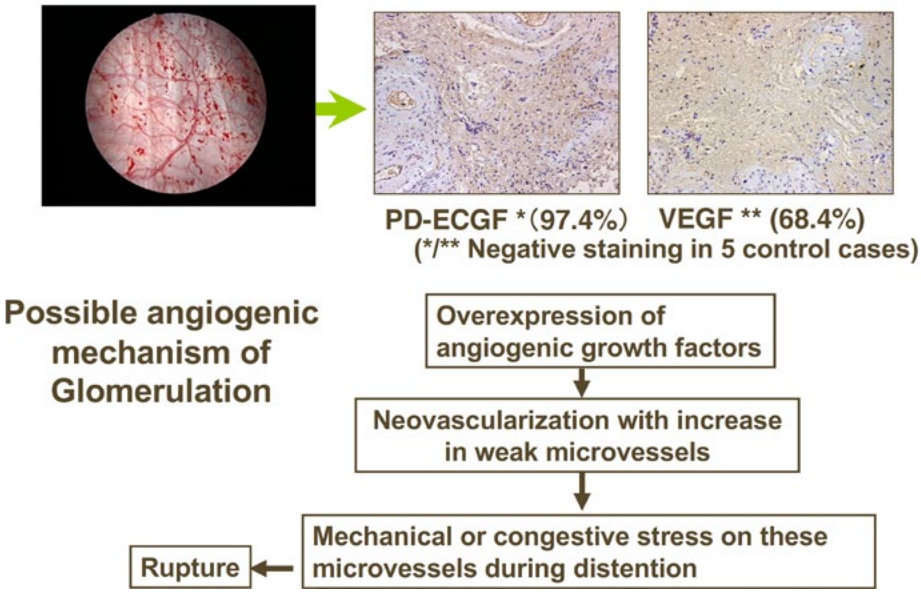

Figure 11. The angiogenic mechanisms inducing glomerulations.
In IC/BPS bladders, overexpression of angiogenic factors such as VEGF and PD-ECGF includes neovascularization with increases in weak microvessels, leading to rupture of microvessels during bladder distention, seen as glomerulations during cystoscopy.

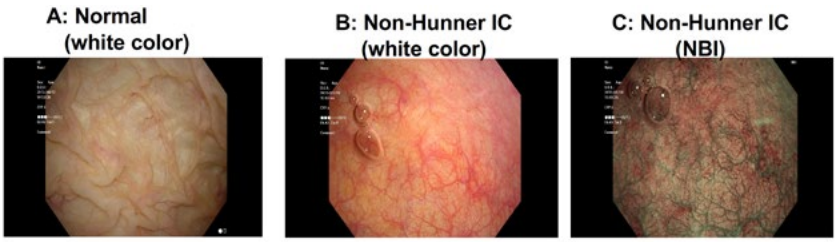

Figure 12. Representative cystoscopic images of the normal bladder (A) and the non-Hunner IC bladder under white light (B) or narrow-band imaging (NBI) (C).
A: The bladder epithelial mucosa was largely whitish in color with multiple folds on the mucosal surface in the normal bladder. Furthermore, the normal mucosal epithelium is stretchable in all directions during bladder distention because it is loosely connected to the underlying muscle layer
B & C: The abnormal bladder epithelium characterized by the stretched, hypervascular mucosa without mucosal folds in the non-Hunner IC bladder.

reticulum stress proteins, and a decrease in cellular adhesive proteins compared to IC/BPS. Other differences included a decrease in proteins associated with the Rap1 signaling pathway which regulates cell proliferation and would healing. (218)

2. NON-HUNNER IC/BPS

IC/BPS patients show limited inflammatory changes in the bladder wall. The bladder epithelium is usually well-preserved, and inflammatory cell infiltration in the lamina propria of non-Hunner IC/BPS bladders is much less remarkable compared to the HIC bladder (219). For the detection of bladder lesions of non-Hunner IC/BPS, cystoscopic identification of glomerulations, which is shown as mucosal bleeding after hydrodistension, has been viewed as a diagnostic method although the recent meta-analysis study concluded that glomerulations in non-Hunner IC/BPS patients do not correlate with symptoms and are also found in patients without IC/BPS (220).

However, previous studies reported that that there was overexpression of angiogenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived endothelial cell growth factor (PD-ECGF) in the bladder of both non-Hunner IC/BPS and HLD patients with higher expression in the latter vs. the former, in association with overexpression of the adhesion factors such as CD44 and TGF-β, which are known to bind with angiogenic factors via heparin-binding and become solidified (**FIGURE 10**) (221,222) . Also, it has been shown that overstretching the bladder wall during bladder filling could be responsible for the rupture of newly developed blood microvessels (e.g., glomerulation) in non-Hunner bladders of IC/BPS patients (**FIGURE 11**) (223). Therefore, the underlying angiogenic mechanisms for neovascularization with overexpression of angiogenic factors such as PD-ECGF or VEGF, could be considered to be bladder-specific lesions in non-Hunner IC/BPS (**FIGURE 10**). Also, for the cystoscopic diagnosis of bladder lesions of non-Hunner IC/BPS, the detection of mucosal hypervascular lesions caused by angiogenesis, which differ from the normal bladder

mucosa **(FIGURE 12),** needs to be standardized instead of using hydrodistension-induced glomerulations as a diagnostic criterion.

IX. DIAGNOSIS

A thorough diagnostic evaluation is essential to exclude other diseases that may mimic the symptoms of IC/BPS, and which therefore may benefit from alternative treatment, and to aid phenotyping of patients with IC/BPS so that targeted treatment can be offered to those who are likely to benefit most. Attempts to define objective diagnostic criteria for IC/BPS have focused on cystoscopy under local or general anaesthesia, bladder distention with registration of bladder capacity and presence of Hunner lesions, bladder wall biopsies evaluated for inflammation, ulcer, fibrosis, mast cells, etc. and urodynamics with registration of bladder capacity, compliance, and bladder stability. Recent studies are starting to suggest that stratification of patients based on certain clinical, cystoscopic, histopathological and urodynamic variables may now or in the future enable targeted therapy based on the specific patient's phenotype. It is hoped that future research efforts will strengthen the evidence base in this area, thereby allowing firmer recommendations to be made.

Unless otherwise stated, what follows is based solely on expert opinion. Level of Evidence:4 Grade of Recommendation: C

1. HISTORY

A general thorough medical history should be taken. Special emphasis should be given to:

- Previous pelvic operations
- Previous UTI
- Bladder history/urological diseases
- Location of pelvic pain (referred pain) and relation to bladder filling/emptying.
- Characteristics of pain: onset, correlation with other events, description of pain
- Previous pelvic radiation treatment
- Autoimmune diseases
- Co-existing somatic conditions (fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, temporomandibular disorder, migraine, vulvodynia)
- Psychological comorbidity (anxiety and depression)

A number of studies have assessed whether any specific symptoms are able to distinguish between Hunner lesion disease and non-Hunner lesion disease. Pain at vaginal penetration, greater pain severity, and increased urinary frequency and nocturia have been suggested in a recent meta-analysis to be more common in those with Hunner lesion disease, but reports are contradictory and there have not been any consistent findings in this regard (224,225,226,227,228,214) .

Regarding psychological comorbidity, a recent systematic review of 34 studies of patients with IC/BPS has revealed the high prevalence of clinical depression and generalised anxiety disorder in this population (3). Furthermore, patients with IC/BPS show higher levels of stress, poor illness coping, and more widespread pain symptoms than healthy controls, with a higher risk of suicidal ideation (229,230) . Although evidence for treatment is lacking, self-management techniques (guided imagery/self-hypnosis, mindfulness, and online health education) may improve symptoms and wellbeing, and so psychological comorbidity should be assessed as part of the initial history with appropriate psychiatric referral as appropriate.

Level of Evidence:3 Grade of Recommendation: C

2. PHYSICAL EXAMINATION

A common physical examination should be performed including palpation of the lower abdomen for

bladder fullness and tenderness:

- Standing: kyphosis, scars, hernia
- Supine: abduction/adduction of the hips, hyperaesthetic areas

In females, physical examination should include a vaginal examination with pain mapping of the vulvar region and vaginal palpation for tenderness of the bladder, urethra, levator and adductor muscles of the pelvic floor. Tenderness might be graded as mild, moderate or severe. (231)

Inspection:

- Vulva
  - exclusion of vulvar/vestibular diseases (vulvitis, dermatosis etc.)
  - evaluation of introital area (endometriosis)
  - tenderness of vestibular glands or vulvar skin (Touch Test: use wet cotton stick or finger tip)

- Vagina
  - tenderness during insertion and opening of
  - speculum
  - cervical pathology
  - vaginal fornices (endometriosis)

- Bimanual physical examination
  - tenderness of urethra, trigone and bladder
  - superficial/deep vaginal tenderness
  - tenderness of pelvic floor muscles (levator, adductor)
  - tenderness in adnexal areas

In males digital rectal examination (DRE) should be performed with pain mapping of the scrotal–anal region and palpation of tenderness of the bladder, prostate, levator and adductor muscles of the pelvic floor and the scrotal content.

3. LABORATORY TESTING

- Urine dipstick (blood, pH, leucocytes, nitrate), urine culture in all. If sterile pyuria culture for tuberculosis.
- Urine cytology in risk groups.
- Investigations for vaginal Ureaplasma and Chlamydia in females and prostatitis in men are optional.

Although the absence of infection is a pre-requisite for the diagnosis of IC/BPS, it is becoming clear that standard quantitative bacterial culture of a mid-stream urine specimen is less reliable than widely thought and many patients with symptoms suggestive of IC/BPS may have an infectious cause that can be successfully treated with antimicrobial agents (232,233) . A study that used specific culture media with longer incubation periods led to the identification of a uropathogen in 50% of patients with IC/BPS, and symptomatic improvement was reported after appropriate antimicrobial treatment

(177). Others have reported a greater incidence of fungal species in the urinary microbiome of patients with more severe symptoms, whereas higher levels of viral isolates (Epstein-Barr virus and Polyomavirus BK) have also been reported in patients with Hunner lesion disease (210,234,235) . However, studies are contradictory and so the relevance of changes in the urinary microbiome is unclear. Future urinary microbiome research should prospectively compare those with Hunner lesion disease to those with interstitial cystitis/bladder pain syndrome and assess outcomes from treatment in a randomized fashion.

While patients with IC/BPS symptoms who are found to have an infectious aetiology, by definition, do not have IC/BPS, it is not unreasonable to empirically treat this syndrome upon initial presentation with a trial of antibiotics given the possibility of infection despite negative culture. The vast majority of these patients will have undergone at least one course of antibiotics after symptom presentation before presenting to the provider who will ultimately make the IC/BPS diagnosis. Repeated courses of antibiotics should be discouraged in the absence of culture documented urinary infection.

4. SYMPTOM EVALUATION

- Voiding diary with volume intake and output for 3 days at initial evaluation. Patient sensation at voiding might be recorded (*see "outcome assessment").*
- At follow-up only number of voiding episodes during day and night is necessary. Morning volume might be recorded as a guide to the patient's largest functional capacity.
- The O'Leary–Sant Symptom Score should be used as the basic symptom score, supplemented with the Quality of Life Score from the International Prostate Symptom Score (*see "symptom scales").*
- Pain should be recorded using a Visual Analogue Scale (VAS) for pain during the last 24 hours (to fit with the voiding diary). Separate scores for the average, mildest and worst pain should be obtained ("*see symptom scales"*)

5. URODYNAMICS

The NIDDK criteria excluded patients with detrusor overactivity at filling cystometry in order not to confuse the picture in clinical trials (48). This does not however mean that detrusor overactivity (DO) cannot coexist with IC/BPS. In the interstitial cystitis database approximately 14% of IC/BPS patients had overactive bladders (13). Whether these patients respond better to antimuscarinics than IC/BPS patients with stable bladders has never been systematically investigated. If so, a rationale for routinely employing urodynamics as a part of the evaluation would follow. A Vanderbilt study with overactive bladder patients concluded that a majority of the 218 patients studied reported either painful urgency and/or pain on bladder filling (16). In another analysis, Ackerman et. al. reports that 35% of OAB patients have some degree of bladder pain and 25% of IC/BPS patients will report urge incontinence (17).

Studies comparing urodynamic findings in IC/BPS to OAB have shown that volumes at first sensation, normal desire, strong desire, and maximal capacity during filling cystometry were significantly lower in the IC/BPS group, and similar findings have been reported in patients with Hunner lesion disease compared to those without (236,237) . However, these findings are not consistently reported and so there is currently no evidence for routine use of urodynamics to phenotype patients in the absence of clinical suspicion as to diagnosis.

Urodynamics, however, is a useful tool to exclude confusable conditions in patients with IC/BPS. Patients with IC/BPS often describe voiding symptoms such as slow stream, straining or dribbling, and bladder outlet obstruction has been reported in up to 60% of women with IC/BPS (238,239) . In females, bladder outlet obstruction may be secondary to dysfunctional voiding, poor relaxation of the external sphincter or bladder neck obstruction. Urodynamics do not reliably differentiate primary myofascial pelvic pain from IC/BPS (240) .In males, infravesical obstruction may also be a differential diagnosis (241). Therefore, uroflowmetry is recommended in all patients with IC/BPS who describe voiding LUTS, and pressure-flow studies are recommended for men with peak flow rate <15ml/second and women with a peak flow rate <11ml/s, or in those where voiding dysfunction is suspected.

Level of Evidence:3 Grade of Recommendation: B

6. POTASSIUM TESTING

Parsons has championed an intravesical potassium chloride challenge, comparing the sensory nerve provocative ability of sodium versus potassium using a 0.4 M potassium chloride solution. The test has proved controversial (242). Pain and provocation of symptoms constitutes a positive test. Whether the results indicate abnormal epithelial permeability in the subgroup of positive patients, or hypersensitivity of the sensory nerves is unclear. Normal bladder epithelium can never be absolutely tight, and there is always some leak, however small (243). It was thought that this test would help stratify patients into those who would respond to certain treatments (perhaps those designed to fortify the glycosaminoglycan layer) (244). Used as a diagnostic test, the potassium chloride test is not valid (245). The gold standard in defining IC/BPS for research purposes until the last decade has been the NIDDK criteria. These criteria are recognized to constitute a set of patients that virtually all researchers can agree have IC/BPS, though they are far too restrictive to be used in clinical practice (51). Thus, this group of patients should virtually all be positive if the KCl test is to have the sensitivity needed to aid in diagnosis. Up to 25% of patients meeting the NIDDK criteria will have a negative KCl test (246). In the group it should perform the best in, it is lacking in sensitivity. When we look at the specificity side of the equation, in the universe of asymptomatic persons, it performs relatively well and is rarely positive, although one study reported a 36% false positive rate in asymptomatic men (247). It is in the patient population with confounding conditions for which we would want help in sorting out IC/BPS from other disorders. Sixty percent of patients with overactive bladder test positive (248) and virtually all patients with irritative symptoms from radiation cystitis and urinary tract infection test positive (246,249) . The results with chronic prostatitis / chronic pelvic pain syndrome in men are variable, but 50-84% of men have been reported to test positive (247,250,251) . In women with pelvic pain results are similar (252). Therefore, the KCl test is very nonspecific, missing a significant number of IC/BPS patients and over-diagnosing much of the population. Prospective and retrospective studies looking at the KCl test for diagnosis in patients presenting with symptoms of IC/BPS have found no benefit of the test in comparison with standard techniques of diagnosis (245,253,254) .

A later modification of the test using 0.3 molar potassium chloride for potential differentiation between patients with IC/BPS and DO showed that the 0.3 M KCl reduces maximum cystometric capac-

ity in IC/BPS and DO, the effect being more pronounced in DO. Urothelial hyperpermeability was not specific to IC. Comparative cystometry using NS and 0.3 M KCl does not help to differentiate IC/BPS from DO (255,256) . The development of a painless modification of the potassium chloride test (257) using cystometric capacity and a 0.2M solution may improve acceptability among patients. The so-called revised or Comparative Potassium Test has shown prognostic value in bladder irrigation studies (258) but is considered optional by ESSIC.

If performed it should be performed according to Daha et al. (257): A Foley balloon catheter (14F) is inserted, and the bladder drained. Instill into the bladder 500 ml saline (0.9%) at a rate of 50ml/min via an infusion set until the maximum capacity is reached. Drain the bladder and measure the saline filling volume. Repeat the instillation and measurement with 500 ml 0.2 M potassium chloride at a rate of 50 ml/min (taking care that filling lines are emptied of all saline before KCl instillation), and calculate the filling volume difference. A difference in bladder capacity > 30% is considered positive. Besides reduction of bladder capacity with 0.2 M KCl there is a stronger feeling of urgency in IC patients compared to the saline filling, which is also clinically relevant.

Level of Evidence:1 Grade of Recommendation: Not recommended

7. CYSTOSCOPY

Cystoscopy under local or general/regional anaesthesia is an essential investigation to identify Hunner lesion disease for which specific targeted treatment is recommended. Therefore, cystoscopy should be performed early in the diagnostic evaluation of patients with suspected IC/BPS.

Level of Evidence:2 Grade of Recommendation: A

8. LIDOCAINE INSTILLATION

The intravesical instillation of lidocaine as a diagnostic test has only been reported in one small case series of 22 women with pelvic pain (259). Instillation of 20 ml of 2% lignocaine solution led to significant pain relief in 68% (15 out of 22), and 13 of these 15 were found to subsequently have features of IC/BPS at cystoscopy. None of the non-responders to lidocaine instillation had cystoscopic features of IC/BPS, suggesting that lidocaine instillations can help to identify a bladder-centric phenotype. However, this is a small series in which positive cystoscopic features of IC/BPS included glomerulations, which are a non-specific finding. The use of this investigation is a promising tool to aid classification of IC/BPS, but further studies are required to confirm these initial findings, and so its use is not routinely recommended at present.

Level of Evidence:4 Grade of Recommendation: D

9. HUNNER LESION DISEASE

The classic Hunner lesion phenotype of IC/BPS as an “elusive” bladder localized area of bladder mucosal inflammation with a corresponding cystoscopic appearance of patches of red mucosa exhibiting small vessels radiating to a central pale scar, and was described by Hunner in 1915 (43,260). **(FIGURES 13, 14, 15).** The finding of a Hunner lesion varies. Some researchers find a Hunner lesion in 50% of their IC/BPS patients (261), while others rarely see one (262). Nevertheless, overall, in series where Hunner le-

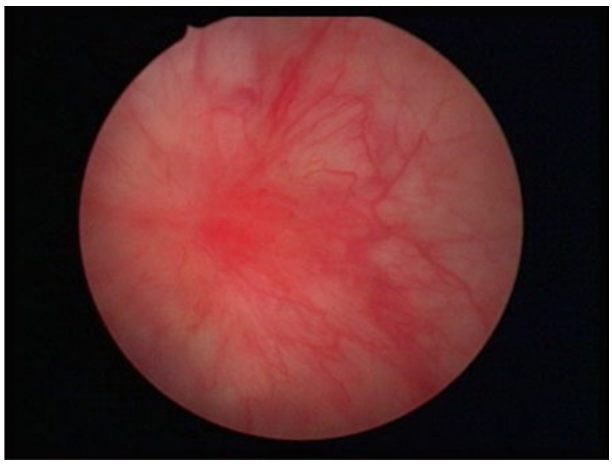

Figure 13. Hunner lesion prior to bladder distention. Courtesy of Jörgen Nordling

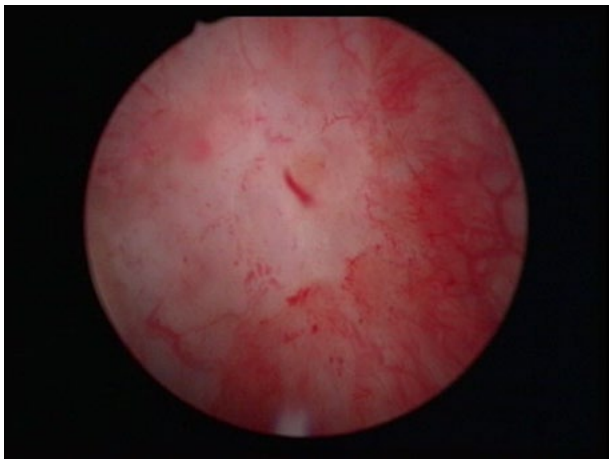

Figure 14. Hunner lesion at 80cm water pressure. Courtesy of Jörgen Nordling

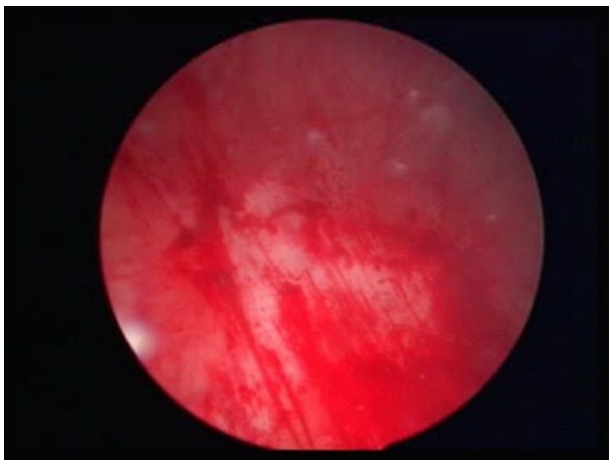

Figure 15. Hunner lesion post distention. Courtesy of Jörgen Nordling

sion has been looked for, the lesions are found in about one-third of patients (33). Identification of this lesion is important, as targeted therapy with fulguration or triamcinolone injection has been shown to be effective in this group (263). Recently, it has also been shown that the extent of the Hunner lesion corresponds to symptom severity, with more extensive lesions associated with more severe symptoms and a smaller bladder capacity (264).

10. GLOMERULATIONS

After 1978, glomerulations, described as punctuate petechial haemorrhages observed after hydrodistention, became the primary cystoscopic feature of IC/BPS (47,241) . (Figures 10 and 11, courtesy of Tomohiro Ueda). However, not all patients with symptoms of IC/BPS have glomerulations (50,51,265,266) and not all patients with glomerulations have symptoms of IC/BPS (248,267) . Neither presence nor severity of glomerulations correlate with any of the primary symptoms of IC/BPS (268), unlike the presence of a Hunner lesion which is significantly associated with bodily pain and urinary urgency (267). A recent review on glomerulations after bladder distension found no diagnostic or prognostic value of this finding (220). Despite ongoing research studies looking at what cystoscopic hydrodistention features might provide prognostic information (269), clinically at this time, the presence or absence of glomerulations on cystoscopy should not be used as a diagnostic or prognostic criteria for IC/BPS.

Level of Evidence:2 Grade of Recommendation: B

11. BLADDER CAPACITY UNDER ANAESTHESIA

Bladder capacity during hydrodistension has not drawn much attention, although it is strongly associated with increased urgency (262). Recent studies have found low bladder capacity under anaesthesia to be associated with more severe symptoms and to be indicative of a bladder-centric phenotype rather that a more systemic phenotype of IC/BPS (270,271) . Furthermore, patients with an anaesthetic bladder capacity of <400ml are more likely to have Hunner lesions and have histological evidence of significantly more acute and chronic inflammation compared with patients with a bladder capacity >400ml (272). Therefore, low anaesthetic bladder capacity may represent a specific, bladder-centric phenotype of IC/BPS. It is recommended that bladder capacity be routinely reported if hydrodistention is performed. Further studies of the prognostic significance and predictive value of this finding are required.

Level of Evidence:3 Grade of Recommendation: B

12. HYDRODISTENSION OF THE BLADDER

Because considerable variation in the duration of distension, repetition of distension, the pressure used for distension, and the measurement of bladder capacity have been described (273), the ESSIC has suggested a standardized procedure for cystoscopy and hydrodistension (274).

A rigid cystoscope is preferred to facilitate taking of adequate biopsies. Glycine or corresponding filling fluid should be used to allow for coagulation after biopsies. Infusion height should be approximately 60-80cm above the Symphysis Pubis. A dripping chamber is used, and the bladder is filled until fluid dribbling stops. If necessary, a digital block is applied around the urethra to prevent leakage. Pre-distension inspection includes observation for radiating vessels, coagulum or fibrin deposits, white spots, hyperaemia, oedema, cracks, scars or any other mucosal changes. Continuous inspection while filling the bladder is advised. When maximum capacity is reached, the distension is maintained for 2-5 minutes. The bladder is emptied, and the colour of the fluid checked for the degree of bleeding. The total volume drained is the measured maximum bladder capacity. During a second filling, the bladder is filled to approximately 1/3rd to 2/3rd of the bladder capacity to achieve optimal vision for inspection and biopsies. The bladder should not be filled to maximum capacity or distended again to avoid further provocation of changes with doubtful reproducibility.

13. INSPECTION

Describe lesions in anterior wall, posterior wall, lateral quadrants and fundus. At the fundus one should be alert for possible artefacts if there is blind introduction of the scope. Bladder mapping by drawing is mandatory. Photographs are recommended but optional.

14. CLASSIFICATION

Grade 0 ..... = normal mucosa
Grade I ..... = petechiae in at least two quadrants
Grade II ..... = large submucosal bleeding (ecchymosis)
Grade III ..... = diffuse global mucosal bleeding
Grade IV ..... = mucosal disruption, with or without bleeding/ oedema

As previously mentioned, the importance of the finding of glomerulations after hydrodistension is, however, questionable as 45% of asymptomatic females, 20% of males with LUTS suggestive of BOO and 85% of females with OAB and no bladder pain demonstrates typical glomerulations after hydrodistension (248,275,276) and 10-34% of patients with IC/BPS do not (50,266) .

15. HOW USEFUL IS HYDRODISTENTION?

It is necessary to distinguish between short term hydrodistension for classification of IC/BPS and long term hydrodistension for treatment. As a diagnostic tool, cystoscopy following hydrodistension is a recommended part of the diagnostic algorithm in order to phenotype patients based on the presence or absence of Hunner lesions, so that targeted treatment can be offered to those with Hunner lesion disease. As a therapeutic measure, hydrodistension results fail to identify any statistically significant differences in post-distention therapeutic benefits when patients are categorized according to presenting symptoms (277). A recent systematic review of 17 studies reported subjective improvement in 57% but the duration is short-lived (mean 2 months) and the quality of the evidence base is weak (278,279) . With 90% of Hunner lesions diagnosable on local cystoscopy (280), hydrodistention can now be reserved for when endoscopic treatment of Hunner lesion under sedation is indicated for therapy or in cases wherein distention is used as a therapy itself.

It is important to keep in mind that the cystoscopic appearance of the bladder wall after hydrodistention may not be constant over time, and the absence of initial findings of glomerulations or terminal hematuria does not preclude further development of these findings of the disease on subsequent evaluation (281). Rare cases of hydrodistension induced bladder necrosis have been described (282).

Level of Evidence:3 Grade of Recommendation: C

16. MORPHOLOGY

Pathological changes in light microscopic and electron microscopic features in patients with IC/BPS have been described including infiltration with inflammatory cells in all or specific parts of the bladder wall. Although these findings are important in our attempt to understand the disease and perhaps as an aid to stratification of patients, there are at this time no pathognomonic findings on biopsy in terms of diagnosis (268). Expert opinion as per the ESSIC suggests the following procedures when biopsy is planned for IC/BPS evaluation (274):

16.1. Biopsies

Bladder biopsy is important primarily to exclude confusable diseases and malignancy, and otherwise should not be routinely done. Certain pathology features may be characteristic for Hunner lesion disease and biopsy can possibly help to phenotype patients in the research setting. Biopsies from patients with Hunner lesion disease typically display marked inflammatory infiltrate with neutrophils, lymphocytes, macrophages, plasma cells and mast cells, with fibrosis and epithelial denudation (24,32) . Bladder biopsy procedures should be performed by using large forceps and include detrusor muscle; alternatively, double punch biopsies or resections of lesions can be used. Flexible cystoscopic biopsy may lead to inadequate sampling and assessment of mast cell count (283). To limit the possibility of perforation, biopsy should be carried out after distention and with the bladder largely decompressed.

16.2. Number of Biopsies

At least 3 biopsies from the two lateral walls and bladder dome should be taken in addition to biopsies from visually abnormal areas. The biopsies are to be immediately fixed in neutral buffered 4% formalin.

16.3. Biopsy Handling

Biopsies are treated conventionally. Six adjacent 3mm sections are cut and placed with 3 specimens on each of two specimen slides. The first slide is stained with H&E, the next with a connective tissue stain suitable for the individual institute. Twenty-four 10 mm sections are then cut, and every third section is mounted on a specimen slide for mast cell counting. The specimens are stained by Lederstain (naphtolesterase) according to routine procedures. Finally, a 3mm section is obtained to ensure the presence of detrusor muscle in the specimens.

16.4. Mast Cell Counting

The use of a measuring grid (e.g. Leitz periplan 6F10_N ocular containing a standardized grid) is necessary. Only mast cells containing nucleus are included. When counting the cells those covering or touching the bottom should be excluded whereas those covering the upper and left line are included. At least 3 biopsies must be the subject of mast cell counting and if possible, one including a lesional area. Biopsies for mast cell counting should contain detrusor muscle.

16.5. The pathology report

Epithelium:

- Not present
- Present
- Dysplasia with grading
- Abnormal but no dysplasia: description is mandatory.

Propria:

- Normal
- Inflammation: description with a grading
- Other findings are described

Detrusor muscle:

- Abnormal muscle cells: describe intrafascicular fibrosis
- Not present
- Present

Mast cell count:

At least three biopsies should be included in the counting. Only the biopsy with the highest number of mast cells per mm2 should be reported. The enzymatic (naphtolesterase) staining is, for the time being, recommended since standardized values are available:

- less than20mast cells/mm2:no detrusor mastocytosis;
- between 20 and 28 grey zone
- more than 28 mast cells/mm2: detrusor mastocytosis.

Larsen recommends examining the detrusor biopsies with tryptase-stained 3 micron thick sections, with every seventh section used for quantification; 27 mast cells/mm2 is considered indicative of mastocytosis (216). These guidelines have been reported to be easy to follow. A statistically significant correlation was found between the cystoscopic aspect and inflammatory infiltration, mast cell count in the detrusor muscle and stromal edema. Maximum bladder capacity was negatively correlated with inflammation, detrusor mast cell count, haemorrhages and the overall cystoscopic aspect (284). Correlations have also been demonstrated between urothelial damage and inflammatory infiltrates and between normal epithelium and detrusor mastocytosis suggesting either 2 different types of IC/BPS or different stages in the pathophysiological process of IC/BPS {Geurts 2011. However, data regarding mast cells is mixed with a recent study showing higher levels of mast cells in non-Hunner lesion patients (285). The question of whether an elevated mast cell count represents a distinct phenotype of BPS independent of the presence of Hunner lesions remains to be determined.

17. BIOMARKERS

The lack of universally accepted clinical diagnostic criteria for different IC/BPS phenotypes affects all aspects of making progress in understanding this disease. Insights into risk factors, pathogenesis, trials for effective therapy, prognosis, and outcome criteria for treatment are all affected by this lack of objective diagnostic criteria. A major factor affecting the controversy over accepted clinical diagnostic criteria is that the current criteria are predominantly symptom specific. An objective biomarker would advance the establishment of reproducible diagnostic criteria for IC/BPS and also aid in monitoring effects of treatment. A biomarker for any disease needs to demonstrate high sensitivity and high specificity. In addition, the marker assay needs to be reproducible in many laboratories and should be suitable for use in a clinical diagnostic laboratory. Several biomarkers (from urine, blood, stool and bladder tissue) have been studied in recent years,

and different phenotypes of IC/BPS may be distinguishable based on these markers.

Many of the published studies have been on biomarkers isolated from urine. Erickson et.al has published excellent reviews of urine markers for IC/BPS (286,287) . The most thoroughly investigated marker is antiproliferative factor (APF) (288,289) . A study of 64 patients with IC/BPS (38 with Hunner's lesions and 26 without), found that 92% of IC/BPS patients had APF activity compared to only 3% of controls (290). Treatment of symptomatic IC/BPS by either hydrodistention or neurostimulation normalized the APF levels concurrent with symptom relief (291). It is not known if other forms of treatment will affect APF levels. Preliminary studies in 58 women with documented IC/BPS demonstrated a sensitivity value of 91.4% and a specificity of 90.6% (292). A later study with 219 symptomatic IC/BPS patients and 325 controls with and without other urological disorders documented the sensitivity as 94% and the specificity at 95% (293). Keay et al. have suggested that APF might inhibit cell proliferation by the downregulation of genes that stimulate cell proliferation along with the upregulation of genes that inhibit cell growth (155). Cell growth inhibition of human urothelial cells appears to be mediated by p53 (294). APF treatment caused significant increases in the paracellular permeability of normal bladder epithelial cell monolayers and the attenuation of tight junctions compared to mock APF, similar to changes seen in IC cells. APF treatment also decreased expression of the tight junction proteins zonula occludens-1 and occludin (295).

APF seems an ideal candidate for a biomarker for symptomatic IC/BPS. There need to be additional studies to determine if it can serve as an IC/BPS marker for patients in remission or for those who have not yet become symptomatic. Furthermore, it is unclear whether AFP can distinguish Hunner lesion disease from non-Hunner lesion disease, and this requires further study. Currently, the findings on symptomatic patients have yet to be replicated by laboratories around the world, and the biologic assay has not proven suitable for commercial development as it currently exists. For whatever reason, this previously promising research tract seems to have reached a dead-end.

There have also been many published studies on heparin-binding epidermal growth factor-like growth factor (HB-EGF) (155,296-299) . HB-EGF is a growth factor found in normal urine. It has been shown that APF inhibits the production of HB-EGF. There have been no large population studies focusing solely on HB-EGF as a biomarker for IC/BPS.

The urinary markers, macrophage migration inhibitory factor (MIF) and the chemokine CXCL10, have been shown to be able to discriminate between Hunner lesion disease and non-Hunner lesion disease, but their ability to predict response to treatment has not been studied and validation of these markers are required before their use can be recommended (300,301) .

Recent results from the MAPP studies indicate some urinary metabolites capable of discriminating female IC/BPS patients from controls. Ethiocholan-3α-ol-17one sulfate (Etio-S) did so with a specificity and sensitivity >90%. Among IC/BPS patients Etio-S levels are correlated with elevated symptom scores and could resolve high- from low- symptom IC/BPS (302). However, patients were not subdivided into those with or without Hunner's lesions and response to treatment has not been assessed. Recent studies show that urine cytokine profiles may differentiate IC/BPS patients from a control group (303). In the future an objective measurement of progression and resolution of symptoms may come from evaluation of urinary biomarkers (304).

A recent study using next-generation sequencing of RNA from bladder biopsies of patients with IC/BPS has demonstrated distinct genetic features compared to controls, with overexpression of VEGF and BAFF correlating with more severe symptoms and a distinct phenotype of IC/BPS (305). In the future, genomic markers may prove clinically useful in diagnosis, phenotyping, prognosis and predicting response to treatment.

Level of Evidence:3 Grade of Recommendation: D

X. CONFUSABLE DISORDERS

1. NON-GYNECOLOGIC

Confusable disorders are those that can be easily misdiagnosed as IC/BPS. Associated disorders are disorders that can occur with some frequency in the IC/BPS population. One does not want to mistake IC/BPS for a confusable disorder, as the ensuing treatment will not be appropriate. However, it may be difficult to ascertain whether the symptoms bothering an IC/BPS patient are primarily due to the IC/BPS diagnosis or an associated disorder like endometriosis or irritable bowel syndrome. The distinction between confusable and associated disorder is an important one in clinical practice and when researching potential therapeutics. Once a clinician has confirmed a clinical diagnosis of IC/BPS, an accompanying disorder is no longer a confusable disorder.

The diagnosis of IC/BPS can made on the basis of exclusion of confusable diseases and confirmation by the recognition of the presence of the specific combination of symptoms and signs of IC/BPS. For the diagnosis, two methods (by recognition of the specific combination of features of the target disease or by exclusion of confusable diseases) might be used in a pool of confusable diseases because:

- Confusable diseases are often more common than IC/BPS, so recognition is mandatory because many can be treated.
- Failure to diagnose a confusable disease would automatically incorrectly yield a diagnosis of IC/BPS.
- Patients may have a confusable disease plus IC/BPS.

IC/BPS may occur together with confusable diseases such as chronic or remitting urinary infections or endometriosis. If the main urinary symptoms are not explained by a single diagnosis (confusable disease or IC/BPS), the presence of a second diagnosis is possible.

For therapeutic reasons it makes sense to identify patients who also have a confusable disease because symptoms and signs may be caused by BPS, the confusable disease, or by both. For prevalence studies of IC/BPS, on the other hand, all cases with IC/BPS should be included, also those with a confusable disease. This approach eliminates the need for separate diagnostic criteria for clinical practice and scientific studies. (**TABLE 5)** summarizes confusable diseases related to BPS and their mode of exclusion. (6).

Following this logic, Hunner lesion disease is a confusable disease that can be diagnosed with cystoscopy. It is not an associated disease but easily mistaken for IC/BPS in those who have not undergone endoscopic examination.

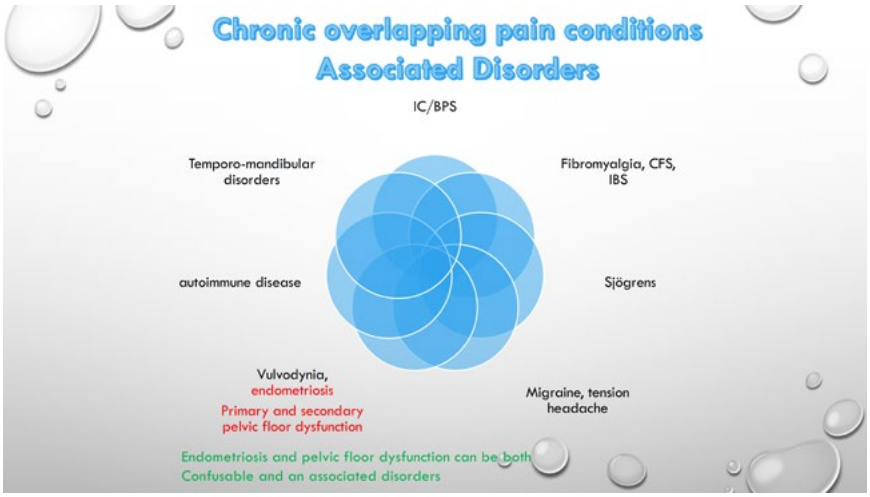

Figure 5. Associated and confusable disorders commonly diagnosed in patients with IC/BPS.

In female populations affected by IC/BPS gynecological diseases may be present in about 20% of patients. There is also an overlapping of musculoskeletal pathologies in 12% of cases (306).

The confusable disorders could be gynecological or non-gynecological; the distinction may be not clearly defined. The treatment should be according to each individual disease diagnosis.

Some of the most frequent non-gynecological disorders in IC/BPS population include:

1.1. Pudendal Neuropathy vs IC/BPS

Pudendal neuropathy is a common feature of syndromes such as dysfunctional voiding, non-obstructive urinary retention, chronic pelvic pain syndromes, and urinary and fecal incontinence. It should be ruled out as a confusable disease in IC/BPS patients. Pudendal neuralgia is a functional entrapment of the pudendal nerve, and pain occurs during compression or stretch maneuvers, such as repetitive microtrauma, orthopedic fracture, straining with constipation and childbirth, falls onto the buttocks, and suture entrapment during pelvic surgery. The main symptom is pain aggravated by sitting/driving/exercise, reduced

by recumbence or standing and relieved by sitting on a toilet. The quality of neuropathic pain varies and can be described as burning, stabbing, ache, or pressure, and can be induced by voiding, defecating, vaginal penetration, or orgasm. It can occur anywhere in the pudendal territory, but primarily includes the perineum and urethra, and extends to suprapubic, inguinal regions and to the upper medial thighs.

Urinary symptoms and rectal dysfunction might occur. Foreign body sensation in the rectum, vagina, urethra or perineum is frequent. Sexual dysfunction can be present. Females may suffer reduced clitoral sensation, pain at vaginal penetration, reduced lubrication and anorgasmia.

Pinprick sensation is tested bilaterally at the level of the clitoris posterior labia and posterior perianal skin. Hyperalgesia is more common than hypoalgesia. Pressure can be placed at the level of the Alcock canal attempting to reproduce pain, bladder or rectal symptoms (the Valleix phenomenon). The para-sacral area is also examined for a back mouse (epi-sacroiliac lipoma). Several tests can measure pudendal neuropathy including: biothesiometry, sacral latency test, sensory-evoked potentials, motor-evoked potentials and motor latency tests. Ultimately an MR neurogram and pudendal nerve block may be important in confirming the diagnosis and determining treatment options. (307,308)

Management

1.Pharmacotherapy

Tricyclic antidepressants were the first medication category

effective in placebo-controlled trials. Other drugs, such as gabapentin, pregabalin, oxcarbazepine, tramadol and duloxetine, significantly reduce

pain and improve sleep, mood, and quality of life.

2.Transgluteal Pudendal Nerve Blocks

Two injections are given at the ischial spine at 1-month intervals. A third is given into the Alcock canal using computed tomography guidance.

3.Surgical Therapy

Transperineal and Transgluteal Approach : Pudendal nerve decompression by the perineal route is a blind procedure carried out under local or regional anesthesia. To suppress the blind character of the procedure, a transgluteal approach has been proposed and the reported surgical success rates range from 60% to 70%. Pain-free status might take some years. Bladder, bowel and sexual dysfunctions show variable improvement (309).

More recently, a transvaginal approach has also been proposed (310).

Until now, the results on pain are the same as those obtained by the Shafik's approach (311), but with the concurrent sections of one or two ligaments of the pelvis (sacro-spinal and/or sacro-tuberous ligaments).

However, the long-term effects of these sections on the stability of the pelvic region are as yet unknown. Up to now, no data are available about a potential effect of the transgluteal or transvaginal procedures on urinary or anal incontinence.

1.2. Urinary tract infection vs IC/BPS

The symptoms of interstitial cystitis/painful bladder syndrome often mimic urinary tract infection, but cultures are negative (312). When interstitial cystitis/painful bladder syndrome is clinically suspected, patients should be asked about suprapubic pain; urinary frequency; urgency; nocturia; and pain of the pelvis, perineum, labia, vagina, or urethra. Physicians should also ask female patients about exacerbations related to the menstrual cycle and sexual intercourse (312-314) . It is best to treat any documented urinary infection and determine if IC/BPS symptoms persist in the presence of negative cultures, in which case the IC/BPS diagnosis is warranted and should be treated.

1.3. Overactive bladder V.S Interstitial cystitis/Bladder Pain Syndrome

There is a gray area where the distinction between OAB and

IC/BPS becomes a relevant and clinically important problem affecting a substantial number of patients (17). This can lead to delays in diagnosis and administration of appropriate treatments, due to the fact that patients can endorse symptoms predominantly suggestive of either OAB or IC/BPS yet have the other condition.

Further complicating matters is that no “gold standard test” exists to differentiate between OAB and IC/BPS. Cystoscopic findings following HD, urodynamic testing, and even clinical history often can coincide. We believe that increased emphasis on the history and physical exam can help to differentiate types of urgency and pain, leading to improved diagnostic rates (315).

Mechanism between OAB and IC/BPS

The bladder microbiome, bacterial infection, inflammation, and urothelial permeability contribute to the development of peripheral afferent hyperexcitability that is fundamental to the development of frequency and urgency in OAB, and pain in IC/PBS. In addition, the higher psychological stress levels, increased prevalence of anxiety and depression, as well as clinical co-morbidities with other visceral pain disorders suggests pathological plasticity within the CNS is an important component in the mechanisms underlying both OAB and IC/PBS (15). Despite our difficulties in differentiating one disease from the other, it is notable that treatment at times overlap, with behavioral therapies, SNS, BTX-A injections, and enterocystoplasty/urinary diversion available in certain instances to effectively treat either condition.

2. GYNECOLOGICAL ASSOCIATED/CONFUSABLE DISORDERS

In female population affected by IC/BPS the gynecological associated disorders may be present in about 20% of patients. There is also an overlapping of musculoskeletal pathologies in 12% of cases. (306) The following comprise the most frequent gynecological disorders in the IC/BPS population:

2.1. PELVIC FLOOR DYSFUNCTION (PFD)

Pelvic floor dysfunction affects the anterior, apical or posterior vaginal compartment. Pelvic floor dysfunction can be hypotonic (LPFD) or hypertonic (HPFD) **[Table 6].** Many patients with IC/BPS have concomitant HPFD, with muscle tenderness, spasms, and voiding dysfunction. (316)

Table 6: Classification of Pelvic Floor Dysfunction

HYPOTONIC DISORDER	HYPERTONIC DISORDERS
Stress Urinary Incontinence	Chronic Pelvic Pain
Pelvic Organ Prolapse	BPS/IC
Fecal Incontinence	Overactive Bladder
	Overactive Bowel
	Overactive Pelvic Floor
	Vulvodynia
	Sexual dysfunction

Several studies have reported that myofascial pain and HPFD are present in 50% to 87% of IC/BPS and/or chronic pelvic pain syndrome. (317) The mechanism is likely very similar to Category IIIB Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CCPS) in the male population. PFD exacerbates IC/BPS symptoms and has been reported to appear in response to events such as bladder inflammation, gait disturbance, and trauma. (318,319)

Patients with IC/BPS have pelvic floor hypertonicity on MRI, which manifests as shortened levator, increased posterior puborectalis angles, and decreased puborectal distances. This pelvic floor hypertonicity in patients with IC/BPS, may contribute to or amplify pelvic pain . (320)

Pelvic floor dysfunction exacerbates IC/BPS symptoms, and has been reported to appear in response to events such as bladder inflammation, gait disturbance, and trauma. (318)

Yong et al. reported a prevalence of 40% of pelvic floor muscle tenderness in a group of 189 women with chronic pelvic pain compared to 32 (13%) in healthy controls. (321)

Other pain disorders, such as irritable bowel syndrome, inflammatory bowel disease, fibromyalgia, and vulvodynia are all found to have a high prevalence in HPFD and myofascial pain and frequently associated with IC/BPS. (111)

2.1.1. PATHOPHYSIOLOGY

In a normal bladder, the peripheral nerve transmission is mediated by A∂-fibers that transfer tension, pain and cold and C-fibers that transfer burning, heat, pain and itching. C-fibers are normally silent, only becoming active in response to bladder inflammation or irritation. An inflammatory disorder of the pelvic viscera, a trauma or exceptional behavior might elicit noxious stimuli to the sacral cord that sets up a pelvic floor muscle dysfunction with sacral nerve hypersensitivity and a sacral cord “wind-up “whereby the viscero-muscular guarding reflex is activated and increases (winds-up) the tone of the pelvic floor during stress or routine daytime activity. (322)

The current model of IC/BPS pathophysiology suggests that central nervous system dysfunction results in aberrant responses to stimulation of pelvic visceral and somatic neurons manifest as chronic pelvic pain out of proportion to demonstrable pathology. As a result of limbic efferent stimulation, the pelvic musculature undergoes tonic contraction. (323)

Pain afferents from the pelvic floor and bladder transmit this noxious stimulus back to the sensitized limbic system, reinforcing efferent contraction of pelvic muscles and perpetuating chronic pain.

(324) Given cross-talk between the pelvic floor and bladder and bowel neurons in the spinal cord (189,193,325,326)

pelvic floor dysfunction may perpetuate voiding dysfunction, defecatory dysfunction, urinary urgency and frequency, and pelvic pain.

In IC/BPS patients, there is an afferent autonomic bombardment that can enhance and maintain a guarding reflex that manifests itself as a hypertonicity of the pelvic floor.

2.1.2. PHYSICAL EXAMINATION

A commonly overlooked finding in patients with CPP is levator muscle spasm and its associated myofascial pain. (327) Patients with HPFD are unable to produce more contractile strength and therefore cannot produce an effective squeeze. A single finger can be introduced in the vagina to assess pelvic floor awareness, and the ability to squeeze and relax the levator ani. Often patients with HPFD will have a "V" configuration of the introitus and, as a finger is advanced, it will drop off the shelf caused by the contracted levator muscles. Active "trigger points" are often identified by an exquisitely tender area palpable at the level of the pelvic side wall within a taut band that reproduces the patient's pain, as well as the referral pattern of her pain

2.1.3. DIAGNOSTIC STUDIES

Muscle activity can be measured using a perineometer or an electromyography probe. (328) Urodynamics include fluctuating or interrupted flow, abnormal voiding studies, elevated urethral pressure and urethral instability. Schmidt and Vapnek observed pain episodes in such patients coinciding with behavioral increase in the sphincter tone, more than in the bladder. (329) When symptoms involve obstructed defecation and rectal pain, defecography should be used to identify the presence of a non-relaxing pelvic floor or even parodoxic activity of the pelvic floor during defecation.

2.1.4. TREATMENT

The pelvic floor physiotherapy should be considered as a first-line treatment in the case of HPFD. The goal of these stretching exercises is to lengthen the contracted muscles by decreasing tension, releasing trigger points in the levator muscles, reeducating the muscles to a normal range of motion and improving patient awareness. (330) The therapy also includes: behavior modification, muscle relaxants, Thiele's massage, sacral and tibial neuromodulation, trigger point injections, and botulinum toxin.

2.2. ENDOMETRIOSIS

Endometriosis and IC/BPS are common causes of chronic pelvic pain (CPP) in women. (331-336)

Endometriosis is determined by the presence of endometrial glands or stroma outside of the endometrial cavity and affects 1–7% of the general population. (337). Retrograde menstruation is the generally accepted mechanism underlying the pathogenesis of endometriosis (338). This mechanism was originally proposed whereby endometrial fragments migrate from the fallopian tubes into the peritoneal cavity during menstruation. More recent data show the prevalence of retrograde menstruation is no different in women with or without endometriosis, suggesting a more complex etiology (339,340).

It is considered that immune dysfunction and the subsequent inability to effectively clear these fragments enables endometrial lesions to form in the peritoneal cavity (341).

Ectopic endometrial debris is cleared from the peritoneum by an innate immune response. Dysregulation in this innate immune reaction in response to ectopic endometrial tissue has been implicated in endometriosis pathophysiology. (342). Common sites of implantation include the ovaries, uterosacral ligaments, cul-de-sac, and the uterovesical peritoneum. (343,344)

As with the normal uterine endometrium, these extrauterine implants remain under the cyclic influence of ovarian hormones and are stimulated to grow and then break down with each menstrual cycle. Endometrial pain is usually a visceral pain and it is caused by inflammation that results from cyclic sloughing of these endometrial glands, by the release of neurokinins and prostaglandins F^2a and E^2. (345)

Endometriosis is considered as not only a chronic inflammatory disorder but also an estrogen dependent disease. (346,347) As a matter of fact E2 concentrations in endometriotic lesions are known to be elevated. (348) MCs may mediate the role of E2 in the pathogenesis of endometriosis that promotes the growth of endometriotic lesions and triggers pain by activating MCs, which subsequently release a variety of mediators. (349)

The painful symptoms (dysmenorrhea, cyclic pelvic pain or deep dyspareunia) are present in up to 70% of such women. (350) It is important to ask about the onset of symptoms like dyspareunia and urinary urgency/frequency and the extent and location of the pain. In IC/BPS, pain usually worsens as the bladder fills and improves after voiding.

During the physical examination, the physician may detect tender nodules and masses in the pelvic region, a tender retroverted uterus, or implants in uterosacral ligaments and to determine whether the tenderness elicited reproduces the pain that the patient typically experiences. (351) Given the similarities between endometriosis and IC/BPS nonspecific symptomatology, as well as pain in the absence of other symptoms it is critical that gynecologists consider IC/BPS as a diagnostic possibility when a patient initially presents with symptoms of CPP.

Laparoscopic-guided biopsy is considered the *"gold standard"* for diagnosis. (352). In women who undergo a laparoscopy to evaluate CPP, the prevalence of endometriosis is 30–90%. (353)

No known causal relationship exists between endometriosis and IC, in part because the origin of both conditions is poorly understood. It is speculated that both diseases are caused by autoimmune disorders, with an unknown factor acting as a trigger for one or both . (354)

Another possible explanation is that neuropathic upregulation leads to neurogenic inflammation and viscerovisceral hyperalgesia, in which chronic noxious stimuli at one site can contribute to referred pain and inflammation at other visceral organs. (316)

There is a high prevalence and association of IC and endometriosis. A study by Chung et al. of 178 women with CPP found that 65% of CPP patients suffered from both active endometriosis and IC, the so called "the Evil Twin Syndrome". (355) In a prospective study carried out of 162 patients with CPP, Paulson and Delgado found that 66% of the sample was diagnosed with both endometriosis and IC. (356) A recent systematic review estimated the prevalence of IC/BPS, and the coexistence of IC/BPS and endometriosis in women with CPP. Nine studies including 1016 patients with CPP showed the mean prevalence of IC/BPS was 61%, of endometri-

osis 70%, and coexisting IC/BPS and endometriosis 48% (range 84 16–78%, CI 44–51%). These data suggest the importance of considering the bladder as the source of pain even where endometriosis is confirmed, and in the case of unresolved endometriosis and persistent pelvic pain, patients must be evaluated to rule out the presence of IC/BPS. (357)

2.3. FEMALE SEXUAL DYSFUNCTION & VULVODYNIA

Female sexual dysfunction (FSD) is a prevalent condition affecting women's health and is present approximately in 40% of women. Common symptoms associated with FSD include diminished vaginal lubrication, pain and discomfort upon intercourse, decreased sense of arousal and difficulty in achieving orgasm.

FSD and IC/BPS are two conditions affecting women's health. Both FSD and IC/BPS significantly impairs a woman's abilities to pursue and enjoy sexual relations. In the group of women affected by FSD, 0.5–12% have the presence of IC/BPS. (358,87,359,84,75) . Up to 54 % of women with IC/BPS were found to often avoid sexual intercourse with their partners and IC/BPS was found correlated with sexual dysfunction. (360,361)

2.3.1. Sexual pain and IC/BPS

IC/BPS is not a disease confined to just the bladder and pelvic area; it is a complex disease that includes the outside of the genitourinary tract. A study investigating the pain characteristics of IC/BPS using whole-body diagram pain locators, found that women with IC/BPS reported significantly more pain all over their body, compared to healthy women without. Only 27% of the IC/BPS pats. presented pain restricted to the bladder and pelvic area. (362). In regards to the pain associated with FSD, vulvodynia may be contributing to flare-ups of IC/BPS symptoms and could be the reason why IC/BPS patients avoid sexual activity. (363)

As expected, women with provocative Vulvodynia (PVD) had more severe superficial and deep dyspareunia. The relationship between PVD and deep dyspareunia is mediated by the associations between bladder/pelvic foor (levator) tenderness and IC/BPS. (364,365)

It may be that contact with a tender bladder or tender levator ani during deep penetration leads to deep dyspareunia. A possible explanation may be cross-sensitization, convergence and subsequent cross-talk of afferent signals within the spinal cord. (191)

2.3.2. Vulvodynia

The International Society for the Study of Vulvovaginal Disease (ISSVD) has redefined the previous concept of *chronic vulvar pain, vulvar vestibulitis or vulvar dysesthesia syndrome* with the new term of Vulvodynia. The definition includes *" an unpleasant altered sensation in the vulva defined as vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable,with the neurologic disorder".* This "burning pain" is suggestive of a neuropathic pain response. Pain can be unprovoked, varying from constant to intermittent, or occurring only on provocation, such in sexual intercourse. Sometimes an area of redness might be visible, but more often the vagina and the vulva show no abnormalities on gynecological or dermatological evaluation.

Classification of Vulvodynia might include localized or generalized , or both, provoked or non-provoked and primary or secondary. (366) The prevalence of vulvodynia has been estimated to range between 4-25%. (367,368)

2.3.3. Pathophysiology

Because both the vestibule of the vulva and the bladder are derived from the urogenital sinus, it could be hypothesized that the coexistence of vulvodynia and IC/BPS in some patients represents a generalized disorder of urogenital sinus-derived epithelium. (369) The etiology of vulvodynia is presumed to involve many factors: infections, altered vaginal acid-base balance, and the upregulation of pro-inflammatory immune responses. (370) Various noxious stimuli could cause changes in the vulvar epithelium: contraction in the pelvic floor, and mast cell activation with subsequent degranulation and release of histamine. This causes chronic pain and inflammation through the stimulation of peripheral neurons of the autonomic nervous system, an upregulation of the pain system, and a possible shift from nociceptive to neuropathic pain. (371) An increased peripheral tactile, pressure, and pain sensitivity in the pats with vulvodynia has been reported histologically. (372,373) . Mast cell hyperactivation has been identified in patients with vulvodynia and degranulation is consider to stimulate peripheral pain transmitting neurons (C and A-δ fibers). (374,375) . Borenstein *et al.* compared vestibular tissue from women with vulvodynia for mast cell count and nerve spreading. They found a significant increase in the total mast cell count and degranulated mast cells in pats with vulvodynia compared to controls. The total nerve fiber area was found to be 10 times higher in the group of vulvodynia compared to the control group. (376)

Neurogenic inflammation plays a role in local pain and inflammation, but also at referred sites. Much of the pain experienced by IC/BPS and vulvodynia patients appears to be neuropathic. (377,378). This may explain why patients with IC/BPS may experience referred pain in the vulva and patients with vulvodynia may experience referred pain in the bladder and urethra. Local vasodilation, edema, hyperalgesia and allodynia are typical in a subset of IC/BPS and vulvodynia. Symptom flares in these patients may in fact be modulated by the estrogens before menses that induces the release of histamine from mast cells resulting in increased amounts of substance P. (379,380) A neuromodulatory role of estrogen on pain transmission at various sites has been clearly documented. (381). A further observation documents in a large community-based study that vulvodynia was strongly associated with childhood physical or sexual abuse. (382)

2.3.4. Peripheral sensitization of Vulvodynia and IC/BPS

The potential underlying mechanism of peripheral pain hypersensitivity noted in both vulvodynia and IC/BPS could be due to sensory nerve upregulation. Previous studies have shown that sensory nerve density is significantly increased in the vulva vestibule and bladder. Compared to the normal controls, patients with vulvodynia were found to have increased nociceptors in their vulvar vestibule (383-385) . Consequentially, this increased density of peripheral nociceptors results in increased sensitivity. It was also found that transient receptor potential V1 (TRPV1) exists in these nociceptive nerve endings and enhances pain signaling. (386,387) Similarly with vulvodynia, it has been highlighted that IC/BPS patient bladders have upregulated sensory innervation and TRPV1 expression. (388-390)

The mechanisms of the association between IC/BPS and vulvodynia are unclear, visceral nerve cross-talking and the anatomic relationship between genital organs and the bladder can be an explanation. Another possible mechanism behind the relationship is abnormal pain hypersensitivity induced by peripheral and central sensitization. The abnormal pain response frequently observed in vulvodynia patients is caused by central or peripheral maladaptive pain processing from local insult, injury, or trauma. Pain conditions

such as fibromyalgia, irritable bowel syndrome, interstitial cystitis, temporomandibular joint and muscle disorders, and chronic fatigue syndrome are common among women with vulvodynia. (117,391-393) . Women with vulvodynia, regardless of type, are likely to have at least two additional pain conditions as Fibromyalgia and IBS, indicating that more severe vulvar pain is significantly associated with multiple comorbidities. (394) In a recent paper a group of 212 women with vulvodynia and 230 without vulvodynia were analyzed. All women with vulvodynia, compared to those without, were substantially more likely to be bothered by night time voiding, and reported the experience of moderate to severe urgency after urination. The findings suggest that women with vulvodynia are substantially more likely to report voiding dysfunction and symptoms of urgency than women with no history of vulvar pain. (395)

The standard clinical test for vulvodynia is the cotton swab (Q-tip) test, measuring vulvar pain ratings on a visual analog scale. Q-tip palpation for tenderness of the vulvar vestibule

was performed on each patient at the 12, 2, 4, 6, 8, and 10 o' clock positions. (372)

2.3.5. THERAPY

Physical therapy plays an important role in the initial management of vulvodynia and IC/BPS.

Internal and external myofascial release and massage with soft tissue mobilization and pelvic floor stretching exercises and biofeedback comprise the initial approach. Strengthening exercises should be avoided because the pelvic floor of these patients must be re-educated for relaxation rather than contraction which in fact would worsen the condition.

The Goals of physical therapy treatment are:
- Normalize pelvic floor resting tone
- Normalize pelvic floor contractile abilities
- Restore sexual function
- Return to recreational exercise

A retrospective study on 24 patients with vulvodynia treated with physical therapy demonstrated in 71% an improvement greater than 50% (396). Myofascial techniques, Trigger-point therapies and Thiele massage for Pelvic Floor overactivity are well documented. (397). Manual therapy involves skilled hands-on techniques intended to increase range of motion, mobilize soft tissue and joints, induce relaxation, reduce pain, and improve function. This can include massage, stretching, trigger point therapy, myofascial release, and joint and scar tissue manipulation performed internally and/or externally. Thiele massage consists of digital pressure and subsequent elongation of the musculature to relax muscles, restoring normal pelvic tone and the ability to coordinate muscle behavior.

It should be noted that vulvar pain can be very distressing, and myofascial techniques should be applied in a manner that is well tolerated. The aim is to reduce overactivity and desensitize the CNS. (398). Adjunctive therapies may be employed including transcutaneous electrical nerve stimulation (TENS), electromyographic (EMG) biofeedback and dilators. Topical lidocaine may be a valuable adjunct to help override a vaginismus response.

A randomized clinical trial compared myofascial physical therapy to global therapeutic massage in IC/BPS patients (n=81). Participants were randomized to either group for ten 60-minute sessions over 12 weeks. A total of 59% of the physical therapy group reported moderate or marked improvement, compared to 26% in the massage group on the global response assessment (P=0.0012). (399)

Use of steroids is currently not recommended to treat vulvodynia. (400)

Lidocaine and Cognitive Behaviour Therapy significantly improved vestibular pain thresholds, quality of life scores, and sexual functioning at 12-month followup. (401)

Kim et al. reported an early experience with the use of topically applied combination of Meloxicam 0,3% (a selective COX-2 inhibitor) combination agent and topical lidocaine 5% with the aim of reducing nociceptive thresholds in patients diagnosed with vulvodynia.

Of the 8 participants, 6 had a subjective improvement in their symptoms with the use of the combination gel after a one-week trial. The most common side effects reported were burning and stinging. (402)

Seven patients who exhibited pain, taut bands and/or trigger points on the pelvic floor and intractable genital pain have been treated with Botox injection 20-40 U BTX A at vestibule, levator ani, or the perineal body. In all patients, pain disappeared VAS improved from 8.3 to 1.4 Mean follow-up 11.6 months, no side effects. (403). Nickel et al., in a non-placebo controlled trial, studied the improvement in sexual functioning in IC/BPS patients who received 300 mg pentosan polysulfate sodium for 32 weeks. They reported a significant improvement in sexual functioning scores at 8th to 32nd week of treatment. The improvement in sexual functioning at the end of the study was also found correlated with symptom resolution ($r = -35$, $p = 0.0002$). (404)

In another uncontrolled study conducted with 103 IC/BPS patients receiving intravesical hyaluronic acid , the short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-9) a significant improvements were noted after 1 to 6 months of dyspareunia and intensity of orgasms. (405)

Intravesical treatment for IC/BPS with lidocaine, heparin and sodium bicarbonate was also found efficacious in pain relief related to sexual intercourse in another uncontrolled study. Welk et al. reported the outcomes of 23 sexually active IC/BPS patients treated with an intravesical solution of lidocaine, heparin and sodium bicarbonate. FSFI pain domain scores before and after instillations were 1.9 ± 0.9 and 3.7 ± 1.6, respectively ($p<0.01$). And a resolution in dyspareunia was observed in 57% of the patients. (406)

Several studies have shown that gabapentin as tricyclic yields significant results reducing pain perception, with more than 80% of patients reporting improvement. More recently, botulinum toxin has been proposed for the treatment of vulvodynia. It was found that the visual analog scale score was reduced from 8.1 to 2.5 ($P < 0.001$), and eight (72.7%) out of 11 patients were satisfied. (407-409) There are treatment modalities with growing interest but limited evidence, including hypnotherapy and acupuncture. Small studies show positive but limited outcome improvements with acupuncture for PVD. (410,411)

There is early work looking at deep brain stimulation, spinal cord stimulators, transcranial magnetic stimulation, somatosensory psychotherapy, mind–body therapies (including yoga and tai chi) and Botulinum Toxin A, but with no long-term trials. Botulinum Toxin A has emerging evidence for use in refractory pelvic pain. (412,413)

XI. CLASSIFICATION AND PHENOTYPING

Accurate phenotyping of patients with IC/BPS is important in order to offer personalized therapy and optimize treatment outcomes. Potential phenotypes based on clinical, cystoscopic, radiological and urodynamic factors, have been suggested, but these require further study to determine their clinical utility in determining disease prognosis and/or treatment outcome (414).

1. HUNNER LESION DISEASE

The most well-described phenotype of IC/BPS is Hunner lesion disease, which has distinct clinical, cystoscopic and histopathological features, and for which specific lesion-directed therapies are available (see treatment section). The finding of a Hunner lesion was historically regarded as a diagnostic criterion for IC. Messing and Stamey introduced glomerulations as another typical finding for IC/BPS and this was included in the NIDDK criteria. Magnus Fall proposed, that patients with Hunner lesion (classic IC) and patients with glomerulations (non-ulcer type) represented two different subtypes (31) with different clinical pictures, different outcomes, and different responses to treatment (261) meaning that patients fulfilling the NIDDK criteria represent at least two different patient populations. Moreover, up to 60% of patients clinically believed to have IC/BPS by experienced clinicians do not fulfil the NIDDK criteria (51) and whether or not these patients are comparable to the patients fulfilling the NIDDK criteria is unknown. Finally, East Asian urologists have proposed that “interstitial cystitis” should be preserved as a disease name for patients with urinary symptoms and cystoscopic findings of Hunner lesion as outlined in the NIDDK criteria (20).

In an attempt to unite these different philosophies into a coherent schema, ESSIC proposed a classification of IC/BPS based on findings during cystoscopy with hydrodistension and morphological findings in bladder biopsies (6) (**Table 2**). The classification includes groups not having had cystoscopy with hydrodistension (groups 1,2,3) as well as groups not having had morphological investigation of bladder biopsies (groups A,B,C). By using this classification glomerulations after hydrodistension are today regarded more or less as a nonspecific finding, while IC/BPS patients with Hunner Lesion has been suggested to be a specific and distinct disease.

Table 2. ESSIC Classification of Bladder Pain Syndrome. *From van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: An ESSIC proposal. Eur Urol 2008, Jan;53(1):60-7.*

		cystoscopy with hydrodistension			
		not done	normal	glomerulations[1]	Hunner's lesion[2]
biopsy	not done	XX	1X	2X	3X
	normal	XA	1A	2A	3A
	inconclusive	XB	1B	2B	3B
	positive[3]	XC	1C	2C	3C

[1] cystoscopy: glomerulations grade II-III
[2] with or without glomerulations
[3] histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis

2. BPS WITH CO-EXISTING FUNCTIONAL SOMATIC SYNDROMES

A review of eleven studies has suggested that in a subgroup of patients, IC/BPS may be one manifestation of a more systemic functional somatic syndrome (FSS) (415). The prevalence of co-existing functional somatic syndromes (e.g. fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, temporomandibular disorder, migraine) is higher in non-Hunner lesion patients compared to those with Hunner lesions or asymptomatic controls, and the presence of multiple FSS are a risk factor for the development of IC/BPS (416,417) . IC/BPS with co-existing FSS is therefore likely to represent another distinct phenotype, but whether these patients will benefit from therapies that are useful in FSS remains to be studied.

3. INPUT

Recently, a novel clinical phenotyping system – INPUT (infection, neurologic/systemic, psychosocial, ulcers and tenderness of muscles)- has been suggested as a tool to enable targeted treatment for all domains simultaneously, where required (418). This system was studied in 239 patients and over 50% of patients reported positive neurological, psychosocial and tenderness domains highlighting the potential diversity of phenotypes of IC/BPS, and the need for multimodality treatment for these patients.

XII. INITIAL CONSERVATIVE TREATMENT AND BIO-PSYCHO-SOCIAL MODEL APPROACH

Complementary therapies for bladder pain syndrome have been shown to be beneficial, though larger, more rigorous placebo-controlled trials are sorely needed. A recent systematic review highlights dietary manipulation and physical therapy as useful modalities and suggests that acupuncture and relaxation therapies might also have a role, but the data for the latter two is somewhat lacking (419). Many patients seem to respond to a variety of complementary and alternative medical options, and they form a basic pillar of treatment and serve to empower patients (420,421) . A bio-psycho-social approach may improve outcomes of conservative management.

1. EDUCATION

Patient education is in the first line management of virtually all treatment algorithms. All guidelines recommend patient education regarding normal bladder function, the chronic nature of IC/BPS, and promoting realistic expectations for management. Patient education about normal bladder function, what is known about IC/BPS, currently available treatment options, and the likely need for trial of multiple therapeutic options and multimodal therapy is important.

Internet education and short message service texting were found to be effective in improving quality of life and disease self- management (422). Health interventions have utilized mobile technology in a variety of ways to increase health knowledge, promote health education, and change health behaviors (423,424) .

2. PATIENT ORGANIZATIONS AND INTERNET SITES

Table 7: Patient organization and internet sites

EDUCATION AND INFORMATION AVAILABLE ONLINE
GUIDELINES AVAILABLE ONLINE:
• **American Urological Association (AUA) Clinical Guidelines** Diagnosis and Treatment Interstitial Cystitis/Bladder Pain Syndrome (2014) https://www.auanet.org/guidelines/guidelines/interstitial-cystitis-(ic/bps)-guideline
• **Deutsche Gesellschaft für Urologie (DGU)** Diagnosis and Treatment of Interstitial Cystitis (IC/BPS) (English version) https://www.awmf.org/fileadmin/user_upload/Leitlinien/043_D_Ges_fuer_Urologie/043-050e_S2k_Diagnosis_Treatment_Interstitial_Cystitis_2019-03.pdf
• **Diagnostik und Therapie der Interstitiellen Cystitis (IC/BPS) (German version)** https://www.awmf.org/uploads/tx_szleitlinien/043-050l_S2k_Diagnostik_Therapie_Interstitielle_Cystitis_2018-10.pdf
• **Royal College of Obstetricians and Gynaecologists United Kingdom** Guideline on Management of Bladder Pain Syndrome. http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.14310/epdf.
• **EAU Guidelines on Chronic Pelvic Pain** https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Chronic-Pelvic-Pain-2021.pdf
• **East Asia** Clinical guidelines for interstitial cystitis/bladder pain syndrome https://onlinelibrary.wiley.com/doi/full/10.1111/iju.14234
PROFESSIONAL SOCIETY AND INFORMATION WEBSITES
• **Society of Interstitial Cystitis Japan (SICJ) (Japanese) http://sicj.**umin.**jp/**
• **International Society for the Study of Bladder Pain Syndrome (ESSIC)** https://www.essic.org/
• **MAPP Research Network** https://www.mappnetwork.org/
• **India: GIBS** https://gibsociety.com

EDUCATION AND INFORMATION AVAILABLE ONLINE
PATIENT SUPPORT AND INFORMATION GROUPS
• **International Painful Bladder Foundation (IPBF)** https://www.painful-bladder.org/
• **Interstitial Cystitis Association (ICA)** https://www.ichelp.org/
• **Pelvic Health Support Canada** https://www.pelvichealthsupport.ca/
• **New Zealand Painful Bladder Support Group NZICSG** https://www.nzpbsg.org
• **Bladder Health UK** https://bladderhealthuk.org/
• **Interstitial Cystitis Network (ICN)** https://www.ic-network.com/
• **ICA Deutschland (German)** https://www.ica-ev.de/
• **Taiwan Interstitial Cystitis Association (TICA) (Chinese)** http://www.ticataiwan.org/
• **Interstitiele Cystitis Patientenvereniging (ICP) (Dutch)** https://icpatienten.nl/
• **Association Française de la Cystite Interstitielle (French)** http://asso-afci.org/
• **Interstitial Cystitis India (ICI)** http://www.interstitialcystitisinindia.org/
• **The Israeli Association for Bladder Syndromes (Hebrew)** http://shalpuchit.co.il
• **Associazione Italiana Cistite Interstiziale (AICI) (Italian)** http://www.aicionlus.org/
• **Asociacion Catalana de Afectados de Cistitis Intersticial/Síndrome del Dolor (ACACI) (Spanish)** http://www.acaci.es/

3. BEHAVIORAL MODIFICATION

Behavior modification includes many aspects of modification of lifestyle and is important in the management of IC/BPS.

Behavioral therapy for IC/BPS can include education, timed voiding (scheduled voiding time and interval), and controlled fluid intake to avoid a very concentrated urine but not drink so much as to exacerbate urinary frequency. Participants in both arms of a large NIH funded randomized placebo-controlled trial evaluating amitriptyline in IC/BPS (425) received a standardized education and behavioral modification program (EBMP). Adherence to the EBMP at 6 weeks was assessed in 4 categories of (A) Symptom management ; (B) Fluid management; (C) Diet modification ; (D) bladder training. For each of these EBMP categories adherence was defined as the overall percentage of participants who reported adhering to each component of the EBMP at each telephone contact or clinic visit.

For the 241 subjects evaluable for EBMP adherence, the rate at 6 weeks was 75% for symptom management, 83% for fluid management, 82% for diet modification and 71% for bladder training. The overall Global Assessment Response rate was approximately 57% for adherers in any of the 4 EBMP categories, whereas it was lower for non-adherers. This rate neared statistical significance for diet modification, which demonstrated only a 41% response

rate among non-adherers (p = 0.051).

Recommendation
Behavioral therapy should be a cornerstone of treatment for patients with BPS.

Level of evidence: 2 Grade of recommendation: B.

4. PHYSICAL THERAPY

Pelvic floor physical therapy with myofascial trigger point release and Thiele massage can be successful in both men and women with chronic pelvic pain and can be self-administered after a period of training (426).

All the studies observed improvement in PFM contraction using various methods, but none were superior over the others. The studies revealed no adverse effects of the interventions used. Patient preferences should be taken into account in clinical decision-making. More studies of high methodological quality on this topic are needed (427).

The vast majority of patients with IC/BPS (non Hunner lesion) need management of their pelvic floor muscles as the primary therapy, complemented by bladder-directed therapies as needed as well as a multidisciplinary team to manage a variety of other regional/systemic symptoms (23).

Physical therapy methods are widely used among patients with chronic pelvic pain and are regarded as particularly helpful. Trigger point therapy shows some promising approaches. Physiotherapy should not be the only treatment in these patients, but rather a component of a multidisciplinary treatment regime with accompanying psychosocial therapy approaches. In accordance with the recommendations for multidisciplinary management of chronic pelvic pain , future studies should consider integration of physical and psychosocial therapy modalities in one treatment regime (3).

Biofeedback and soft tissue massage may stimulate the relaxation of the pelvic floor muscles Trans-vaginal Theile massage was also reported to be effective for 9 of 10 patients of the same group (428).

An NIH study (429) to determine the feasibility of conducting a randomized clinical trial was undertaken to compare 2 methods of manual therapy (myofascial physical therapy and global therapeutic massage) in patients with urological chronic pelvic pain syndromes. The global response assessment response rate was 57% in the myofascial physical therapy group compared to 21% in the global therapeutic massage treatment group. This statistically significant difference (P=0.03) was primarily driven by the response seen in women (24 women) compared to the men (24 men) enrolled in this small pilot study. A follow-up randomized trial comparing similar treatments but only in women with IC/BPS and demonstrable pelvic floor pathology showed a clear benefit of directed myofascial physical therapy. In the myofascial physical therapy group, 59% of IC/BPS women had a positive Global Response compared to 26% of IC/BPS women who were randomized to the global therapeutic massage group (p=0.0012) (430).

Recommendation
Physical therapy of selected and motivated patients with IC/BPS, particularly those with demonstrable pelvic floor dysfunction, is indicated.

Level of evidence: 1. Grade of recommendation: A

5. STRESS REDUCTION

It is long been observed that mental stress is one of the factors which aggravate the symptoms of IC/BPS. Rothrock et al (431) reported that when comparing patients with IC/BPS and healthy people, increased pain and urgency caused by stress were observed only in patients with IC/BPS.

Case-cohort studies have confirmed that patients diagnosed with IC/BPS experience considerably more stress than patients without the condition (432).

Stress was shown to correlate with both the severity of symptoms and quality of life. In another study of patients with IC/BPS identified in urology tertiary care clinic populations (433), mental health disorders were identified in 23 % of IC/BPS female cases compared to 3% of female control subjects. Medications for anxiety, depression or stress were taken by 37% of patients with IC/BPS compared to 13% of female controls.

Mindfulness based stress reduction has been shown to be effective in a small randomized controlled trial (434). World-wide patient support groups, including the Interstitial Cystitis Association (ICA) (435), the International Painful Bladder Foundation, and the Interstitial Cystitis Network, are important sources of information for patients with IC/BPS. Patients with IC/BPS frequently suffer depression, which may negatively impact upon the quality of life (432) and perhaps symptoms.

Recommendation
Stress and depression are related to poorer quality of life and increase in severity of symptoms.

Level of evidence: 1 Grade of recommendation: A
Reduction of stress and depression may contribute to an overall improvement in quality of life and perhaps even symptoms

Level of evidence: 4 Grade of recommendation: C

6. DIETARY MANIPULATION

The understanding of the mechanisms by which diet affects IC/BPS is limited; however, there are common bothersome foods and beverages (**Figure 16**), as well as individual variations that elicit flares (436,437) .

Acidic beverages, coffee, spicy food, and alcohol may aggravate the symptoms of most patients with IC/BPS (438,439) . However, this has proven difficult to prove and Nguan et al (440) reported that there was no statistically significant difference in pain and other symptoms, when they evaluated the influence of the changes in urinary pH on the symptoms of 26 patients with IC/BPS by instilling pH5.0 and pH7.5 saline solutions into the bladder. One of the best studies designed to determine the effect of particular foods, beverages and/or supplements (comestibles) on IC/BPS symptoms was undertaken by Shorter et al (441). One hundred and four patients with IC/BPS were asked to indicate on a validated questionnaire whether each of 175 individual items worsened, improved or had no effect on symptoms. Of the patients surveyed, 90% indicated that the consumption of certain foods or beverages caused symptom exacerbation. The comestible items that had the most effect were caffeinated, carbonated and alcoholic beverages, certain fruits, artificial sweeteners and spicy foods.

Foods/beverages identified as most bothersome to patients with IC/BPS	Foods/beverages identified as least bothersome to patients with IC/BPS
Coffee (caffeinated)	Water
Coffee (decaffeinated)	Milk, low-fat
Tea (caffeinated)	Milk, whole
Cola carbonated beverage	
Non-cola carbonated beverage	Bananas
Diet carbonated beverage	Blueberries
Caffeine-free carbonated beverage	Honeydew melon
Beer	Pears
Red Wine	Raisins
White Wine	Watermelon
Champagne	
	Broccoli
Grapefruit	Brussels Sprouts
Lemon	Cabbage
Orange	Carrots
Pineapple	Cauliflower
Cranberry juice	Celery
Grapefruit juice	Cucumber
Orange juice	Mushrooms
Pineapple juice	Peas
	Radishes
Tomato	Squash
Tomato products	Zucchini
Hot peppers	White potatoes
Spicy foods	Sweet potatoes/yams
Chili	
Horseradish	Chicken
Vinegar	Eggs
Monosodium glutamate	Turkey
	Beef
NutraSweet	Pork
Sweet'N Low	Lamb
Equal (sweetner)	Shrimp
Saccharin	Tuna fish
	Salmon
Mexican food	
Thai food	Oat
Indian food	Rice
	Pretzels
	Popcorn

Figure 16. Experience with specific foods and beverages reported by patients with IC/BPS. Gordon B, Shorter B, Sarcona A, Moldwin RM. Nutritional considerations for patients with interstitial cystitis/bladder pain syndrome. J Acad Nutr Diet 2015, Sep;115(9):1372-9.

Dietary manipulation was ranked in the top five frequently used treatments in a cohort study of the Interstitial Cystitis Data Base (ICDB) (442). As the influence of diet is variable with regard to food, beverage, and patient, there is no reason for patients to be uniformly on a strict diet. It is advised that each patient experiment to find out the foods that tend to aggravate their symptoms and avoid them. The ICA home page, (http://www.ichelp.org/) introduces the foods often avoided by patients with IC/BPS. The use of an elimination diet (eliminate all foods on the list) and then gradually reintroducing them one by one, will facilitate the development of a patient directed individualized diet strategy. In some cases when diet appears to play a major role in symptoms, a registered dietician nutritionist can become a critical part of the treatment team. Gordon et. al. comprehensive review of dietary issues is worth reading and provides a helpful handout for patients (436).

Recommendation
Personalized dietary manipulation should be part of the therapeutic strategy for patients with IC/BPS.

Level of evidence: 2 Grade of recommendation: B

7. BIO-PSYCHO-SOCIAL MODEL

The psychological impact of IC/BPS can be pervasive and severe (443,444) . The demographic findings suggest that the early stages of illness are a particularly vulnerable period (445,446) . Early access to psychological intervention may interrupt the development of these conditions. Untreated psychosocial factors worsen symptom presentation and prognosis.

The review by Grundy et al. highlights that higher psychological stress levels, increased prevalence of anxiety and depression, and clinical co-morbidities with other visceral pain disorders suggest that pathological plasticity within the CNS is an important component in the mechanisms underlying IC/BPS (15).

It is widely accepted that psychosocial factors play a substantial role in IC/BPS (447,448) . IC/BPS may be understood as a biopsychosocial disorder, whereby biological (physiological), psychological, and social factors interact to produce the symptoms experienced in IC/BPS (449-451) .

A recent systematic review indicated that psychosocial comorbidity is significantly elevated in those with IC/BPS (3). Individuals with increased symptom severity, psychosocial impact, and worse QoL are directed to receive additional psychological support such as cognitive behavioral therapy or counseling (452-454) .

There has been a shortage of psychosocial intervention studies. These have included a mindfulness-based stress reduction course (434), an online video-education system (424) , and a 90-min interview aimed at facilitating the link between stress, emotional conflict, and symptoms, and encouraging emotional expression (455). Kanter et al. identified three emergent patient experience concepts; debilitating effects; unpredictable and unrelenting disease course; significant isolation. Patients voiced strong preference for physicians who provided 1) education regarding the condition; 2) an array of treatment options; 3) organized treatment plans; 4) optimism and hope regarding treatment outcomes (456).

The role of healthcare practitioners is fundamental to informing patient perceptions of their illness and providing adequate support for their own self -management approaches (457). The ultimate goal of caring the patients is improving patients' quality of life. The goal is enhanced by a variety of approaches. These include focusing on the biological organ, proper phenotyping, focusing on comorbid conditions, and focusing on accompanying psychological problems. Education plays a major role as does group support and introduction of an electronic health system approach which facilitates self-management. The Taiwan Interstitial Cystitis Association and E-health system provides such an approach.

The MAPP Network study is the first to directly assess a large cohort of male and female patients with urologic chronic pelvic pain syndromes (UCPPS) using a broad range of psychosocial variables (458). Participants with UCPPS reported more psychosocial difficulties, including higher levels of current and lifetime stress, poorer coping and more self- reported cognitive deficits, than healthy control individuals matched for age and sex who did not have pain (229). However, the level of psychosocial problems was not solely attributed to the severity of UCPPS symptoms, suggesting that a reduction in the symptoms associated with UCPPS alone would be insufficient to produce clinically significant improvements in quality of life for some patients. It's not surprising that the presence of nonurological chronic overlapping pain conditions (fibromyalgia, IBS and/or CFS) in the UCPPS cohort was associated with higher rates of depression and anxiety, as well as greater UCPPS symptom severity (459). Several psychological variables —such as catastrophizing, a lowered sense of mental and, particularly, physical well- being, and the presence of life stressors — were associated with a low probability of symptom improvement over a 12-month period (460).

Many clinicians (and patients) assume that once symptoms improve, quality of life will similarly improve. MAPP Network findings have demonstrated that this assumption might not be the case if the patient has substantial coexisting psychosocial comorbidities or severe non-urological pain (459,460) . Furthermore, psychosocial dysfunction (that is, depression, anxiety or catastrophizing) was more commonly identified and was associated with more severe UCPPS symptoms and poorer outcomes in patients with comorbid nonurological symptoms than in those without such comorbidities. Thus, greater emphasis should be placed on the early identification and treatment of nonurological symptoms and psychosocial dysfunction as separate and exacerbating clinical factors in UCPPS.

The extent to which psychosocial factors play a role in IC/BPS is controversial and by no means universally accepted. Depression, anxiety, catastrophizing may be primarily consequences of the symptomatology rather that related to causation, and it may be more productive in the long run to see them in this perspective. Otherwise it can appear that the patient is responsible for their symptoms and response (or lack thereof) to therapy.

XIII. ORAL THERAPY

Oral medications have been a mainstay of the treatment of IC/BPS and a variety of drugs have been used for this purpose. Unfortunately, the evidence for the use of many of these drugs is rather poor. There is a lack of randomized placebo-controlled trials and most of the studies are heterogenous and not comparable. Management of pain remains a crucial focus and the recognition, translation and classification of pain symptoms is of high importance to enable proper selection among the plethora of analgesics.

1. PAIN MANAGEMENT AND ANALGESICS

1.1. Evaluation of pain

Management of patients with IC/BPS symptoms needs a multidisciplinary approach and any physician dealing with this difficult disease has to be familiar with the idea that collaboration with other specialties is highly advantageous. Additionally, patients with IC/BPS generally seek urologic care not only for the lower urinary tract symptoms, but also for the associated pain. In any case, they deserve pain relief. Pain severity can be assessed through the following steps:

- evaluation of pain severity
- medical history, also focused on pain characteristics
- physical/ neurological examination
- investigation of pain origin
- regular monitoring

An easy and widely used pain evaluating tool is **PQRST**:

P: Palliative or Provocative factors

Ask patients if there is something that makes pain less or more intense

Q: Quality
Ask patients what the pain looks like

R: Radiation
Ask patients if pain spreads in anywhere else

S: Severity
Ask patients to evaluate pain severity

T: Temporal
Ask patients is pain is permanent or it comes and goes

1.2. Pain measurement

The description of pain among patients is a difficult issue, as it is a subjective feeling and even measurement scales are heterogeneous and usually not comparable. The use of more than one of clinical scales in each for pain evaluation could be useful, but actually tailoring pain measurement seems to be more realistic. Some of the most commonly used pain evaluation tools include:

- verbal rating scales: patients categorize pain as mild, moderate or severe
- Visual analogue (VAS), Likert or Numerical Rating scale (NRS)
- Brief Pain Inventory (BPI), McGill Pain Questionnaire (461-463)

Urologists are usually not familiar with BPI and McGill's questionnaire, which are rather complicated, using several types of visual analogue scales grouped together and finally assessing pain. In these cases, a multidisciplinary approach may be useful.

1.3. Pharmacologic Management

Urologists using pharmacologic agents to control pain among patients with IC/BPS need to become familiar with a wide variety of analgesics. Some analgesics may not be commonly prescribed by urologists, and some require close monitoring. Adequate knowledge of pharmacokinetics as well as the assessment of beneficial versus harmful effects are necessary for management of pain in patients with IC/BPS.

The use of analgesics for the treatment of IC/BPS includes a great variety of drugs which can be used for varying durations, with several dosage schemes and different mechanisms of action. Some of them target local inflammation and others target the central nervous system. It is also critical to examine the limited role of opioids in a chronic disorder like IC/BPS in order to achieve therapeutic control and avoid toxic and addictive effects.

1.3.1. Acetaminophen

This is very little evidence for a possible use in chronic pain syndromes, like IC/BPS. It can be administered in patients with mild pain and with caution for hepatotoxicity (464-466) .

1.3.2. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs are often given to patients with symptoms of IC/BPS. This is largely a symptomatic treatment and has the disadvantage of serious systemic adverse events after prolonged usage (467). NSAIDs are known to act on the cyclooxygenase (COX) enzyme, either as COX1 inhibitors or more selective COX2 ones. Blocking COX1 enzyme may be followed by the platelet, gastric and renal complications, while blocking the COX2 may lead to congestive cardiac failure, especially in patients with increased risk of cardiovascular disease. Both COX inhibitors seem to have equal effectiveness on pain, with the COX2 ones more useful in the acute phase. Evidence supporting the beneficial action of NSAIDs in IC/BPS is rather low, with superiority versus placebo and acetaminophen (468-470) .

Lower potency drugs, like ibuprofen, should be used as a first step and mainly in cases with mild pain. More potent agents, like diclofenac, can be a second step or for patients with more severe pain. COX2 selective NSAIDs should be regarded as of high potency and reserved for special cases, especially when the administration of non-selective drugs carries a high risk of serious adverse events.

Regardless which NSAID is selected, the possible benefit versus the respective harm must be evaluated before initiating treatment, keeping in mind the specific medical history of each patient.

1.3.3. Neuropathic analgesics

Gabapentin is a representative of the analgesic category of anticonvulsants with a mainly central action and a known effectiveness on neuropathic pain including diabetic neuropathy (471) and postherpetic neuralgia (472). There have been some small trials with patients with IC/BPS symptoms. As part of a combination treatment with amitriptyline and the NSAID etodolac, gabapentin has been suggested to be effective for patients with IC/BPS, but its individual efficacy wan not evaluated (473). Another study suggests a synergic action of gabapentin with morphine (474). In an animal model of IC/BPS gabapentin was able to reduce bladder hypersensitivity (475).

Pregabalin is another anticonvulsant representative with a similar action to gabapentin in neuropathic pain. It has also shown an ability to reduce bladder hypersensitity in IC animal models (476). Its effectiveness for treating pain associated with fibromyalgia has aroused a great interest, as it could be also effective in those patients with pain due to IC/BPS and concomitant fibromyalgia (477). Ketamine is an N-methyl-D-aspartate (NMDA) antagonist, acting also in opioid receptors. The effectiveness of ketamine in neuropathic pain has already been proven, including patients with chronic pelvic pain. Nevertheless, it is a potentially addictive agent with numerous possible serious adverse events including the possibility of inducing severe bladder inflammation that can mimic the most severe cases of interstitial cystitis (478-480) .

1.3.4. Opioids

Opioids can be a quite effective analgesic choice but are usually one of the last choices for pain treatment, not only for patients with IC/BPS, but also in any kind of chronic non-malignant pain syndrome (481). Patients may be guided to the opioids when other therapies and options seem to be inadequate. The potential for addiction in the long-term administration of opioids for nonmalignant pain is high, although the actual risk is controversial (482,483) . The marketing of oxycodone hydrochloride by Purdue Pharma left a legacy of misinformation among physicians and the public (484). With regard to narcotic use, the role of multidisciplinary medicine is important, as urologists need to collaborate with other specialties for a tailored therapy and a more effective monitoring. The most common side effects of the use of opioids are sedation, nausea, mild confusion, pruritis and constipation, while respiratory depression is rare. The long-acting formulations of opioids, as well as their co-administration with NSAIDS, cyclooxygenase inhibitors, acetaminophen, and tricyclic antidepressants, seems to be more effective (485). Since 2004, the European Association of Urologists has included opioids in the treatment of pelvic pains syndromes and IC/BPS specifically (58). The guidelines in this case are quite tailored and confirm that the use of opioids must be with a high level of consciousness regarding risks. Certainly, opioids should not be a first-line therapy for IC/BPS. Additionally, the multidisciplinary approach and dose titration are recommended, while the psychiatric profile of each patient must be evaluated. Patients must, also, be fully informed about the serious and non-serious adverse events of this therapy and need to sign an informed consent and treatment

contract before the initiation of this therapeutic scheme, knowing that there is not much evidence, supporting that one opiate is better than another. Only one provider should be authorized to treat any patient with opioids.

Morphine is a first-line opioid in the treatment of non-malignant neuropathic pain, including IC/BPS, used when other analgesic alternatives and direct disease treatment has failed. Starting with the lowest effective dose is important. An alternative use of fentanyl patches could be beneficial, especially for those patients who cannot receive an oral treatment, but dose titration is more difficult (486,487) .

Methadone is another opioid with a strong analgesic action, but its usefulness in IC/BPS could not be supported adequately (488). Similarly, meperidine has been found to be equal to morphine when administered intramuscularly, but with a poor recommendation in its oral formulation (489).

Some opioids are available in a slow or modified release preparations. Oxycodone, hydromorphone, and hydrocodone are representatives of this class of opioids, and they are useful in cases where tolerance remains a problem. Although they seem to be more safely administered, they need to be so closely monitored as morphine (490).

Codeine and tramadol are quite useful for mild and moderate pain, as they are regarded as opioids of less potency. However, the additional serotoninergic and adrenergic activity of tramadol, along with less addiction and fewer side effects compared to morphine, should be considered when looking for an effective alternative in patients with refractory pain. Optimal dose is not reliably established (491).

The committee believes that chronic opioids are best considered mainly in patients who do not respond to nonopioid analgesics and have not responded to standard therapies as outlined in the treatment algorithm at the end of this chapter. When their use is being considered, it is best to engage a pain management expert and move this portion of care to a pain clinic that will be responsible for all prescribed analgesics and can institute a pain contract with the patient so that one provider will have knowledge of all prescribed opioid and nonopioid analgesics. All patients and their families should be educated on the use of rescue medication in the event of accidental overdose and have such medications available (492,493) .

General recommendation for pain management

Patients with IC/BPS usually complain about their pain symptoms in addition to their voiding dysfunction, and thus, need to be treated for pain not only by urologists but in a multidisciplinary way. Evidence suggests a surfeit of analgesic agents as suitable for IC/BPS pain therapy, with a variety of potency and grades of recommendation. It has to be obvious that treating pain in IC/BPS patients may be complex and needs a detailed consultation. Also, initiating pain treatment with simple analgesics and low doses of the drugs could be more beneficial, while close monitoring is the gold standard to avoid serious adverse events in patients with long term analgesic treatment, especially with opioids. Figure 17 presents an algorithm for analgesic use.

Level of Evidence: 4 Grade of Recommendation: C

2. ANTIDEPRESSANTS

2.1. Amitriptyline

Amitriptyline is a tricyclic antidepressant which that blocks H1-histaminergic receptors, while stabilizing mast cells and inhibiting mediator stimulated vascular leakage. Its ability to reduce pain in

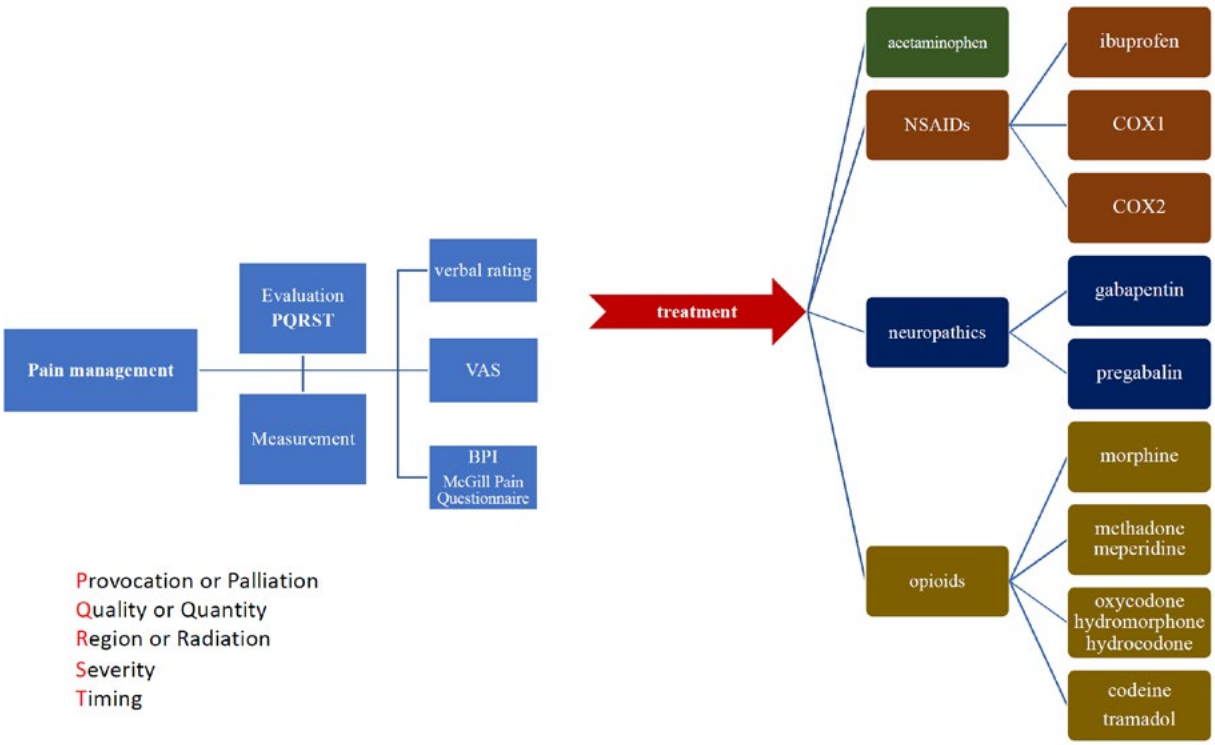

Figure 17. Analgesic options for treatment of IC/BPS and HLD

IC/BPS patients is based on the inhibition of the pain signal from the bladder to the respective level of the central nervous system. Amitriptyline may also have a beta-adrenergic stimulative action, enhancing bladder urine storage (494).
In the study of Hanno and Wein, the 75mg dose of amitriptyline proved to be quite effective in the most patients who could tolerate the drug. Almost one-third of the patients could not tolerate the drug at the 75mg dose because of sedation. Eighteen of 28 patients who could tolerate the drug had major relief of symptoms within 3 to 6 weeks of onset of therapy with a mean follow-up of 14.4 months (495).
In a prospective, double-blind, placebo-controlled study of amitriptyline, fifty patients were randomized to placebo or a titrated dose of amitriptyline up to 100mg daily. After a follow-up of 4 months, there had been a 30% improvement in symptoms of the amitriptyline group in comparison to 13% in the control group (496). Studies with longer monitoring have, also, shown an improvement in symptom scores in up to 64% of patients who could tolerate the side effects of the treatment (497).
In a large multicenter, randomized, double-blind, placebo controlled clinical trial of amitriptyline in IC/BPS treatment naïve patients, the benefit of amitriptyline plus behavioural modification was compared to that of behavioral treatment alone. Hence, both placebo and amitriptyline patients had been advised on an education and behavioral modification program. A dose of at least 50mg of amitriptyline was significantly more effective in this select group of patients compared to placebo. However, there was no significant difference when comparing the effectiveness of amitriptyline plus behavioral treatment with education and behavioral modification program alone looking at an intent to treat population (498) largely due to the sedation side effect of amitriptyline and the significant improvement with behavioural modification in the treatment naïve population. Despite the lack of comparable randomized control trials and meta-analyses, amitriptyline remains the drug whose exclusive efficacy for IC/BPS has been proven better than any other oral therapy.

Level of Evidence: 2 Grade of Recommendation: B

2.2. Other antidepressants

There are several studies investigating the efficacy of drugs like doxepin, desipramine and duloxetine in IC/BPS symptoms. Their overall therapeutic benefits are rather poor (499-501) .

2.3. ANTIHISTAMINES

The well-evidenced role of mast cells in the pathophysiology of IC/BPS could provide a possible targeted oral treatment with antihistamines. Actually, the sixty-year-old studies of Simmons using pyribenzamine showed some clinical improvement in IC/BPS patients, although in a short follow-up (502,503) .
Further uncontrolled studies on antihistamines included hydroxyzine, a H-1 receptor antagonist, which could be regarded as the most used antihistamine for IC/BPS patients. Some research has suggested hydroxyzine as an effective treatment, but the NIDDK randomized controlled trial demonstrated no significant statistical benefit when compared to placebo (504-506) .
The H-2 histamine receptor antagonist, cimetidine, has also been investigated as a possible oral treatment for IC/BPS. A wide variety of results and effectiveness has been described from a total relief of pain and symptoms in some studies to a significant reduction in some others. The rate of symptom remission varies as well. A prospective, placebo controlled RCT with 36 patients who received oral cimetidine or placebo showed clinical efficacy, but the statistical analysis inside and between groups was rather unclear (507). Despite being widely available and relatively inexpensive, it is not commonly used in this condition.

Level of Evidence: 3 Grade of Recommendation: C

3. IMMUNOSUPPRESSANTS

3.1. Cyclosporine

Cyclosporine is an immunosuppressant most used for patients with transplanted organs. The application of this drug for patients with IC/BPS was initially investigated in a Finnish clinical trial, in which the bladder capacity improved and pain reduced in most of the enrolled patients. The preferred dosage of cyclosporine in this study was 2.5-5 mg/kg daily for 3-6 months with a maintenance dose of 1.5 to 3mg/kg daily. Symptoms reoccurred when the drug was stopped (508).
The results of this clinical trial have been supported by a more recent one with a longer follow-up up to 60.8 months. The authors reported that the vast majority of IC/BPS patients treated with cyclosporine had a total relief of pain, while those who stopped therapy had a remission of the symptoms. Those who resumed treatment showed again a significant respond. Apart from pain, bladder capacity doubled throughout the monitoring (509).
In a more recent American study, cyclosporine was shown to be effective primarily in patients with Hunner lesion disease with a 75% response rate (510).
Compared to sodium pentosan polysulfate, cyclosporine has been shown superior in all clinical parameters after a follow-up of 6 months, while, in a basic research study, patients treated with cyclosporine had lower urinary levels of epidermal growth factor (511,512) . Separating those patients with IC/BPS with a Hunner-lesion from those without, cyclosporine seemed to be primarily effective in those with HLD (513).
The effectiveness of cyclosporine in HLD patients is undeniable, but this immunosuppressant needs to be closely monitored because of its common adverse events on renal function and blood pressure as well as a rare risk of malignancy. Drug level and toxicity monitoring with special attention to renal function and blood pressure should be done at least every 3 months, and more often on initiation of therapy. Drug level monitoring may allow dose reduction to minimize risk of side effects.

Level of Evidence: 2 Grade of Recommendation: C

3.2. Other immunosuppressants

Investigation on the effect of immunosuppression on IC/BPS has suggested other drugs apart from cyclosporine, without evidence of efficacy.
Suplatast Tosilate (IPD-1151T), an immune regulator interfering with the cytokine cascade affecting the production of IL-4 and 5, has been studied related to its its anti-allergic activity with regard to asthma, atopic dermatitis and rhinitis. Despite encouraging results in the study of Ueda et al (514), subsequent trials in USA and Japan, did not show the expected benefits and further clinical trials have not been planned (515).

Level of evidence 1: Not recommended

Corticosteroids, like prednisone, have been used mainly in refractory IC/BPS patients with mixed responses, either positive or discouraging. Actually, side effects following the long-term use of this treatment remain a significant handicap (516-519). Azathioprine and chloroquine derivatives have been, also, described in an old study with a moderate response among patients with refractory IC/BPS (520).

Level of Evidence: 4 Not recommended

3.3. Adalimumab

The role of cytokine in the development of IC/BPS has already been discussed and remains a challenge for novel treatment methods. Adalimumab is a Tumor Necrosis Factor-α (TNF-α) (a pro-inflammatory cytokine) inhibitor. It is used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa, uveitis, and juvenile idiopathic arthritis. Efficacy for IC/BPS proved to be no better than placebo in a study where this drug had been administered subcutaneously for 12 weeks. The significant changes in symptom scores were finally attributed to the placebo effect (521).

Level of Evidence: 1. Not recommended

4. SODIUM PENTOSAN POLYSULFATE

The role of the glycosaminoglycan (GAG) layer in the control of permeability of the urothelium is known to be important and has already been discussed in the section of IC/BPS etiology. The protection or the enhancement of the integrity of the GAG layer is theoretically important in order keep the urothelium impermeable to urinarycomponents. This is the main target of sodium pentosan polysulfate (PPS), a synthetic sulfated polysaccharide available in oral formulation which is excreted into the urine and may replenish the damaged GAG layer. PPS is the most investigated treatment for IC/BPS and the only oral drug approved by the American Food and Drug Administration (FDA) for the pain of IC/BPS.

In addition to the activity on the damaged GAG layer, PPS had an antihistaminic action through its feedback with mast cells and a possible anti-inflammatory mechanism of action through binding of molecules that can act as inflammatory stimulants in the urine (522,523) .

In the study of Parsons, 200mg or 300mg of PPS were daily given to patients with IC/BPS in equally separated doses 4 times or twice respectively. After 8 weeks of monitoring, over 90% of patients experienced a remarkable relief (524). In another randomized, placebo-controlled trial using a dose of100mg three times daily PPS was found to be effective in pain and urgency compared to placebo (525).

Further investigation on PPS includes RCTs with rather ambiguous and conflicting results. In an early, large multicenter, placebo controlled RCT 200mg of PPS twice daily for 4 months had no efficacy compared to placebo (526).

In the first pivotal study for FDA approval, 100mg of PPS three times per day for three months showed a slight improvement in the global response assessment in 28% versus 13% in the placebo group (527). FDA requested a second clinical trial. In this second RCT with the same dosage scheme and duration, controlled again by placebo, patient self-evaluation showed a global improvement of 32% of those on PPS, reporting 50% or more overall improvement. In the placebo group the respective rate was only 16%. The drug was approved by FDA for the pain of interstitial cystitis, as the parameters of frequency, nocturia and voided volume had not been significantly affected (528).

A National Institutes of Health study included comparison of six months of treatment with PPS with and without hydroxyzine versus placebo. No significant difference among groups was found (506). When PPS-only groups were explored and compared to placebo, results were similar to those with the above studies for FDA (529) . FDA mandated two phase four trials given questions about the drug's efficacy. The first was a 32 week dose-response trial with cohorts receiving 300mg daily, 600mg daily, and 900mg daily. While side effects increased with dose, efficacy did not (530). The second trial had cohorts receiving 300mg vs. 100mg vs placebo for 24 weeks. The study was halted because interim results did not demonstrate a treatement-effect vs placebo at any dose (529).

Until recently it was thought that despite questionable efficacy, PPS was a safe and well-tolerated medication (531). Long-term benefit was seen in 6-17% of patients (532). However recent reports have noted that pigmentary maculopathy, a vision threatening condition, can result from long-term exposure to the drug (533-537). FDA has placed a black box warning on the label. Patients on this drug need regular ophthalmology follow up.

Level of Evidence: 1 Grade of Recommendation: D

5. OTHER ORAL MEDICATIONS

5.1. Quercetin

Quercetin is an over-the-counter bioflavenoid with anti-inflammatory effects and has been investigated as a possible therapy for patients with IC/BPS. The administration of 500mg twice daily for two weeks had favorable affect in the symptoms of almost all patients, but there has been no further evidence to support those results (538).

Level of Evidence: 4 Grade of Recommendation: D

5.2. Antibiotics

While one empiric trial of an antibiotic can be justified in patients presenting initially with IC/BPS symptoms (539), there is no evidence that even intensive antibiotic therapy should play a role in the treatment of this disease. Infection, if discovered, should be regarded as a confusable disease and treated appropriately. In the absence of culture documented infection, antibiotics have no place in therapy (540). This issue is different from the consideration of infection as a possible initiating event in the etiology of the development of persistent symptoms.

Level of Evidence: 2 Grade of Recommendation: not recommended

5.3. Sildenafil

An interesting way of coping with IC/BPS symptoms could be the relaxation of bladder detrusor. The role of the phosphodiesterase type 5 inhibitors (PDE5Is) has been explored. In a small placebo controlled RCT, 25mg sildenafil daily was compared to placebo for 3 months in women with IC/BPS. Patients were closely monitored and evaluated with O'Leary-Sant IC symptom and problem indices, visual analog scale scores and a bladder diary. Urodynamic parameters were also monitored. Treatment effectiveness was regarded as significant when the documented improvement exceeded 50%. Sildenafil was found to be significantly more effective compared to placebo. Sildenafil was also well tolerated among patients in this study (541).

The high PDE5 expression in human bladder detrusor muscle could stimulate more investigation for PDE5Is and a possible proof of efficacy would not be a surprise.

Level of Evidence: 2 Grade of Recommendation: D

6. ORAL THERAPY IN CLINICAL TRIALS

6.1. Tanezumab

The inhibition of nerve growth factor as a treatment against pain in IC/BPS patients could be a promising means of therapy. Hence, the use of tanezumab, a humanized monoclinic antibody with a specific activity in inhibition of nerve growth factor has been investigated in a placebo controlled RCT, showing encouraging improvement on pain symptoms compared to placebo, after 6 weeks of administration. Moreover, tanezumab was found to be significantly effective even in frequency and urgency against placebo treatment (542).

Pooled analyses deriving data from three small clinical trials, included patients with CP/CPPS and IC/BPS exploring the population with the best response to the treatment with tanezumab. Statistical analysis has shown a statistical difference only in the reduction of pain in the group of women with IC/BPS, compared to placebo. Confirmation of this activity could establish tanezumab as a potent medication against pain in patients with IC/BPS (109).

The occurrence of osteonecrosis and central nervous system side effects resulted in the temporary cessation of the research for tanezumab for pain. However, further data evaluated by FDA have prompted a restart of some studies.

6.2. Certolizumab pegol

Agents inhibiting the action of TNFa on the immune system might also be beneficial for IC/BPS. Certolizumab pegol has been used to treat Crohn's disease, rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. It is a fragment of a monoclonal antibody specific to tumor necrosis factor alpha. In an 18-week randomized, double-blind, placebo-controlled trial, certolizumab pegol was found to be effective in pain endpoints compared to placebo (543).

7. THE ROLE OF CANABBINOIDS

7.1. Beta-caryophyllene

The endogenous cannabinoid system (ECS) is involved in a variety of physiological processes including metabolism, pain-sensation, neurotransmission and inflammation. The effects of the ECS are mediated by two cannabinoid receptors; cannabinoid receptor 1 (CB1R) and 2 (CB2R) and the most common endocannabinoids, are N-arachidonylethanolamine or anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Both of them have higher affinity to CB1R, while 2-AG to show a high affinity to CB2R, as well. Beta-caryophyllene (BCP) is a constituent of clove oil and has been found in cannabis. It has been reported to act as a CB2R agonist and it could be worthy of investigation as a treatment for IC/BPS. In a mice model, orally administered BCP significantly reduced the number of adherent leukocytes in submucosal venules and additionally, oral BCP was shown to provide analgesia for IC/BPS-induced pain. Intravesical route of treatment has, also, shown encouraging results (544).

7.2. Palmitoylethanolamide

A congener of the endocannabinoid AEA, palmitoylethanolamide (PEA) has been studied in several models for treating symptoms in patients with pelvic inflammation, including IC/BPS. PEA has been used in micronized (m-) and ultra-micronized (um) formulations and the m-PEA products have been found to be effective in patients with IC/BPS after six months of follow-up in open label studies (545,546) .

Table 8: Primary oral therapy choices for IC/BPS and HLD

Modality	Representatives	Level of Evidence	Recommendation
Analgesics	Acetaminophen NSAIDs Neuropathics Opioids	4	C
Tricyclic Antidepressants	Amitriptyline	2	B
Antihistamines	Pyribenzamine Hydroxyzine Cimetidine	3	C
Immunosuppressants	Cyclosporine	2	C
	IPD-1151T Prednisone	1 4	Not recommended
Permeability regulators	Pentosan polysulfate	1	D
Other treatments	Quercetin	4	D
	Antibiotics	2	Not recommended
	Methotrexate	4	Not recommended
	Montelukast	4	Not recommended
	Nifedipine	4	Not recommended
	Misoprostol	4	Not recommended
	Sildenafil	2	D
	L-Arginine	2	Not recommended
	Adalimumab	2	Not recommended
Cannabinoids	Palmitoylethanolamide	2	D

Table 8: Primary oral therapy choices for IC/BPS and HLD

Modality	Representatives	Level of Evidence	Recommendation
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Tricyclic Antidepressants	Amitriptyline	2	B
Antihistamines	Pyribenzamine Hydroxyzine Cimetidine	3	C
Immunosuppressants	Cyclosporine	2	C
	IPD-1151T Prednisone	1 4	Not recommended
Permeability regulators	Pentosan polysulfate	1	D
Other treatments	Quercetin	4	D
	Antibiotics	2	Not recommended
	Methotrexate	4	Not recommended
	Montelukast	4	Not recommended
	Nifedipine	4	Not recommended
	Misoprostol	4	Not recommended
	Sildenafil	2	D
	L-Arginine	2	Not recommended
	Adalimumab	2	Not recommended
Cannabinoids	Palmitoylethanolamide	2	D

The ECS represents a pharmacological target for the treatment of IC/BPS. However, current evidence a suggest a high caution of the systemic administration of cannabinoids and a close monitoring of the possible side effects, including cardiovascular dysfunction, digestion failure and psycho-activity.

Level of Evidence: 2 Grade of Recommendation: D

8. CONCLUSION

One can sympathize with the conclusions of the Cochrane Database when reviewing this oral treatment section of the current chapter. “We are uncertain whether some treatments may be effective in treating patients with BPS because the certainty of evidence was generally low or very low. Data were available for a relatively large number of trials, but most had small sample sizes and effects of treatments often could not be estimated with precision. … Larger, more focused trials are needed to improve the current evidence base.” (547) Nevertheless, patients need help now, and the educated provider can come up with a plan based on the current knowledge base to intelligently treat these patients.

TABLE 8 summarizes the primary oral treatment choices for IC/BPS.

XIV. INTRAVESICAL THERAPY

The urothelium is not just a physical barrier between blood and urine but can express a host of receptors having a functional significance in micturition reflex. The identification of a cannabinoid, nicotinic, neurokinin receptors and potassium ion channels in urothelium have revealed the role of urothelium as an excitable cell layer that responds to stretch and conveys messages to underlying afferents in the bladder. (548) There is also mounting evidence to demonstrate expression of adrenergic, bradykinin, and transient receptor potential (TRP) receptors in urothelium in proximity to afferent nerves. (549,550) Urothelium is the primary nonneuronal source for the release of molecules such as adenosine triphosphate(ATP), acetylcholine, and nitric oxide, which are known to affect micturition. (551)

The data on use of intravesical therapy has been generally poor due to the limited number of controlled accessible studies on intravesical therapies for IC/BPS and non-standardized response criteria. (552,553) This situation is thankfully improving. What follows are treatments that have been reported in the recent literature, some of which are commonly used. Older therapies that are rarely used now include **silver nitrate** (104,554-557) and **chlorpactin WCS90**. (47,558-563) These have not been included in this current edition of the Consultation, but have level 3 evidence to support a grade C recommendation based on original reports. **(Table 9)**

1. DMSO (DIMETHYL SULFOXIDE)

Level of evidence 1, Grade of Recommendation: B

Dimethyl sulfoxide (DMSO) has been used for medical treatment and as a pharmacological agent in humans since the 1960s. It is the only intravesical agent approved for the treatment of intersti-

Table 9: Intravesical therapy efficacy by Oxford criteria

MEDICATION	LEVEL OF EVIDENCE	RECOMMENDATION
Dimethyl Sulfoxide 50%	1	B
Heparin	3	C
Hyaluronic Acid	1	C
Chondroitin Sulfate	1	C
Hyaluronic Acid plus Chondroitin Sulfate	1	C
Lidocaine	1	C
Silver nitrate	3	Not recommended
Chlorpactin WCS90	3	C
Pentosan Polysulfate	4	D
Vanilloids	1	Not recommended
BCG	1	Not recommended
Oxybutinin	4	D
Oxybutinin	4	D

tial cystitis by the Food and Drug Administration. {GafniKane 2013. DMSO is believed to reduce inflammation, relax muscles, eliminate pain, dissolve collagen, and degranulate mast cells. It has long been used as a therapeutic agent for IC/BPS. Its mechanism of action, however, has not been clarified. Peeker et al reported that in a randomized study, frequency and pain were improved in Hunner lesion patients, although no improvement was observed in maximum bladder capacity. (564) Perez- Marrero et al reported that in a non-randomized controlled study, 53% of the patients showed remarkable improvement in subjective evaluation (placebo 18%), and 93% in objective evaluation (placebo 35%). (565) Around an 80% improvement rate has been reported in case series and retrospective studies. (566-572)

With regard to side effects after instillation of DMSO, most patients recognize a garlic-like odor, which disappears within a day, and about 10% of patients report an irritative symptom flare on initiation of treatment which resolves with or without intervention. (573) It is hypothesized that these transient exacerbations occur as the result of mast cell degranulation.

The number of significant side effects is considered to be small. Cataracts have been reported in animal studies, though not in humans. (574,575) Negative effects on bladder compliance have been noted in rat detrusor. (576) DMSO may accelerate the absorption of other drugs instilled simultaneously, which could be a source of side effects.

The instillation method has not been standardized. Generally, 50cc of a solution of medical grade 50% DMSO is instilled into the bladder. If pain occurs immediately following instillation, local anesthesia (e.g. 20ml of 2% lidocaine solution) may be instilled. Average retention time is considered to be 20 minutes. (573) The instillation is performed weekly for 6-8 weeks. After an initial course, treatment is suspended until symptoms recur. If a good result was obtained, another 6 week course (often followed by monthly maintenance) can be initiated. The long-term effect is unknown, although there is no upper limit for the duration of the treatment.

It is often administered as a cocktail combined with other medications sometimes including a steroid, heparin, sodium bicarbonate, and/or lidocaine. (577,578) The combination of triamcinolone and DMSO has been shown to increase bladder capacity and increase voiding intervals in a large, uncontrolled series of newly diagnosed patients. (579) Tutolo et al, in a prospective RCT reported that while Intravesical chondroïtin sulphate 2% is a viable treatment with minimal side effects, DMSO should be used with caution and with active monitoring of side effects. (580) In 2015, Tomoe reported DMSO was useful after hydrodistension in IC/BPS with Hunner lesions in both maintaining and improving the effectiveness. Further, in her study, DMSO did not have any particular efficacy in the treatment of IC/BPS in the absence of Hunner lesions. (581) A review of adverse reactions that have been reported in the literature has been reported since the last consultation report. (582).

A preparation of DMSO was recently approved for use in Japan as the result of a phase 3 placebo-controlled trial. It was administered intravesically biweekly for 12 weeks in patients with bladder-centric phenotype (primarily Hunner lesion disease). This preparation has little garlic odor side effects, and a placebo-controlled trial was thus possible. It was well-tolerated and improved symptoms, voiding parameters, and global response compared with placebo, adding to its history of safety and efficacy over the last 55 years. (219)

2. HEPARIN

Level of Evidence: 3, Grade of Recommendation: C

Side effects are rare and primarily related to effects of intravesical catheterization and slight chance of bladder hemorrhage. The glycosaminoglycan (GAG) layer on the bladder urothelium is a kind of muco-polysaccharide, working as a non-specific defense mechanism. It is believed that a deficiency or abnormality of GAG secondarily causes inflammation of the bladder by increasing the permeability of the bladder mucosa, leading to the pathologic cascade of IC/BPS. Heparin has similarities to the GAG layer of the bladder. When instilled into the bladder, theoretically it might replace the damaged GAG layer as originally shown by Hanno. (583,584) Kuo reported that the International Prostate Symptom Score, as well as bladder capacity at initial desire to void and maximum bladder capacity, improved significantly. (585) According to the report by Parsons et al in an uncontrolled study symptoms were reduced in 56% of patients treated 3 times weekly for 12 weeks. (586) These reports suggest the efficacy of heparin, however, there is no randomized comparative study to give conclusive evidence. One study indicated that intravesical heparin instillations may prolong the response to dimethyl sulfoxide treatment. (587) In another report, significant symptomatic benefits accrued from the addition of heparin to intravesical lidocaine solution treatments. (588)

No significant side effects have been reported, as it does not affect systemic coagulation parameters. In the case of patients with hematuria, however, it may exacerbate local hemorrhage. The instillation method has not been standardized. Generally, 10,000-40,000 units of heparin are instilled and diluted in 10 ml. It is unusual to have pain or irritation as a result of instillation, and retention times can be 30 minutes or more. Instillation frequency can be up to every other day and it is often administered at home by the patient. Parsons et al reported that when 40,000 units of heparin combined with 1 to 2% lidocaine was instilled 3 times a week for 2 weeks, about 80% efficacy was obtained with relief of symptoms in 12 hours. (589) There is no upper limit for the duration of the treatment, but

a long-term effect is unknown. Heparin for intravesical use is not approved by drug regulatory authorities.

3. HYALURONIC ACID

G Level of Evidence: 1, Grade of Recommendation: C

Hyaluronic acid, like heparin, is a muco-polysaccharide, that could theoretically improve or repair a damaged GAG layer of the bladder mucosa. Several reports have indicated efficacy in non-placebo controlled trials. (258,590,591) L (244,592-597) In the summer of 2003 Bioniche Life Science Inc and in the spring of 2004 Seikagaku Corporation reported double-blind, placebo-controlled, multicenter clinical studies of their hyaluronic acid preparations (40mg or 200mg per cc respectively) and neither showed significant efficacy of sodium hyaluronate compared to placebo in large phase 3 trials. These negative studies have not been published in peer reviewed literature. Neither preparation has been approved for use for IC/BPS in the United States. At the same time, no significant side effects were observed.

Forty-eight patients with typical symptoms and a positive potassium (0.4 M) sensitivity test were treated with weekly instillations of 40 mg hyaluronic acid for 10 weeks. Visual analogue scale scores showed symptom relief due to hyaluronic acid therapy, irrespective of bladder capacity. The improvement was particularly evident in patients with a reduction in Cmax < 30% compared to patients with a reduction of < 30% with 0.2 M KCl solution (P = 0.003). Long-term effects were investigated in a study of 70 patients previously treated with hyaluronan. (598) Of the initial 70, 48 improved. Of these, 50% reported complete remission with no further therapy. Another 41.7% of patients with symptom recurrence improved after retreatment. In a Korean study, intravesical instillation of 40mg of HA in 50ml of saline once a week, for 4 weeks, significantly improved VAS score, PUF, ICSI and ICPI in refractory IC/BPS. Previous treatment modalities did not affect the efficacy of the instillation and the presence of Hunner lesion was unrelated to outcomes. (599)

It has been suggested that HA and lidocaine be combined for instillation. In a non-randomized controlled open-label trial, 48 women with refractory IC/BPS were enrolled and divided in three groups: the trial group received HA, alkalinized lidocaine (AL) and sodium bicarbonate once a week for 8 weeks and then monthly for 4 months with a subsequent follow-up of 24 weeks, while the two control groups received HA, and AL plus sodium bicarbonate respectively following the same procedure. The HA+LA and the LA groups showed a rapid improvement of symptoms at week 2, while the HA treatment was ineffective until week 4. In the later stage of the treatment, symptoms in AL group recurred, probably because AL relieves symptoms through its anesthetic activity, but it cannot repair the defect of the bladder mucosa. Once the instillation was stopped or the frequency was reduced, the effect disappears gradually. (600) In a randomized prospective study, IC/BPS patients were randomized in two groups: group A received HA directly with a catheter and group B received HA with electromotive drug administration (EMDA). The VAS score and the micturition frequency were significantly lower in group B at 6 and 12 months. The difference between the two groups was not significant at 24 months, demonstrating a lack of long-term efficacy. (601) Shao et.al. showed a prolonged effect of bladder distension when combined with instillation of hyaluronic acid. (602) A study by Hung suggested that hyaluronic acid improves pain symptoms more than frequency and urgency. (603)

Ketamine abuse especially in the younger population, is an emerging issue in many countries, and ketamine cystitis (KC) is a growing disease which more and more urologists may encounter. The clinical presentation of ketamine cystitis varies and may mimic IC/BPS. KC patients present with severe irritative symptoms and an irregular, thickened, inflamed bladder wall on endoscopy. A case report by Ying-Lun Ou et al. showed a complete reversal change after intravesical HA instillation. (604)

4. CHONDROITIN SULFATE

Level of Evidence: 1, Grade of Recommendation: C

Chondroitin sulfate is the only sulfatated glycosaminoglycan located on the urothelial luminal surface and contributes to the urothelial barrier function. (605) Its efficacy was suggested for the first time 2002 when used alone (606) and in another trial when used in combination with hyaluronic acid. (607) Intravesical chondroitin sulphate demonstrated beneficial effects in patients with a positive potassium stimulation test in two non-randomised, uncontrolled, open-label pilot studies. Steinhoff (606) treated 18 patients with 40 mL instilled intravesically once weekly for 4 weeks and then once monthly for 12 months. Thirteen of 18 patients were followed for the entire 13-month study. Twelve of these patients responded to treatment within 3–12 weeks. A total of 6/13 (46.2%) showed a good response, 2/13 (15.4%) had a fair response, 4/13 (30.8%) had a partial response, and 1/13 (7.7%) showed no response. In a second trial 24 refractory patients with IC/BPS were treated with high-dose (2.0%) chondroitin sulphate instillations twice weekly for 2 weeks, then weekly with 0.2% solution for 4 weeks, and monthly thereafter for 1 year. (608) The average symptom improvement reported in 20 patients completing the trial was 73.1% (range: 50– 95%). The time to optimum response was 4–6 months. A more concentrated 2.0% solution was needed in eight patients to maintain results. Chondroitin sulphate instillation was effective and well tolerated in the therapy of various chronic forms of cystitis associated with a possible GAG layer deficit including IC/BPS in a large multicenter observational study. (609)

Two large, randomized placebo controlled trials of chondroitin sulfate as monotherapy for IC/BPS were carried out in North America by Watson. Sixty-five patients with IC/BPS were treated in a prospective, randomized, double-blind, inactive vehicle-controlled, 12-week study (6 weeks treatment, followed by 6 weeks follow-up). At the primary endpoint analysis (week 7), 22.6% of the vehicle control group were responders compared with 39.4% of the active therapy group, however, the difference was not significant. (116) A follow up randomized placebo-controlled trial with 98 female patients showed only minor improvements in IC/BPS symptoms and pain and failed to demonstrate a statistically significant drug effect vs. placebo. (610) The authors concluded that the study did not support the use of intravesical chondroitin sulfate as a monotherapy for this condition. In 2013 an individual participant data (IPD) metaanalysis was conducted to define the efficacy of intravesical 2% chondoitin sulfate in IC/BPS patients. {Thakkinstian 2013) Two hundred thirteen patients were included in this analysis. At the end of the treatment di overall global response assessment (GRA) rates were 43.2% in the chondroitin group and 27.4% in the control group and the chance of having become a responder with chondroitin sulfate was 55%, significantly higher than with placebo. The small decrease in total ICSI score and urine frequency between the two groups was less impressive and not statistically significant.

A prospective single centre study assessed CS effectiveness for treating IC/BPS in IC/BPS patients who had failed prior DMSO treatment. The global response to treatment was 80% at 10 weeks and 70% at 24 weeks. No significant side effects were reported. (611)

A recent small RCT compared effectiveness of intravesical chondroitin sulphate (CS) 2% versus dimethyl sulfoxide (DMSO) 50% in patients with IC/BPS. Seventy-three percent of patients receiving CS reported moderate or marked improvement and achieved a reduction in VAS scores, vs 14% on DMSO due to pain during and after instillation, intolerable garlic odor and lack of efficacy. CS group performed significantly better in pain reduction (-1.2 vs. -0.6) and nocturia (-2.4 vs. -0.7) and better in total O'Leary reduction (-9.8 vs. -7.2). The trial was stopped due to high number of dropouts with DMSO. (612)

5. CHONDROITIN SULFATE AND HYALURONIC ACID COMBINATION THERAPY

Level of Evidence: 2, Grade of Recommendation: C

The combination of hyaluronic acid and chondroitin sulfate forms a viscous agent, and was proposed several years ago for treatment of IC/BPS by Cervigni and colleagues. (607,613,614) It may also improve sexual function in female patients with IC/BPS. (615) The solution has been approved in parts of Europe for use as an intravesical therapy. It has been shown in a pilot study to relieve some symptoms of radiation cystitis. (616) In 2016 a randomized, open-label, multicenter study involving 110 women were randomized to receive 13 weekly instillations (3 months) of HA (1.6% - 800mg) and CS (2.0% - 1g) (Ialuril®; IBSA) or 50% DMSO solution (RIMSO®; Bioniche), with a 2:1 allocation ratio (HA/CS:DMSO). This study showed that treatment with HA/CS appears to be as effective as DMSO with a potentially more favorable safety profile. Both treatments increased health-related quality of life, while HA/CS showed a more acceptable cost-effectiveness profile. (617) In a recent paper Keane et al. confirmed these results. (618)

In 2019 Özkıdık compared the efficacy, safety and tolerability of intravesical hyaluronic acid (HA), chondroitin sulfate (CS) and combination therapies (HA+CS) in patients with IC/BPS over 24 months. All groups showed a significant improvement both in the parameters included in the 3-day micturition diary and self-reported questionnaires compared to the baseline values or scores recorded at the beginning of the study. The combination therapy was superior to both monotherapies in terms of improvement in HRQoL score and the difference was statistically significant ($p = 0.02$). Combination therapy provides better results than the monotherapies to obtain symptomatic relief in patients with IC/BPS. (619) Sherif et al. evaluated the safety and efficacy of intravesical instillation of hyaluronic acid/chondroitin sulfate in the treatment of refractory IC/BPS in 36 pts. An initial response to treatment in all parameters at variable degrees was noticed at 2 weeks after the last instillation when compared to the baseline, and these changes were statistically significant ($p<0.001$). Progressive improvement in all test parameters was noticed at 3 months after treatment, and this improvement was statistically significant compared with baseline and 2 weeks after treatment, respectively ($p<0.001$). Intravesical instillation with both hyaluronic acid/chondroitin sulfate in the treatment of refractory painful bladder syndrome is safe, effective, and well tolerated by all patients with no recorded side effects. (620)

6. PENTOSAN POLYSUFATE

Level of evidence: 4, Grade of Recommendation: D

Pentosan polysufate (PPS) is a mucopolysaccharide similar to heparin, with a similar postulated mode of action when used locally. Like other muco-polysaccharides, it has not been well-studied clinically. Bade et al in a randomized controlled trial found benefit in 4 patients out of 10 on PPS versus 2 of 10 on placebo. (621) A placebo-controlled study of 41 patients found the addition of a 6 week course of intravesical PPS to a regimen of oral PPS significantly improved results. (622)

Lander et al. determined the effect of intravesical instillation of PPS encapsulated in liposomes for refractory interstitial cystitis patients in an open label uncontrolled study. Patients received 400 mg of Pentosan Polysulfate (PPS) encapsulated into liposomes as an intravesical instillation performed every 2 weeks for 3 months. Clinically significant decreases in symptom scores greater than 50% were seen in virtually all outcome measures at 3 month follow up. All subjects reported remarkable subjective improvement in pain symptoms marked by decreased use of narcotics and increased enjoyment of daily activities. Intravesical Pentosan Polysulfate encapsulated into liposomes can significantly decrease frequency, urgency, pain and improve quality of life for two months after deployment. Additional studies are needed to determine cellular effects of glycosaminoglycan restoration, ideal doses, dosing intervals, safety and cost-effectiveness of this innovative therapy. Patients who received the PP/Liposome mixture experienced relatively rapid relief of symptoms. Some were able to stop narcotics use. Nearly all subjective outcome measures at 3 months showed a 50% or greater decrease in symptom and bother scores. Patients were followed for greater than 1 year and several of the patients noted durable and sustained relief of symptoms for greater than 15 months. (623)

7. VANILLOIDS (CAPSAICIN, RESINIFERATOXIN)

Level of Evidence: 1, Grade of Recommendation: -Not Recommended

It would seem reasonable that capsaicin, a C-fiber afferent neurotoxin, could alleviate the pain of IC/BPS by desensitizing bladder afferents. Resiniferatoxin is a potent analog of capsaicin, an alkaloid derived from chili-pepper that promotes the temporary depletion of substance P, a neuropeptide responsible for the transmission of pain impulses through peripheral sensory nerve fibers of type C. (624) Resiniferatoxin (RTX) is considered to have a stronger action than capsaicin, by desensitizing C-fibers more quickly, and causing less initial irritation. This action should inhibit the transmission of impulses to the central nervous system, and potentially alleviate the symptoms of IC/BPS.

Efficacy was indicated in five relatively small clinical trials. (625-629) No severe side effects were reported. A randomized multicenter placebo-controlled clinical trial of RTX failed to demonstrate benefit over placebo. (630)

Liu et al. compared the efficacy and safety of intravesical instillations. PubMed, the Cochrane Library, and Embase were searched. The primary outcome were interstitial cystitis problem (ICPI) and symptom (ICSI) scores. Eleven RCTs covering 8 agents with 902 patients were enrolled. According to the results of the ICPI and ICSI, Resiniferatoxin (0.1 μM) was more effective than other therapies. Combination therapy of hyaluronic acid and chondroitin sulphate ranked second in ICSI, third in ICPI, and first in the visual analog scale (VAS). Among regimens included for complication comparison, chondroitin sulphate was safer than other agents, with a probability of 78.5%. (631)

8. BACILLUS CALMETTE-GUERIN (BCG)

Level of Evidence: 1, Grade of Recommendation: Not recommended

BCG instilled in the bladder is thought to stimulate the immunological system. Seven articles reported on a BCG instillation therapy. Zeidman et al first reported that 5 patients who did not respond to other therapies showed symptomatic improvement. (632) Peters et al conducted a randomized double blind study showing a 60% improvement compared to 27% placebo response with good long-term results at 27 months. (633,634) Sixty-five percent of the patients experienced burning sensation, 41% irritation of the bladder, and 35% pelvic pain. One patient was reported to have dropped out due to joint pain. Peeker et al conducted a randomized double-blind study comparing intravesical BCG and DMSO and failed to find any efficacy with BCG. (564) A very large, multicenter randomized placebo controlled trial conducted by the National Institute of Diabetes, Digestive, and Kidney Disorders failed to identify benefit from BCG, although the side-effect profile was surprisingly similar to that of placebo. (635)

9. OXYBUTYNIN

Level of Evidence: 4, Grade of Recommendation D

Barbalias et al observed significant improvement when combining intravesical instillation of oxybutynin with bladder training (636) Oxybutynin on the bladder wall seems to be well tolerated with anticholinergic action and anaesthetic function too. Randomized trials are lacking.

10. LIDOCAINE

Level of Evidence: 1, Grade of Recommendation: C

Lidocaine is a local anesthetic that relieves pain by blocking sensory nerves in the bladder. It can be administered by electromotive drug administration (EDMA). (637-640) Using EMDA, ionized lidocaine is actively introduced into the bladder using an electrical current. Three articles reported that lidocaine and dexamethasone were instilled following hydrodistention. According to the report by Rosamilia et al, 85% of the patients had a good result, with the effect persisting for 6 months in 25%. (640) Other positive results are noted in case reports. (641,642) A report on a pharmacokinetic effect demonstrated pharmacologic levels of lidocaine absorption into the bladder tissue. (643) In a large, placebo controlled randomized trial, 102 adult patients (99 women) with a clinical diagnosis of IC/BPS were randomized from 19 centres in the USA and Canada to receive a daily intravesical instillation of alkalinized lidocaine or placebo (double-blind), for 5 consecutive days. (644) Treated patients had significant

sustained symptom relief for up to 1 month. The response rate in the active group was 30% vs 9.6% with placebo. However, further randomized, placebo-controlled trials are needed to ascertain efficacy, optimal treatment parameters, and length of response to intravesical lidocaine preparations. (406) Advantages seem to be immediate response, low-cost of generic medication, and ability of patients to self-administer at home. In a comprehensive review of lidocaine and bladder pain syndrome, Henry et.al. conclude that only weak evidence exists for supporting its clinical use currently. It appears to be a promising candidate drug to interrupt the self-perpetuating neuroinflammatory cycle found in IC/BPS. In the absence of more definitive clinical trials with various lidocaine preparations, it is reasonable to try daily instillations of 10-20ml of a 2% lidocaine solution with or without alkalinization for 7 days to see if a clinical response justifies ongoing treatment. (645)

11. OTHERS

Liposomes have been widely studied as drug carriers for a variety of chemotherapeutic. Agents improving the delivery by altering pharmacokinetics and reducing toxicity.

Empty or with entrapped drugs, liposomes can act as a topical healing agent. These studies encouraged investigation of empty liposomes as a therapeutic agent for bladder injury. (548) The use of liposomes as lipid-based biocompatible carriers for drugs administered by the intravesical bladder sparked a lot of interest. The lipidic bilayer structure of liposomes facilitates their adherence and penetration across to the apical membrane surface of luminal cells in the bladder epithelium. Recent clinical studies have tested multilamellar liposomes composed entirely of sphingomyelin as a novel intravesical therapy for interstitial cystitis. (646)

A two-center, double-blind, randomized, placebo controlled, study assessed lipotoxin to treat refractory IC/BPS as Intravesical instillation of liposomal formulated botulinum toxin A (lipotoxin). A total of 31 patients were assigned to intravesical instillation of lipotoxin (onabotulinumtoxinA 200 U with 80 mg sphingomyelin), 28 were assigned to onabotulinumtoxinA 200 U in normal saline and 31 were assigned to normal saline alone. Results shown Improvements in the pain scale and O'Leary-Sant symptom scores occurred in all 3 groups by 4 weeks after treatment. Lipotoxin instillation was associated with a statistically significant decrease in O'Leary-Sant symptom scores, ICSI, ICPI and the VAS pain scale, and an increase in GRA. However, there was no difference in improvement among the 3 groups. No significant adverse events

Lipotoxin failed to demonstrate a positive proof of concept compared to onabotulinumtoxinA or placebo. However, a single intravesical instillation of lipotoxin was associated with decreased IC/BPS symptoms compared to baseline in patients with moderate to severe IC/BPS. The effect was likely due to a significant placebo effect. (647)
Tacrolimus has the same mechanism of action of Cyclosporine A, effective in intractable cases of Hunner lesion disease. The aim of a four year pilot proof of concept study was to demonstrate if tacrolimus instilled in the bladder is effective in treating IC/BPS. Tacrolimus dissolved in DMSO/sterile water was instilled in the bladder of 24 patients with refractory IC/BPS symptoms. In 6 to 63 months follow up improvement was shown in 13 out of 24 patients. No side

effects were reported except for post-instillation flare-up. Blood levels of tacrolimus reached similar safe levels irrespective of using either DMSO or water for preparing the solution. Intravesical tacrolimus dissolved in DMSO/water was found effective in 54% patients of intractable IC/BPS without significant side effects. (648)

XV. BOTULINUM TOXIN (BTX-A) (INTRAMURAL)

Level of Evidence: 2, Grade of Recommendation: B

Intradetrusor BTX-A, a widely used treatment for refractory overactive bladder symptoms due to both neurogenic and idiopathic detrusor overactivity, also has a role to play in treatment of IC/BPS and HLD. It is a protein that is produced naturally by Clostridium botulinum. The toxin is taken up by endocytosis at nerve terminals where it stops the vesicular release of neurotransmitters at the synapse. The therapeutic potential is related to factors beyond its known ability to temporarily inhibit the release of acetylcholine and other neurotransmitters. It also has analgesic properties and can reduce peripheral sensitization by inhibiting the release of several neuronal signaling markers, including glutamate and substance P, and reducing c-Fos gene expression (33). BTX-A disrupts fusion of the acetylcholine-containing vesicle with the neuronal wall by cleaving the SNAP-25 protein in the synaptic fusion complex. The net effect is selective paralysis of the low-grade contractions of the unstable detrusor, while still allowing high-grade contraction that initiates micturition. Additionally, BTX-A seems to have effects on afferent nerve activity by modulating the release of ATP in the urothelium, blocking the release of substance P, calcitonin gene-related peptide and glutamate from afferent nerves, and reducing levels of nerve growth factor (649). Side effects include dysuria and incomplete emptying that may require catheter drainage for an indeterminate period after therapy (650).

Reports of case series/ cohort studies

In an early clinical study, thirteen IC/BPS patients were injected with 100–200 IU of BTX-A (abobotulinumtoxin A or onabotulinumtoxin A) into 20–30 sites submucosally in the trigone and floor of the bladder. Overall, nine (69%) patients noted subjective improvement, and ICSI scores improved by 70% ($P< 0.05$). There were significant decreases in daytime frequency, nocturia and pain, and a significant increase in first desire to void and maximal cystometric capacity. However, dysuria occurred in a majority of patients and persisted in a minority for several months after initial injection. Three patients required clean intermittent catheterization for 2-3 months following therapy (651).

To ascertain effect of repeat injections a total of 13 IC/BPS patients were followed up for 2 years. Fifty-eight injections were administered with a mean of 4.8 ± 0.8 injections per patient. The mean interval between two consecutive injections was 5.25 ± 0.75 months. At 1 and 4 months follow-up, 10 patients reported a subjective improvement. Mean VAS scores, mean daytime and night-time urinary frequency decreased significantly. The three non-responders to the first intravesical treatment session underwent further treatment 3 months later with satisfactory results. At 1 and 2 year follow-up, the beneficial effects persisted in all patients (652)

Trigonal-only injection seems effective and long-lasting since 87% of patients (n = 23) reported improvement after a 3-month follow-up period in a study by Pinto *et al*. in a mixed cohort of women with IC/BPS and HLD (653). Over 50% reported continuity of the beneficial effect 9 months after the first treatment. When retreatment was needed, similar results were obtained. No cases of urinary retention were reported. The authors concluded that this treatment is safe, effective and can be repeated. It appeared to be effective in both cohorts of patients.

These results are in contrast with those in another study from Kuo of BTX-A (onabotulinumtoxin A) in 10 patients with HLD only. One hundred units were injected suburothelially into 20 sites in five patients, while 100 U were injected into the trigone in the remaining five. None of the patients became symptom-free; two showed only limited improvement in bladder capacity and pain score (654).

In a later study of IC/BPS and HLD, positive results were reported by the same group. Lee and Kuo treated patients with refractory IC/BPS and HLD, with 100 U of BTX-A injection plus hydrodistention followed by repeated injections every six months for up to two years or until the patient wished to discontinue. Of the 104 participants, 56.7% completed four BoNT-A injections and 34% voluntarily received the fifth injection due to exacerbated IC symptoms. With a follow-up period of up to 79 months, O'Leary-Sant symptom and problem indexes (ICSI, ICPI, OSS), pain visual analogue scale (VAS) functional bladder capacity, frequency episodes, and global response assessment (GRA) all showed significant improvement ($p < 0.0001$). Those who received repeated injections had a better success rate during the long-term follow-up period. The incidence of adverse events did not rise with the increasing number of BoNT-A injections (655).

A retrospective cohort study evaluated efficacy and safety after intravesical treatment with onabotulinumtoxin A (BTX-A) versus BTX-A with hydrodistension (BTX-A+HD) in 39 females and 2 males with IC/BPS ± HLD after a mean follow-up of 153 months (656). After three months, pain reduction on the Visual Analog Scale (VAS) was 4.5 points with 22 patients reporting total pain relief with better pain reduction in the BTX-a+HD group. A significant improvement was also found with regard to voiding function and night-time frequency in both groups. Half of the patients requested retreatment after fading of symptom relief, while lack of continuation was due to complete pain relief. Complications occurred in 27% of cases including UTI, voiding dysfunction and urinary retention.

Randomized (controlled) trials

Kuo and Chancellor analysed the difference between hydrodistension and hydrodistension plus intravesical, sub mucosal BTX-A in women with HLD (657). Of the 67 patients, 44 were divided in two groups: one received 200 U and the other 100 U, and cystoscopic hydrodistension was performed after 2 weeks. The remaining 23 patients received hydrodistension only. There was symptomatic improvement in all groups. However, in the hydrodistension group, 70% had returned to their previous symptoms after the first month, while in the BTX-A-treated groups, there was improvement of VAS, functional bladder capacity and cystometric bladder capacity at 3 months. At 12 and 24 months, the results in the active group were 55 and 30% versus 26 and 17% in the hydrodistension group.

In a small pilot series 20 women with IC/BPS were either treated with saline or onabotulinumtoxin A (BTX-A) injected *periurethrally* (658). At three months follow-up there were no differences for any parameters determined with a female modification of the Chronic Prostatitis Symptom Index (CPSI), AUA Symptom Index, Graded Chronic Pain Scale, Perceived Stress Scale, or symptom improvement Visual Analog Scale (VAS).

Manning et al. randomly allocated 54 women with IC/BPS to blinded treatment with either hydrodistension with saline or to hydrodistension + injection with 500 U AboBTXA (Dysport®) into the bladder wall (659). Subjective outcome was assessed with the O'Leary-Sant questionnaire consisting of problem (OLS-PI) and symptom (OLS-PI) index scores. At three months follow-up there was no significant difference in subjective IC/BPS bother between the two groups, however there was a significant improvement between pre- and posttreatment evaluation in both groups. The postinterventional UTI rate was high, affecting 12 study participants (5 in control group and 7 in BTXA group).

In a multicenter, randomized, double-blind, placebo-controlled patients with IC/BPS and HLD were randomized to hydrodistention plus suburothelial injections of BTX-A 100U or the equivalent amount of normal saline. Pain was assessed using a VAS at week 8 after treatment. Secondary endpoints included voiding diary and urodynamic variables. A total of 60 patients including 40 in the Botox and 20 in the N/S groups were enrolled. At week 8, a significantly greater reduction of pain was observed in the BTX-A group compared to the N/S group (2.6 vs. 0.9, p=0.021). The other variables did not differ significantly between groups except for cystometric bladder capacity, which was increased significantly in the Botox group. The overall success rates were 63% (26/40) in the Botox group and 15% (3/20) in the N/S group (p=0.028). Adverse events did not differ between the groups (660).

To ascertain effect of isolated BTX-A treatment only, Akiyama et al undertook a single-center, prospective, open labeled, randomized comparative study. Patients with refractory IC/BPS were randomly divided into two groups: immediate injection or 1 month delayed injection of botulinum toxin type A after allocation. The rate of treatment response and changes in symptom scores and frequency volume chart variables were compared between groups 1 month after allocation. Using subjects of both groups as a single cohort, predictive factors for treatment response at 1-month post-injection and the duration of response were explored. In a total of 34 patients the response rate was significantly higher in the immediate injection group (72.2% vs 25.0%, p = 0.01). All symptom measures showed significant improvement. When both groups were combined as a single cohort, the response rate was 73.5% at 1 month, 58.8% at 3 months, 38.2% at 6 months and 20.6% at 12 months. The mean duration of response was 5.4 months. The authors also found BTX-A to be more effective in patients with relapse after previous hydrodistension, thus enhancing its value in refractory cases (661).

Chuang et al. performed a double-blind, randomized, placebo controlled trial in patients with IC/BPS and HLD. Study participants were assigned to either intravesical instillation of lipotoxin (onabotulinumtoxinA 200 U with 80 mg sphingomyelin(n= 31)), onabotulinumtoxinA 200 U in normal saline (n=28) or normal saline alone (n=31). Decrease of pain on a VAS scale occurred in all three groups; however, there were no statistically differences between the groups in terms of the ICSI (Interstitial Cystitis Symptom Index) and ICPI (Interstitial Cystitis Problem Index OSS). Average improvement for VAS was -1.64 ± 2.52 (95% CI -2.57 - -0.71), for OSS -7.38 ± 8.75 (95% CI -10.58 - -4.17), for ICSI -4.00 ± 4.28 (95% CI -5.57- -2.42), for ICPI_-3.35 ± 5.11 (95% CI-5.23- -1.47). No hematuria or UTI was observed in the patients. Dysuria occurred in one patient in the lipotoxin group, in 2 in the onaBoNTA group and 1 in the N/S group. No serious AEs were reported (647).

The effect on injection location was analyzed by Jiang et al in women with IC/BPS and HLD. The efficacy and safety between intravesical bladder body versus trigonal onabotulinumtoxina injection in patients refractory to previous conventional treatment were tested in form of a prospective, randomized, clinical trial. In total 39 women were treated (20 in the bladder body, 19 in the trigone); all had a decrease of pain on a VAS scale without significant differences between groups (body 5.60 ± 1.50 preoperatively to 3.15 ± 2.18 postoperatively; trigonum 5.32 ± 2.24 to 2.68 ± 1.86, p=0.82) (662). Secondary outcome parameters included changes of Global Response Assessment (GRA), urinary frequency episodes, O'Leary-Sant score (OSS), and urodynamic study and showed no significant differences between groups. Side effects at two months included dysuria in 45% (bladder body) and 52% (trigonum group) of patients; one patient in the bladder body group had a UTI.

Pinto et al. performed a pilot, single center, randomized, double-blind, placebo controlled phase 2 study. Patients with IC/BPS were randomized to either intravesical OnabotulinumtoxinA 100 U (n=10) or saline as placebo (n=9). 12 weeks after the treatment patients in the treatment group had significantly less pain on a VAS scale than in the placebo group (-3.8 ± 2.5 vs -1.6 ± 2.1, p <0.05). The proportion of study participants who had a 50% or greater VAS pain score reduction was 60% in the OnaBotA group and 22% in the placebo group. The secondary end points including O'Leary-Sant scores (-9 ± 4.7 vs -7.1 ± 4.6, p <0.05), micturition frequency, and quality of life similarly improved significantly. At 12 weeks mean PVR was 5 ± 13 ml for OnaBotA vs 0 ml for placebo (663).

Despite Kuo and Chuang et al's finding of BTX-A ineffectiveness in disease with HLD (647,654), several authors reported similar results for patients with or without Hunner lesions present at treatment, indicating pain is targeted by BTX-A, regardless of cystoscopic phenotype (655,657,660,664).

RCTs have demonstrated efficacy of single and repeated injections with BTX-A with few and mild side effects in IC/ BPS and HLD. Further studies will be needed to obtain conclusive evidence for its efficacy, duration of effect, retreatment schedule, site of injection and side-effect profile. At this point it appears that a 100-unit total dose in 10 unit aliquots limited to the bladder base is as effective as injection points mapping the entire bladder mucosa.

XVI. NEUROMODULATION

Level of Evidence: 2, Grade of Recommendation: C

Sacral nerve stimulation (SNS) involves implanting permanent electrode(s) to stimulate S3 or S4 roots. As early as 1989, Tanago et al showed that stimulation of S3 may modulate detrusor and urethral sphincter function (665). FDA approved the usage of sacral neuromodulation for treating refractory detrusor overactivity in 1997 and for urinary urgency and frequency in 1999. Although the effectiveness of SNS for detrusor overactivity is largely confirmed by a good number of studies, relatively few papers report the effect of SNS in treating IC/BPS.

A possible mechanism of neuromodulation in treatment of pain is based on the gate-control theory; Non-painful input closes the gates of painful input resulting in prevention of pain sensation from traveling to the central nervous system. Another possible mechanism of action is reduction in the pelvic floor hypertonicity, as myofascial pain and hypertonic pelvic floor dysfunction is observed in majority of the IC/BPS patients (316). A potential role of urinary chemokines as a measure of treatment response has been reported (296). Percutaneous S3 nerve root stimulation improved symptoms and normalized urinary heparin-binding epidermal growth factor-like growth

factor levels and antiproliferative activity in patients with IC/BPS. Peters et al. suggested that treatment response may coincide with a decrease in the urine levels of chemokines, especially a decrease in the monocyte chemoattractant protein-1 (666).

Zerman et. al reported a case of 60-year-old woman treated for severe IC/BPS pain by SNS implant. Pain and accompanying bladder dysfunction were improved by temporary and permanent sacral nerve stimulation for up to six months (667). Siegel et al (668) assessed the postoperative outcome of sacral neuromodulation in 10 patients with intractable pelvic pain. Visual analogue scale (VAS) pain scores decreased by 55% from baseline and at a median of 19 months, 6 patients reported significant improvement in pelvic pain. Maher et al (669) showed that temporary stimulation was effective in 73% of 15 women with refractory IC/BPS. Mean voided volume during treatment increased and mean daytime frequency, nocturia and pain decreased significantly. As indicated by the Short Urinary Distress Inventory and SF-36 Health Survey, the quality-of-life parameters of social functioning, bodily pain and general health significantly improved during the stimulation period.

In their report in 2003, Comiter et al (670) prospectively investigated the effect of SNS on a series of 17 patients with refractory IC/BPS. At an average of 14-month follow-up, mean daytime frequency, nocturia and mean voided volume improved significantly. The average pain decreased from 5.8 to 1.6 points on a scale of 0 to 10 and Interstitial Cystitis Symptom and Problem Index scores (ICSI and ICPI) decreased from16.5 to 6.8 and 14.5 to 5.4, respectively. Of the 17 patients 16 (94%) with a permanent stimulator demonstrated sustained improvement in all parameters at the last postoperative visit. Whitmore el al (671) applied percutaneous sacral nerve root stimulation on 33 patients with refractory interstitial cystitis. Significant improvements were also seen in frequency, pain, average voided volume, maximum voided volume, ICSI and ICPI scores. Peters et al (672) reported a reduction of narcotic usage in 18 IC/BPS patients following SNS for a mean of 15.4 months, although the dose reduction was modest (36%) and only 4 of 18 discontinued the narcotics. However, Elhilali and colleagues (673) found that both of two patients with interstitial cystitis reported no improvement following sacral neuromodulation. Zabihi et al (674) more extensively stimulated S2-S4 by implanting electrodes into the epidural space through the sacral hiatus. 23 of 30 (77%) patients had successful trial stimulation and were permanently implanted. The symptom score was improved by 35% (p=0.005) and pain score improved by 40% (p=0.04). Patients reported an average of 42% improvement in their symptoms.

In the first prospective, single-blind, crossover trial of sacral nerve stimulation (SNS) versus pudendal nerve stimulation (PNS) for patients with IC/BPS (n =22), PNS gave an overall 59% improvement in symptoms, whereas SNS gave an overall 44% improvement (P = 0.05). Most patients who tested both, a sacral and pudendal electrode chose PNS as the better site. Follow-up showed marked improvements in voiding variables and validated IC/BPS symptom questionnaires. Over 90% of patients treated with neuromodulation stated that they would undergo implantation again (675).

Long-term results were verified in a retrospective study of 78 patients treated from 1994 to 2008. Permanent sacral neuromodulation implantation was performed in patients who showed at least 50% improvement in their symptoms with a temporary peripheral nerve evaluation test. Median follow-up was 61.5 ± 27.7 months. Good long-term success of sacral neuromodulation was seen in 72% of the patients. The explantation rate was 28% and revision rate was 50%. The most frequent reason for explantation was poor outcome (54% of the failed patients) (676). In another observational, retrospective, case-controlled review, 34 female patients underwent permanent device implants with mean follow-up of 86 ± 9.8 months. Mean pre and postoperative pelvic pain and urgency/frequency scores were 21.61 ± 8.6/9.22 ± 6.6 (p < 0.01), and mean pre-/postoperative VAS pain scores were 6.5 ± 2.9/2.4 ±1.1 (p < 0.01) (677).

In a recent systematic review of sacral neuromodulation in treating chronic pelvic pain by Mahran et al. (678) significant overall improvement in VAS pain scores was observed (weighted mean difference = -4.36%, 95% CI = -5.24 to -3.48, p <0.001). The most common adverse events were lead migration and malfunction (8%) followed by pain at the implantation site (5.4%), wound infection (4%), spontaneously resolved seroma (2.7%) and implantable pulse generator erosions without infection (1.1%). Five percent of patients were reported to have either device failure or removal and 10% of the patients underwent implant revision or replacements. Five patients required device or implantable pulse generator battery changes due to ended battery life.

SNS is still considered an investigational procedure for IC/BPS by the Consultation. Pudendal nerve stimulation has shown better results. Therapeutic benefits of both appear to be significant in selected cases. Strict patient selection and detailed discussion with patients prior to surgery is mandatory. Long-term results should be collected and reported, and trial results discussed with patients before employing this treatment modality.

Percutaneous tibial nerve stimulation (PTNS) has been also reported to treat IC/BPS (679,680). Recently, a single-arm, dual-center, pilot study reported the rate of overall symptom improvement in IC/BPS patients who were treated with PTNS. A total of 21 subjects were enrolled, 16 initiated and 10 completed the treatment course. There were no adverse events and 70% of the cohort had some degree of improvement (681). However, there is still limited data on efficacy of PTNS.

XVII. SURGICAL THERAPY

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a chronic and debilitating disease. Major reconstructive surgical options should be considered only when all conservative treatment has failed. The patient should be informed of all aspects of surgery and understand consequences and potential side effects of surgical intervention. An experienced surgeon familiar with the particular surgical technique should perform the procedure.

XVIII. HYDRODISTENTION

Level of evidence: 3; Grade of Recommendation: D

Hydrodistension, alternatively known as bladder overdistension or cystodistension, was first reported in 1930 by Bumpus (682) and has been used for many years not only as a diagnostic or classification tool but also a treatment modality of IC/BPS. There is no standardized technique in hydrodistension but the basic concept is filling bladder to its maximum capacity at a fixed pressure (no higher than 80cm water) which is maintained for a set period of time (278). In 1975, Dunn (683) reported complete resolution of subjective symptoms in 16 out of 25 patients (64%) using Helmstein's method (684). Since then, various studies have used heterogeneous outcome parameters with minority of patients reporting improvement in

symptom for a relatively short period time (277,279,291,685,686). As most studies are retrospective and uncontrolled, therapeutic role of hydrodistension in IC/BPS is still controversial.

1. FULGURATION / TRANSURETHRAL RESECTION / STEROID INJECTION HUNNER LESIONS

Level of Evidence: 1; Grade of Recommendation: A

In 1914, Hunner presented his first report of eight cases of rare type of bladder ulcer in women and recommended open resection of the ulcerative lesion in the treatment of IC (43). However, unsatisfactory results soon placed open resection in disrepute. With improvement in cystoscopic technology, transurethral fulguration and resection have become popular (687). Bugbee or loop electrodes are commonly used for fulguration or coagulation of the Hunner lesion. Various studies have investigated the therapeutic role of transurethral operation on the Hunner lesion (556,688-691). Patients included in these studies experienced amelioration of symptom with different treatment response durations and frequent recurrences. Peeker et al. reported a retrospective series of 259 transurethal resection of Hunner lesion in 103 patients (692). Under general anesthesia, Hunner lesion were identified and each one was resected, including at least a half of the underlying muscular coat. Ninety-two patients experienced amelioration of symptoms with an average response duration of 23 months. Hillelsohn et al. reported a retrospective series of 106 transurethral fulgurations of Hunner lesions in 69 patients. Twelve months after initial fulguration, 13.1% of the patients required repeat treatment and the rate increased to 57.2% at 48 months. Until recently, there had been no reports on recurrence patterns of the Hunner lesion and the comparative evaluation of treatment methods (Hunner lesion coagulation versus resection). In a retrospective analysis of 91 patients with IC, Han et al. reported that the recurred Hunner lesions involved previous as well as *de novo* areas which made recurrence pattern unpredictable (693). Ko et al. first reported a single–center, prospective, randomized controlled trial including 126 patients with Hunner lesion and compared the efficacy and safety of transurethral resection and transurethral coagulation. No differences were observed in the recurrence-free time, decreased daytime frequency, nocturia, urgency episodes, pain and symptom questionnaires between the groups over 12 months (694). Several reports have described the use of Neodynium:Yag laser for ablation of Hunner lesion with small bowel perforation due to forward scatter of laser energy as the most serious complication (695-697). Transurethral resection, fulguration, coagulation or laser ablation of the Hunner lesions are recommended treatments for patients with IC/BPS ESSIC type 3X. These endoscopic surgeries are usually combined with hydrodistension. One retrospective study of 44 patients has reported that transurethral resection combined with therapeutic hydrodistension increased bladder capacity and improved voiding symptoms more than did transurethral resection alone (698). Decreased bladder capacity from repetitive transurethral resection or fulguration of Hunner lesion is a controversial issue (699,700). It would be difficult to sort out the effect of fulguration from the natural history of disease given that frequency of fulguration is guided by response to therapy. Transurethral intravesical submucosal injection of corticosteroid (triamcinolone) was also reported to have symptomatic effects comparable to the results observed after resection or fulguration in some uncontrolled studies (701-704).

2. CYSTOLYSIS – PERIPHERAL DENERVATION

Level of Evidence: 3; Grade of Recommendation: - not recommended

Hunner simply dissected bladder from surrounding tissue. Initial results were encouraging, however after 3 years of follow-up, symptoms reoccurred. Worth and Turner-Warwick attempted to do more formal cystolysis and were more successful with regard to symptoms (705). After seven-year follow-up, Worth found bladder areflexia to be a significant complication of this procedure. Patients had to use Credé technique or even be on intermittent self-catheterization (706). Albers & Geyer reported symptom recurrence after 4 years in most of the patients (707). Cystolysis, peripheral denervation of bladder is not indicated for IC/BPS.

3. AUTONOMIC DENERVATION

Level of Evidence: 4; Grade of Recommendation: not recommended

Visceral pain is transmitted in most cases by the sympathetic nervous system. Gino Pieri (708) applied this principle to the bladder pathology and suggested resection of the superior hypogastric plexus (presacral nerves), paravertebral sympathetic chain, and gray rami from S1-3 ganglia (Level 4). This was repeated by Douglass (709) a few years later. Immediate results were very good, however Nesbit (710) showed that the long term results were short lived.

Based on the contribution of S2-S4 segments to bladder innervation, Moulder and Meirowsky (711) used S3 neurectomy in 3 patients with good long term follow-up. Larger series were reported by Milner (712,713) and Mason (714) but results after five years were not encouraging. To improve results selective dorsal sacral root neurectomy, unilateral or bilateral, was introduced by Bohm and Franksson (715). The outcomes of this procedure were unclear. Both sympathetic and parasympathetic denervation is not indicated for IC/BPS.

4. SURGERIES USING INTESTINAL SEGMENTS

The global definition of IC/BPS and its phenotypes is currently under active debate. A recent report after 2018 International Consultation on Interstitial Cystitis Japan concluded that the Hunner lesion disease is pathologically and clinically distinct from the non-Hunner lesion disease, suggesting that the Hunner lesion disease and the non-Hunner lesion are separate disease entities. (22) As various aforementioned surgical treatment options are based on conventional classification system that puts together IC/BPS and HLD in a single category, this recommendation might need revision in the future.

4.1. Bladder Augmentation – Cystoplasty

Level of Evidence: Level 3; Grade of Recommendation: C

Bladder augmentation - cystoplasty has been commonly used for refractory IC/BPS for more than 60 years. First reports of ileocystoplasty from 1958 were very promising. (716) Later publications

were less sanguine with results varying from 25% (717) to 100% (718,719). Cystoplasty is usually done with or without bladder resection. Cystoplasty alone was reported as early as 1967 by Turner-Warwick and Ashken (720), advocating augmentation with removal of the diseased tissue. Several subsequent studies indicated that cystoplasty with subtrigonal cystectomy offers better results than without subtrigonal cystectomy (719,721,722). These were all retrospective studies and conclusions should be taken with reservation.

Cystoplasty with partial or total removal of the bladder requires bowel tissue substitution. Different bowel segments are used to enlarge the bladder. It is the general consensus that the intestine segment used for bladder augmentation should be detubularized (723). Experiences with different bowel segments (ileum, ileocecum, cecum, right colon, sigmoid colon, stomach) have been reported. There is no significant difference among bowels segments with regard to the outcome, except for gastric tissue substitution which is associated with dysuria and persistent pain due to production of acids. Using intestinal segments for bladder substitution is considered to be highly morbid. Recently Osman et al. reported a systematic review on 20 studies using bowel segments for IC/BPS published from 1990 onwards; 85% of included studies (17 out of 20) reported postoperative complications in 357 patients (92 cases of total cystectomy and orthotopic neobladder, 10 cases of total cystectomy and ileal conduit and 101 subtotal cystectomy and augmentation cystoplasty, and 154 procedures not identified). A total 102 complications were documented overall with the most common being sepsis of any type followed by recurrent urinary tract infection, bowel obstruction, ileus, bowel frequency, hernia, metabolic change, stomal problems. Six (1.3%) postoperative deaths were reported. Five patients died from unrelated causes and on patient committed suicide due to persistent pain, having previously undergone primary urinary diversion followed by total cystectomy for persistent pain (724).

4.2. Cystoplasty with Supratrigonal Resection

Level of Evidence: Level 3; Grade of Recommendation: C

Cystoplasty with supratrigonal resection (i.e. trigone-sparing) has been reported in various studies (717,718,721,722,725-730). Von Garrelts described excellent results in eight of 13 patients with a follow-up of 12-72 months. Bruce et al. reported satisfactory relief of IC/BPS symptoms by ileocystoplasty and colocystoplasty in eight patients. Dounis and Gow reported improvement in pain and frequency in seven IC/BPS patients after supratrigonal cystectomy with ileocecal augmentation. Kontturi et al. used segments of colon and sigmoid colon in 12 cases with 100% symptom-free outcome in five patients augmented with sigmoid colon over 4.7 years of follow-up. Two of seven cases augmented with colon required ileal conduit and cystectomy. Linn et. al followed six IC/BPS patients for 30 months, and reported that all were symptom free and voided spontaneously. The report by Nielsen et. al was less favorable. Six out of eight patients (75%) had good results. Van Ophoven et. al reported the long-term (mean 57 months) results of orthotopic substitution enterocystoplasty in 18 women with IC/BPS, using ileocecal (n = 10) or ileal (n = 8) segments with two failures. In the group augmented with ileum, three patients required self-catheterization and one a suprapubic catheter. Peeker et. al found that patients with end-stage HLD had excellent results following ileocystoplasty but not in the patients with non-HL disease. Long-term follow-up (median 89 months (2 to 258)) on this paper was published with the same conclusion for Hunner lesion disease, while both continent diversion and iliocystoplasty were unrewarding in patients with type 2X IC/BPS. There is some weak evidence that cystoplasty with supratrigonal resection may benefit some selected patients with end stage ESSIC type 3C IC/BPS. It is reasonable to consider provided patients recognize that a follow up surgical procedure may be required if symptoms do not respond.

5. CYSTOPLASTY WITH SUBTRIGONAL CYSTECTOMY — ORTHOTOPIC CONTINENT BLADDER AUGMENTATION

Level of evidence: 3; Grade of Recommendation: C

Cystoplasty with subtrigonal cystectomy — orthotopic continent bladder augmentation (i.e. with trigone removal but preservation of the bladder neck) in the management of IC/BPS has been reported less often (731-734). Because of the need of ureteral reimplantation, it is associated with some risks of urine leakage, ureteral stricture and reflux (733). Linn et al. (726) had three failures in 17 patients and half of the patients with good symptomatic response required self-catheterization. Nielsen et. al (717) had better results following orthotopic substitution with low bladder capacity (200 mL versus 525 mL, respectively).

Orthotopic continent bladder augmentation, particularly when removing the trigone, may cause incomplete voiding requiring intermittent self-catheterization. Therefore, patients considering such procedures should be advised accordingly and must be considered capable of performing, accepting, and tolerating self-catheterization. Nurse suggested that the decision on whether to do a subtrigonal or supratrigonal cystectomy be based on the results of trigonal biopsy, with the former procedure indicated in the patient with trigonal inflammation (717). There is no compelling evidence that subtrigonal cystectomy with cystoplasty has any outcome advantage over supratrigonal cystectomy, but it tends to be associated with more complications and poorer functional bladder rehabilitation.

6. URINARY DIVERSION WITH OR WITHOUT TOTAL CYSTECTOMY AND URETHRECTOMY

Level of Evidence: 3; Grade of Recommendation: B

In patients who have not responded to less invasive interventions, urinary diversion can result in major quality of life improvements. Techniques include simple conduit or continent urinary diversion. Continent diversion may be preferable for cosmetic reasons in younger patients. Simple urinary diversion with formation of an ileal conduit is the most common surgical treatment for IC/BPS (735). Initially, diversion can be done without cystectomy and only if bladder pain is persistent, cystectomy can be considered. Bladder de-functionalization alone produced symptom-relief in multiple reports (736-739). Whether or not cystectomy should be performed at the same time as urinary diversion is somewhat controversial. Nordling and Redmond et al. reported that urinary diversion for IC/BPS does not require concurrent cystectomy (739,740). About 80% of patients seem to have clinically significant improvement after urinary diversion, but secondary cystectomy does not seem to improve refractory pain. Meanwhile Osman et al. concluded that total removal of the bladder tended to result in success defined

as symptom improvement as compared with subtotal cystectomy or whole bladder in situ (724). Often diversion is performed as a next step after unsuccessful bladder augmentation. To avoid further bowel resection, a bowel segment used for cystoplasty can often be converted to a conduit (741). In some patients, chronic inflammatory changes have been observed in the cystoplasty pouch resembling interstitial cystitis (742,743) perhaps suggesting that a urinary component is an etiologic agent for the syndrome. Similar bowel changes, however, have been described when cystoplasty is performed for pathology other than interstitial cystitis, suggesting that these pathologic findings are not a direct result of the exposure of bowel to IC/BPS urine (744). Urinary diversion with and without cystectomy may be the ultimate option for refractory patients. Continent diversion may have better cosmetic and life style outcome but recurrence of pain in the pouch is a real possibility. In patients who would prefer only one major surgical procedure, a simple conduit diversion without cystectomy would be a reasonable approach. One can promise the patient that urinary frequency should no longer be a problem, and while pain may improve dramatically, if it doesn't it can be treated through pain management techniques.

XIX. OUTCOME ASSESSMENT

Level of evidence 2, Grade of recommendation C

1. STANDARDIZED IC/BPS CASE DEFINITION

A brief survey that reliably segregates IC/BPS from other urologic disorders would make the ability to diagnose the syndrome reliable, inexpensive, and available to all healthcare providers. It would aid in epidemiologic studies as well. A case definition for IC/BPS was developed by adapting the RAND/University of California, Los Angeles Appropriateness Method. (71) This involved a panel consisting of nine experts with experience in IC/BPS and related diseases, literature review of case definitions of IC/BPS, initial ratings of symptoms as indicators of the IC/BPS diagnosis, and discussion and a second set of ratings to establish criteria for diagnosis through patient reports. This resulting IC/BPS case definition **(Figure 18)** was able to discriminate between IC/BPS patients and patients with confusable disorders (overactive bladder, endometriosis,

1. In the past 3 months, have you ever had a feeling of pain, pressure, or discomfort in your lower abdomen or pelvic area -- that is, the part of your body that is above your legs and below your belly button?
   - YES
   - NO

2. In the past 3 months, have you had a strong urge or feeling that you had to urinate or "pee" that made it difficult for you to wait to go to the bathroom?
   - YES
   - NO [GO TO QUESTION 4]

3. Would you say this urge to urinate is mainly because of pain, pressure or discomfort or mainly because you are afraid you will not make it to the toilet in time to avoid wetting?
   - PAIN, PRESSURE, DISCOMFORT
   - FEAR OF WETTING

4. In the past 3 months, before you urinate, as your bladder starts to fill, does your feeling of pain, pressure, or discomfort usually:
   - GET WORSE?
   - GET BETTER?
   - STAY THE SAME?

5. In the past 3 months (when you were having symptoms), how many times on average have you had to go to the bathroom to urinate during the day when you are awake?

ENTER NUMBER OF TIMES: _____

IC/BPS Case Definition = Pain plus (Urgency or Frequency)

Pain criteria = 'Yes' answer to item 1
Urgency criteria = 'Yes' answer to item 2 plus response of 'pain, pressure or discomfort' for item 3
Frequency criteria = response of 10 times or greater on item 5

Figure 18. Rand interstitial cystitis epidemiology (RICE) IC/BPS case definitions. Berry SH, Bogart LM, Pham C, Liu K, Nyberg L, Stoto M, et al. Development, validation and testing of an epidemiological case definition of interstitial cystitis/painful bladder syndrome. J Urol 2010, May;183(5):1848-52.

vulvodynia) with adequate sensitivity and specificity. It was subsequently successful in establishing population-based estimates for IC/BPS disease prevalence (92,94). If this could be adapted for use in screening by primary care physicians, the potential benefits in early diagnosis of IC/BPS are evident.

2. CLINICAL SYMPTOM SCALES

IC/BPS symptom scales are currently utilized to measure treatment outcome and are especially valuable in clinical research studies as well as for guiding therapy for individual patients. Symptom scales have enabled patients to be categorized by symptom severity and are also valuable to follow results of treatment in patients with IC/BPS.

There are 5 published IC/BPS symptom questionnaires: the University of Wisconsin IC Scale (Figure 19), the O'Leary-Sant IC Symptom Index (ICSI) and IC Problem Index (ICPI) (Figure 20), the Pelvic Pain and Urgency/Frequency (PUF) Scale (Figure 21), the Bladder Pain/ Interstitial Cystitis Symptom Score, and the Genitourinary Pain Index (745) (Figure 22).

The University of Wisconsin IC Scale includes 8 IC/BPS symptom items which capture severity of symptom expression, as well as 17 non-IC/BPS items (746,747). It was the first published IC/BPS symptom scale, and underwent appropriate psychometric assessment. Its use has declined in recent years.

The O'Leary-Sant ICSI and ICPI indexes are validated tandem questionnaires that were originally developed by focus groups, subjected to test-retest reliability analysis, and validated by administration to IC/BPS patients and asymptomatic controls (748,749). The questionnaires each center on 3 questions related to urgency/frequency and one on bladder-associated pain. The ICSI inquires about symptom severity, and the ICPI assesses the degree of bother. The scores on the ICSI and the ICPI correlate quite highly, suggesting that the ICSI may be sufficient for clinical or research use (750).

The Pelvic Pain, Urgency, Frequency (PUF) questionnaire (751) was designed to include questions that reflect a wide variety of IC/BPS symptoms. One-third of the questions address pelvic pain, including pain anywhere in the pelvis: the vagina, labia, lower abdomen, urethra, perineum, testes, penis, or scrotum. The PUF was developed as an IC/BPS screening tool and was not subject to psychometric analysis. Higher scores were found to correlate with a higher likelihood of a positive potassium sensitivity test (PST). To the extent that the PST is suspect, the reliability of PUF data comes into question. A large study utilizing the PUF questionnaire concluded that up to 23% of United States women have IC/BPS (751); his makes one wary as to the utility and face validity of the PUF.

After a review indicated that the existing IC/BPS patient-completed measures did not meet current standards for the development of patient reported outcomes (752,753), a new measure of IC/BPS symptoms (the Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS)) was developed (754) . The BPIC-SS is based on defined standards for patient-completed measures, including patient and clinical input. The BPIC-SS appears to successfully discriminate IC/BPS patients from OAB patients and healthy controls. It has not been validated to discriminate IC/BPS patients from those with confusable diseases (e.g. endometriosis or UTI). The BPIC-SS appears more discriminative than the PUF or the ICSI. As a result, the BPIC- SS has been implemented into the standard sets within the FDA´s guidance for patient reported outcome development and has been used in recent IC/BPS trials (755). Finally, although developed for the purpose of screening into trials, the BPIC-SS could also potentially be used for measuring outcome results during clinical trials. The questionnaire is available free of charge (http://www.prolutssh.com).

The Genitourinary Pain Index (GUPI) is a 9-item instrument which was developed by the NIH-funded Urologic Pelvic Pain Collaborative Research Network (745). The GUPI is applicable to men and women to assess Pain symptoms, Urinary symptoms, and Quality of life as separate sub-scales, and overall as a total score (Figure 22). It was found to discriminate between men with chronic prostatitis or IC/BPS, those with other symptomatic conditions (dysuria, frequency, chronic cystitis), and those with none of these diagnoses. It also discriminated between women with IC/BPS, those with incontinence, and those with none of these diagnoses. The GUPI demonstrated good internal consistency within subscale domains, and GUPI scores correlated highly with scores on the O'Leary Sant ICSI and ICPI. The GUPI was highly responsive to change, and the change in score was similar in both male and female responders. A change of 4 points was the minimum clinically perceptible difference, and a reduction in 7 points robustly predicted being a treatment responder.

3. PLACEBO-CONTROLLED TRIALS

IC/BPS has been a difficult condition for which to assess therapeutic impact. There is a 50% incidence of temporary remission unrelated to therapy, with a mean duration of 8 months (4). In a chronic, devastating condition with primarily subjective symptomatology, no known cause, and no cure, many patients are desperate and may appear to respond to any new therapy. A skeptical view of outcomes is essential (**Figure 23**), as patients can be victims of unorthodox health care providers using unproven forms of therapy, some medical, some homeopathic, and some even surgical.

Where possible, the results of randomized controlled studies should be used for decision making. Placebo, double-blind studies are optimal in this disorder for which there is no generally effective standard therapy. Placebo effects influence patient outcomes after any treatment which the clinician and patients believe is effective, including surgery. Placebo effects plus disease natural history and regression to the mean can result in high rates of good outcomes, which may be misattributed to specific treatment effects. (132,756-759) Until recently, relatively few IC/BPS treatments have been subjected to placebo-controlled trials.

While in many diseases an argument can be made against using a true placebo control as opposed to an orthodox treatment of approved or accepted value (760), a good case for true placebo comparison can readily be made for IC/BPS. The vagaries of the natural history, the general lack of progression of symptom severity over time, and the fact that it is not life threatening, mean that there is little to lose and much to gain by subjecting new treatments to the vigorous scrutiny of placebo control. Many patients who volunteer for such trials have already run the gamut of accepted (though generally unproven) therapies. It has long been recognized in protocols that use subjective criteria for assessment that "improvement" may be expected in up to 35% of placebo-treated patients (761). As the spontaneous remission rate (though temporary) for IC/BPS is 11%

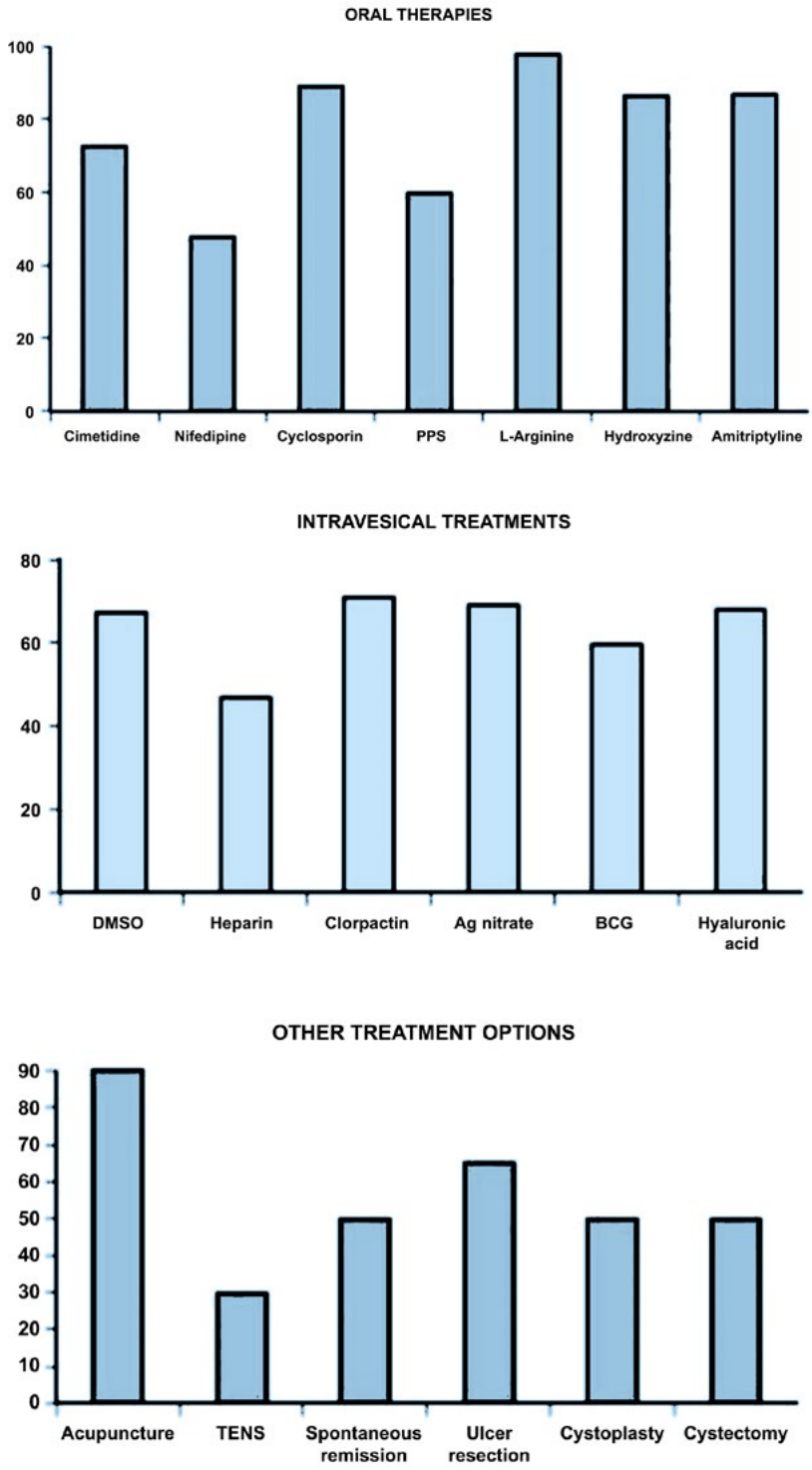


Figure 23. Selected reported treatment outcomes in uncontrolled studies in IC literature: percentage of patients initially improved.

(520) to 50% (4) , combined with the placebo improvement it can be difficult to prove efficacy.

Even in placebo controlled trials, it is reasonable to surmise that some degree of unblinding may occur as a result of somatic or psychological side effects of the active arm, impairing the validity of the trial results and giving the active arm a slight edge over placebo (762,763). Failure to recognize unblinding can easily bias results of a study and has not been routinely measured in clinical trials (764). When occurring late in a study after one would expect onset

of a therapeutic effect, unblinding could be the result of side effect profile or drug efficacy. Early in the trial it reflects poor placebo or study design. The degree of blinding needs to be ascertained throughout the trial. This is of specific concern in IC/BPS and any disorder where primary outcomes may be subject to patient-specific psychological and physiological factors.

The ethics and necessity of placebo-controlled trials have been questioned, especially in situations in which an effective treatment exists and also where delay in treatment has been shown to result in disease progression (765-767) . However, there are methodological concerns with equivalence and non- inferiority active agent comparison trials (768). These include an inability to determine if the treatments are equally good or equally bad, and the possibility that successive non-inferiority trials can lead to a gradual decrease in treatment efficacy. Although the use of placebo-controlled trials raises ethical concerns when proven effective treatment exists for the condition under investigation, they are ethically justified, provided that stringent criteria for protecting research subjects are satisfied (769) .

The value of placebo-controlled trials is aptly illustrated by the decisions of pharmaceutical manufacturers not to pursue FDA approval in the United States for seemingly promising intravesical therapies for IC/BPS (594,770) after placebo-controlled trials failed to establish efficacy. These include low concentration hyaluronic acid (Bioniche, Canada), high concentration hyaluronic acid (SKK, Tokyo), and resiniferatoxin (ICOS, Bothell, Washington, USA). Nalmefene, an initially promising oral therapy in the 1990's (771), also failed phase 3 trials (IVAX, Miami). Placebo trials are impractical in surgery and it can be difficult to evaluate surgical reports. The many older medications currently used off-label might not meet success if tested in the stringent manner in which new molecular entities are tested. The expense of testing therapies currently used off-label often requires dependence on the largesse of government agencies like the National Institute of Health.

4. ALTERNATIVE CLINICAL TRIAL DESIGNS

In addition to classic randomized, blinded clinical trials, there are alternative randomized and non-randomized clinical trial designs that may be considered when testing the efficacy of treatments. These include *factorial* designs, *within-group* designs, and *crossover* designs, among others (772). *Factorial* trials aim to assess two or more treatments in a single trial. The NIDDK-funded Interstitial Cystitis Clinical Research Network (ICCRN) conducted a 2X2 factorial study, in which participants were randomized to four groups: oral pentosan polysulfate (PPS) alone, oral hydroxyzine alone, PPS plus hydroxyzine, or placebo (506). This study design is efficient as it allows the investigators to test the efficacy of two treatments, and it also reduces the number of participants who receive placebo (when compared with a standard RCT with 50:50 randomization). One major disadvantage of a factorial design is that the two treatments may interact, which can reduce the study power and complicate the statistical analysis. *Within-group* designs (or time-series designs) are non-randomized studies in which measurements are made before and after participants receive the intervention. Therefore, each participant serves as his/her own control. Due to a lack of a control group, within-group designs are subject to confounding from learning effects and regression to the mean. One type of within-group study is an "N-of-one" trial, in which participants repeatedly alternate between active forms of the treatment and placebo. In order to be feasible, N-of-one studies must use treatments that have relatively quick onset of action, and with limited carryover effects after cessation. In *crossover* designs, half of the participants are randomized to start with the control intervention and switch to the active treatment, and the other half starts with the active treatment and switches to control. These study designs are attractive to study participants, as they are guaranteed to receive the active treatment at some point. However, as with within-group studies, any carryover effect from the active treatment may contaminate the results. Therefore, there is typically a 'washout' period (no treatment) included between arms of crossover trials. Another disadvantage of crossover designs is that the study length needs to be doubled to accommodate each participant receiving active treatment and placebo.

5. CHRONIC PAIN CLINICAL TRIAL OUTCOMES AND OUTCOME INTERPRETATION: IMMPACT RECOMMENDATIONS

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has published recommendations for core outcome domains for chronic pain clinical trials (461,773). It is recommended that these domains should be considered in all clinical trials of treatments for chronic pain conditions, including IC/BPS. These domains include: (1) Pain, (2) Physical functioning, (3) Emotional functioning, (4) Participant ratings of improvement and satisfaction with treatment, (5) Symptoms and adverse effects, and (6) Participant disposition. In addition, IMMPACT recommends that the type of trial, the study design, the statistical analysis methods, the magnitude of the estimated effects, the risk-benefit profile of alternative treatments, the clinical importance of the reported changes, the presentation of the outcome data, and the limitations of the approaches be considered when interpreting the results of chronic pain clinical trials (774). In IC/BPS clinical trials, particular attention should be paid to the composition of the study sample. Patients with long-standing disease or compromised bladder capacity or widespread pain ("central sensitization") might be less responsive to treatments directed toward the bladder itself. In addition, the concept of statistical versus clinical significance is paramount when interpreting objective responses to treatments. Investigators should, but rarely do, point out differences between statistical improvement and what they consider to be clinically significant improvement (775). As Gertrude Stein reportedly stated, "A difference, to be a difference, must make a difference". An increase in bladder capacity of 30cc may be statistically significant but clinically irrelevant. Number needed to treat and number needed to harm data (776) may be particularly important in IC/BPS but have not typically been included in efficacy analysis.

CONCLUSIONS:

In 2022 for IC/BPS there are no accepted biologic disease markers that can be used for the assessment of response to therapy. The RICE IC/BPS case definition holds promise as a potential screening tool for IC/BPS in primary care. Multiple validated questionnaires exist to follow disease progression and response to therapy. The IMMPACT recommendations suggest that as well as symptom scores, any future study on a pain syndrome must involve more general assessments of psycho-physical functioning. International recognition of an agreed upon definition and inclusion and exclusion criteria of IC/BPS will help future studies to fulfill the highest standards available, and placebo-controlled,

double blind, randomized controlled trials, where possible, will provide the highest level of evidence to move the field forward.

XX. THE IMPACT OF IC/BPS (QUALITY OF LIFE, COST)

Many IC/BPS patients experience a long delay from symptom onset to diagnosis, due to misdiagnoses (e.g. 'recurrent UTIs', 'overactive bladder') and a general lack of familiarity with IC/BPS by the medical community. Even after a correct diagnosis, IC/BPS symptoms often prove to be refractory to treatment. The impact of these symptoms can be profound. Numerous studies have demonstrated that overall well-being/ quality of life of IC/BPS patients is significantly lower than the general population in both physical and mental aspects (93,777-779), with a similar impact as other debilitating chronic conditions such as rheumatoid arthritis and dialysis-dependent renal failure (777).

The individual and societal costs of IC/BPS are substantial. Mean annual direct medical costs for IC/BPS patients are approximately twice that for those without IC/BPS (780,781), and mean annual indirect costs (work loss, reduced productivity) are 84% higher (782). One study found that 10% of IC/BPS patients were unable to work at all due to their symptoms (783), and another found that 19% of employed IC/BPS patients had experienced lost wages due to their symptoms in the preceding 3 months (784).

XXI. PRINCIPLES OF MANAGEMENT

The information currently available in the literature does not lend itself to easily formulating a diagnostic or treatment guideline that will be acceptable to a wide range of practitioners. Different groups of "experts" would undoubtedly create different "best practices". (785) The compromise approach devised by an experienced cross-section of urologists and gynecologists from around the world at the International Consultation on Incontinence 2004 meeting in Monaco (60) and subsequently modified at the 2008 and 2012 meetings in Paris (786,787) and the 2016 Tokyo meeting (1) has been reviewed and updated by the committee and allows for significant latitude to reflect varying individual practice patterns and to account for patient preference.

An underlying principle is that, where possible, decisions on the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) and Hunner lesion disease (HLD) should be evidence based (788). Unfortunately, high level evidence of efficacy is lacking for many common treatments, either because such studies have not been done, failed to differentiate patients with HLD from IC/BPS and/or failed to demonstrate efficacy vs placebo. (789-792) . While there is no shortage of literature on treatment trials, the vast majority have small sample sizes and effects of treatments cannot be estimated with precision. (547)

Another principle is that we should be guided by patient perceived and driven outcomes. Newer symptom scores are based on this principle (745,754) and the Food and Drug Administration in the United States is asking pharmaceutical companies to develop more patient reported outcome measurements as a requirement for successful future drug development. (793)

Many patients prefer noninvasive therapies (794), and it would seem reasonable to start with physical therapy and/or oral or intravesical therapies as per patient preference if conservative non-medical interventions (i.e. education, diet, behavioral modification, stress reduction) fail to result in significant symptom amelioration. Use of surgical therapies should be approached with some caution. It has been reported that women with IC/BPS have had significantly more pelvic surgeries than controls, and the majority were performed prior to diagnosis of BPS, possibly for pain related to undiagnosed BPS. (795,796). This is one of many health disorders where patient education is critical and allows the patient to be instrumental in developing a personalized treatment algorithm that they can modify based on their ongoing quality of life.

Two major constructions may provide the foundation for the basic principles of management.

The first is the early diagnosis of Hunner lesion disease through local cystoscopy or cystoscopy under sedation with bladder distention. This changes the treatment algorithm and can provide an initial surgical option through direct treatment of the lesion that yields generally reliable good clinical results, albeit not permanent. (20,29,32) . These results may surpass those in patients with unremarkable histopathological findings on cystoscopy and biopsy. (797)

The second is the natural history of interstitial cystitis/bladder pain syndrome. Up to one half of all patients may exhibit symptom improvement with time, with or without regular follow-up and receiving a new treatment. (4,5). Symptom duration is associated with more severe symptoms only in limited populations. Symptom duration is not associated with risk for chronic overlapping pain comorbidities or mental health comorbidities (76,134). To the extent we can prevent catastrophizing we can expect less long-term pain symptoms. (133,798)

As no single treatment works well over time for a majority of patients, the treatment approach should be tailored to the specific symptoms of each patient and a multidisciplinary approach may be required with input from primary care providers, registered dietitians, physical therapists, pain specialists, gastroenterologists, and gynecologists and urologists with expertise in management. (799)

Time tends to be the ally of the patient and the provider. It does not make sense to throw a wide variety of treatments at the patient immediately upon determining the diagnosis. There is no long-term advantage, and one loses the benefit of the often-salutary natural history of the disorder, prone to symptoms waxing and waning. If your initial multimodality therapy is ineffective, the practitioner has nowhere to go but more invasive and possibly more morbid therapies that may or may not relieve symptoms. It is better to follow conservative principles, allay patient anxiety and catastrophizing, and begin a specific intervention, adding to it if necessary or substituting another therapy if it is ineffective.

Treatment strategies should proceed from conservative to less conservative in the majority of patients. Of course, symptom severity, clinician judgment, and patient preference will play key roles in the decision as to where in the algorithm to begin therapy. In the rare instance when an end-stage small, fibrotic bladder has been confirmed and the patient's quality of life suggests a positive risk-benefit ratio for major surgery, reconstructive surgery can be considered early in the algorithm. Pain management should be continually assessed in all patients.

XXII. MAJOR FINDINGS FROM THE MAPP RESEARCH NETWORK

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network was established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), to study IC/BPS and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). For research purposes, these conditions are collectively referred to as urologic chronic pelvic pain syndrome (UCPPS) (800). The MAPP Network includes investigators with diverse clinical and research expertise, including in urology, gynecology, non-urologic chronic pain conditions, epidemiology, biostatistics, molecular and cellular biology, neurobiology, psychology and psychometrics, microbiology, and basic science pre-clinical animal models, among others. The group uses this multi-disciplinary expertise to promote a systemic characterization of UCPPS that extends beyond a sole focus on the urologic system to include a broad scope of potential physiological contributors.

During its first phase (MAPP I, 2009-2014), the MAPP Network characterized 424 UCPPS patient participants (233 females and 191 males with a clinical diagnosis of IC/BPS or CP/CPPS) in a central 12-month prospective cohort study (801). This study design was observational ('treated natural history') with the participant's physician managing clinical care, including prescribing treatment. Participants were assessed in an initial baseline "deep phenotyping" session that included numerous urologic and non-urologic patient-reported measures to determine symptom profiles, a physical exam, quantitative measures of pain sensitivity, and neuroimaging (via fMRI) to examine central nervous system structure/function, as well as collection of diverse biological samples for characterization of biomarker and microbiome profiles. UCPPS participants were followed prospectively for one year with additional in-clinic data and samples collection and on-line patient-report assessments to compare baseline factors to clinical phenotype and changes in underlying biology over time. In addition, 415 healthy control and 200 "positive control" (i.e., patients with diagnosed non-urologic chronic overlapping pain conditions [COPCs]) participants were characterized through an identical baseline deep-phenotyping visit. To complement the clinical studies investigators developed relevant animal models for UCPPS to test hypotheses on pathophysiology and provide a platform for in vivo studies based on MAPP Network clinical insights. All studies were highly-integrated to promote a systemic characterization of UCPPS and designed to address the MAPP Network's central goals of providing an improved evidence-foundation for development of future clinical studies, and ultimately to improve clinical management. In the second phase of this program (MAPP II, 2014-2022), the Network is characterizing UCPPS patient participants at baseline and during an extended 36-month observational period, as part of the Trans-MAPP Symptom Patterns Study (SPS) protocol. This study is in progress and will expand the patient phenotyping greatly from the first phase.

A detailed summary of the MAPP network findings to date has been published (802). Below is a brief summary of some of the potential clinical implications of these findings.

Multimodal Management. A high percentage of UCPPS participants had accompanying non-urologic COPCs, which suggests an important role for multimodal management and the frequent need for therapies that extend beyond the pelvic viscera. This finding also raises the question whether patients would do best managed in medical environments capable of addressing these varied needs, i.e., "Centers of Excellence."

Prognosis. MAPP Network studies have provided novel insights into symptom severity in UCPPS patients, finding that those afflicted with COPCs such as IBS, CFS, and FMS frequently endorse the highest pain severity and, perhaps not unexpectedly, have a higher risk of depression and anxiety. This information is critically important for the clinician from the perspective of identifying other "therapeutic targets" and patient counseling. Improved prognosis of UCPPS patient's symptoms over time (e.g., likelihood of worsening or improving) is one of the major clinical goals of the MAPP Network and is being further addressed in the extended observational period in the MAPP II study.

Etiological crossover. In standard urological practice, there is a tendency for men presenting with pelvic pain of unknown etiology to be classified within the general context of "prostatitis" (Prostatitis Type III, CP/CPPS), a condition associated with limited effective therapies. Data generated within the MAPP Network reveal a strikingly high prevalence of painful bladder filling and/or painful urinary urgency in male participants, suggesting a clinical and perhaps etiological crossover between IC/BPS (predominately female) and CP/CPPS (male). This finding illustrates the importance for clinicians to query male patients with chronic pelvic pain about bladder symptoms, as an affirmative response may lead to a change in diagnosis and subsequent therapy.

Urological Pain & Urinary Urgency-Frequency Outcomes. To date, it has been common to combine pain, irritative voiding symptoms, and other measurements, such as quality of life, together to derive a composite score and use that to assess outcomes of clinical trials and track clinical progress. One of the most important findings of MAPP I is that this approach may not be appropriate. The MAPP Network has shown urological pain and urinary urgency/frequency each have a different impact and severity pattern over time, and thus should be assessed separately in UCPPS patients in both a research and potentially clinical setting. This has major implications for the design of research studies and in terms of how clinicians follow patients in standard practice. Just as important, new instruments based upon these findings may impact how outcomes (i.e., improvement) are assessed and patient cohorts screened in future clinical trials.

Symptom Flares. Once a diagnosis of UCPPS has been made, clinicians typically begin therapy to treat pain that is known to be chronic, but is often assumed to be stable in severity and character. MAPP Network symptom flare data has dispelled this traditional notion by demonstrating that flares occur in almost all patients with widely differing frequencies, severities, durations, symptoms, and triggers. The finding that flares are common and can have a very profound psychosocial impact strongly suggests they need to be a priority in clinical evaluation and management. An understanding of flare characteristics can be helpful to selection of therapy emphasizing mitigation of flare-specific symptoms. For example, factors that trigger symptom flares (e.g., foods, beverages, physical activity) may need to be modified in a patient-centric manner and as part of a systemic approach to management. In addition, individualized strategies for addressing flares need to be developed based on an understanding of the patient experience rather than preconceived approaches. These therapies may be as simple as a warm bath or control of constipation to more aggressive interventions such as intravesical instillations.

Psychosocial Dysfunction. One of the primary clinical goals for UCPPS patients is to improve their quality of life. Many clinicians (and patients) make the assumption that once symptoms improve, the quality of life will similarly improve. MAPP Network findings

have demonstrated that this may not be the case if the patient has substantial coexisting psychosocial comorbidities or severe non-urologic pain. Furthermore, psychosocial dysfunction (i.e., depression, anxiety, catastrophizing behaviors) was more commonly identified in patients with co-morbid non-urological symptoms and was associated with more severe UCPPS symptoms. Therefore, we may need place greater emphasis on early identification and treatment of non-urologic symptoms and psychosocial dysfunction as separate and exacerbating clinical factors in UCPPS.

Pain – Centrally acting Therapies. MAPP Network insights into structural and functional brain changes in UCPPS have revealed similarities to other chronic pain syndromes and confirm that the pain some UCPPS patients experience is more complex than simply neuropathy localized to the pelvis. Importantly, these observations may explain the frequent favorable response to centrally acting therapies for some UCPPS patients (being investigated further in ongoing MAPP II studies) and provide potential new targets for future medical or even surgical interventions. In MAPP I studies quantitative sensory testing (QST) has demonstrated global pain processing abnormalities in UCPPS patients, particularly notable in those UCPPS patients with concomitant pain beyond the pelvis. While the potential utility of neuroimaging approaches in clinical management (versus research studies) will need to be further weighed, QST is relatively simple to apply and may ultimately be useful for clinical use to phenotype patients for selective therapies.

Biomarker anomalies for diagnostic algorithms. Although not yet validated for clinical use, the development of biomarkers for UCPPS in the MAPP Network is showing promise with initial studies showing correlation between markers (such as toll-like receptors) and distinct clinical features. Identification of subgroup of UCPPS patients who over- or under-express specific biomarkers (or a panel of biomarkers) may help us understand underlying mechanism, identify new molecular targets, predict responsiveness to therapies, and may add predictive value to UCPPS diagnostic algorithms in the future.

Antibiotic Stewardship. The majority of UCPPS patients have had multiple unsuccessful empiric courses of antibiotics throughout their clinical history without improvement in symptoms. Therefore, routine use of antibiotics in the absence of an identified infection is discouraged. Newer molecular-based techniques used in the MAPP Network have the potential to uncover a wide range of organisms in UCPPS patients that would be missed using standard culture methods. The identification of new bacterial genre, as well as any changes in microbial diversity between patients and healthy individuals or between patients with distinct symptom profiles holds great promise in characterizing new host-microbial relationships in UCPPS. These insights may promote new approaches to treatment or prophylaxis in some patients.

XXIII. FUTURE DIRECTIONS IN RESEARCH

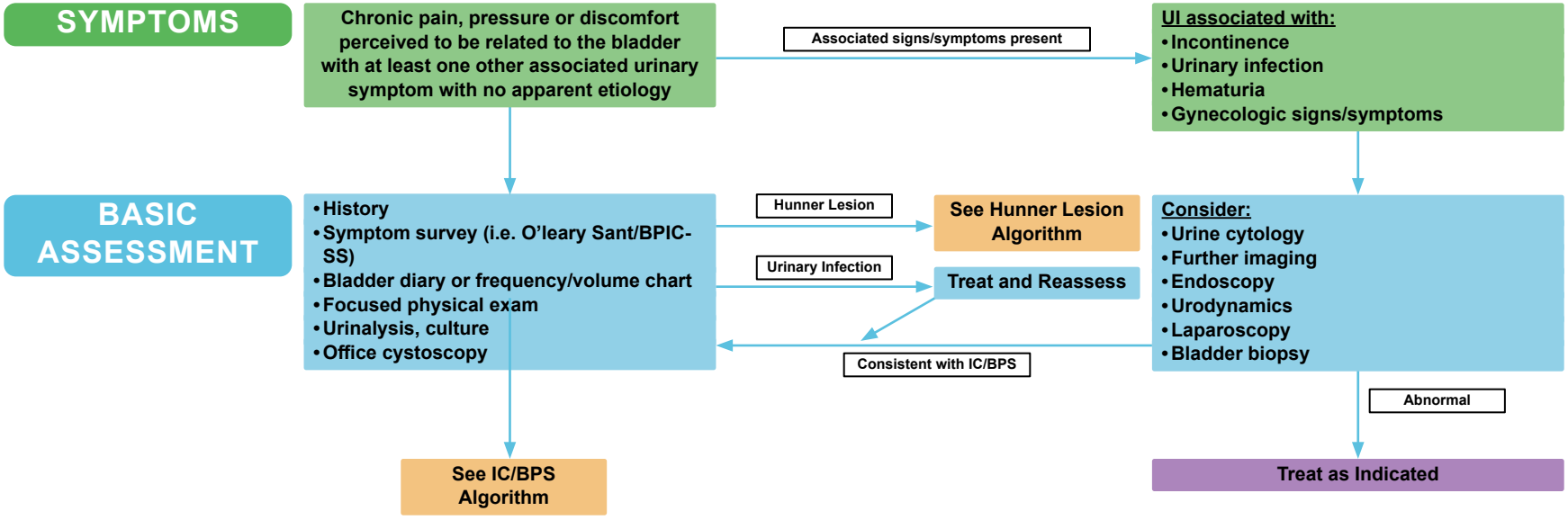
The committee believes that further research is needed in many broad areas:

1. Pathology of IC/BPS
2. Biomarker development
3. Immunology of IC/BPS
4. Neurological aspects with particular attention to the relationship of IC/BPS to overactive bladder
5. The relationship of IC/BPS to chronic prostatitis/ chronic pelvic pain syndrome in men

The following specific issues would benefit from major research initiatives:

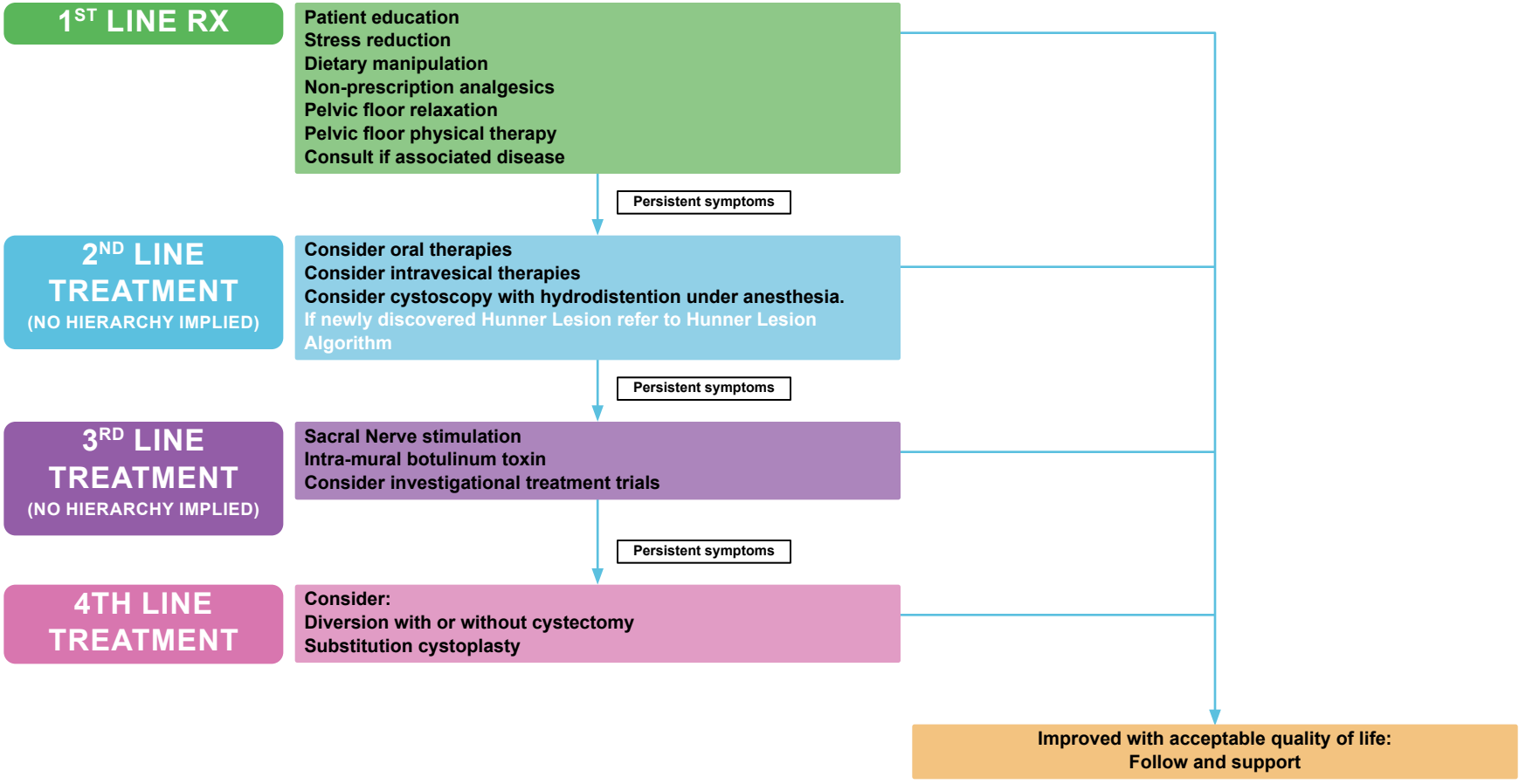
1. To improve symptom-based classification to identify the degree of bladder and non-bladder symptoms.
2. To identify bladder-specific pathology (urothelial changes, ulcer, hypervascularity and the potential role of narrow band imaging (803). Does the degree of true bladder inflammation correlate with results from specific treatments? Are there other markers that could be used to segregate therapeutic approaches? For the diagnosis of a Hunner lesion, using a cystoscope is indispensable. Checking for Hunner lesions using narrow band imaging has been reported to be useful and could improve diagnostic accuracy of Hunner lesions.
3. Further consensus to bridge the Asian concept of the hypersensitive bladder with the Western concept of bladder pain syndrome must continue.
4. To identify a bladder pain syndrome-specific biomarker (NGF or other neurotrophic factors, angiogenic growth factors, urothelial markers such as antiproliferative factor, cytokines/ chemokines profile, uroplakin [antibody, splice variant]).
5. To identify bladder-specific or systemic immunological processes (cytokines/chemokines profile). Such research may also help to identify the difference in the disease process between bladder pain syndrome and over active bladder (lower urinary tract symptoms with and without pain, respectively).
6. If we can identify the “bladder-related” and “nonbladder” (=outside the bladder) components that contribute to the symptoms, we should be able to develop the agent(s) to control bladder pain based on its pathology.
7. Establish patient data bases in different regions and conduct longitudinal follow-up to understand the natural history of the disease and to examine the differences in disease natural history among regions.
8. Develop an easy-to-use tool for non-specialists to readily identify co-morbid conditions that may impact on the need for additional consultation and suggest specific treatment pathways.
9. Develop a simple, non-invasive diagnostic test for IC/BPS.
10. Develop a practical multi-disciplinary care model and test it in various settings. This would include psychological interventions for those with psychological comorbidities, dieticians, physiotherapists, pain specialists, and patient support groups in addition to a specialist for any associated non-bladder related disorders.
11. Study the clinical utility of psychological screening tools in phenotyping and how this might impact clinical outcomes
12. Develop a screening tool to accurately identify HLD based on clinical and non-invasive factors.
13. Establish what role if any intravesical lidocaine has in diagnosis and phenotyping
14. Develop science-based recommendations to maximize the benefit of dietary modification in preventing and alleviating symptoms.

DIAGNOSIS: INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME (IC/BPS), HUNNER LESION DISEASE (HLD)



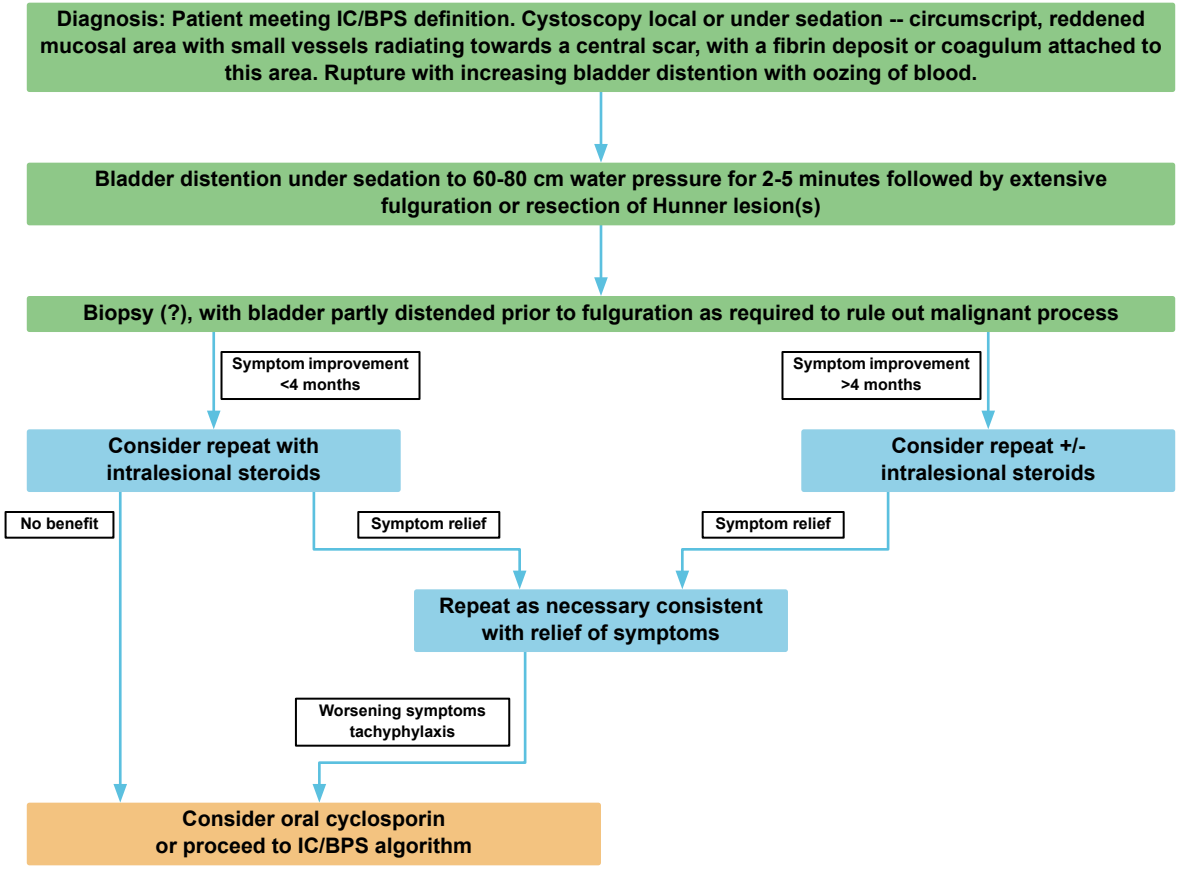
Algorithm for Diagnosis/C/BPS and HLD symptom complex: 2023 International Consultation an Incontinence.
Early cystoscopy is recommended to differentiate IC/BPS syndrome from MLD.

TREATMENT: INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME (IC/BPS)



- Pain management is a primary consideration at every step of the algorithm
- Patient enrollment in an appropriate research trial is a reasonable option at any point
- Consultation with a provider experienced in treating IC/BPS and Hunner lesion disease should be considered
- Only DMSO and pentosan polysulfate are approved by FDA for IC/BPS Indication

HUNNER LESION DISEASE



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COMMITTEE 19

MANAGEMENT USING CONTINENCE PRODUCTS

Co-Chairs
Fader, Mandy (United Kingdom)
Murphy, Catherine (United Kingdom)

Members
Bliss, Donna (United States)
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Cottenden, Alan (United Kingdom)
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Ostaszkiewicz, Joan (Australia)

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MANAGEMENT USING CONTINENCE PRODUCTS

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APPENDIX 1 2013

APPENDIX 2 2013

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LIST OF ABBREVIATIONS

AB ..... Antibiotics.
ABP ..... Antibiotic prophylaxis.
ASB ..... Asymptomatic bacteriuria.
AUR ..... Acute urinary retention.
BWU ..... Bodyworn urinal.
CAUTI ..... Catheter-associated urinary tract infection.
FI ..... Faecal incontinence.
HRQOL ..... Health related quality of life
IAD ..... Incontinence-associated dermatitis.
IASD ..... Incontinence-associated skin damage.
IC ..... Intermittent catheter(isation).
ICD ..... International classification of diseases.
IUC ..... Indwelling urethral catheter(isation).
KHQ ..... King's health questionnaire.
LT ..... Long-term.
PD ..... Perineal dermatitis.
PFMT ..... Pelvic floor muscle therapy.
QOL ..... Quality of life.
RCT ..... Randomised control trial.
SCI ..... Spinal cord injury.
SPC ..... Suprapubic catheter(isation).
ST ..... Short term.
SUI ..... Stress urinary incontinence.
UC ..... Urethral catheter(isation).
UDS ..... Urodynamics.
UI ..... Urinary incontinence.
UTI ..... Urinary tract infection.

A. INTRODUCTION

Not all bladder or bowel incontinence problems can be cured completely, and the challenge for those whose symptoms persist is to discover how to deal with incontinence to minimise its impact on their quality of life. This usually includes using continence products.

Our definition of products for the management of continence are those that that either enable the containment of bladder or bowel leakage (either inside or outside the body) or drain the bladder, including associated accessories and strategies to optimise use or reduce harm. Conservative interventions designed to **treat** symptoms (e.g., pelvic floor trainers) are included in Chapter 8 and in other chapters relevant to the patient group e.g., Frail Older Adults.

Even those whose incontinence is ultimately treated successfully may have to live with symptoms for a time - for example, while they wait for surgery or pelvic floor muscle training to yield its benefits – and they may temporarily use continence products during this waiting period. Others may use them as an adjunct to a treatment that reduces their leakage without eliminating it. Still, others may use products intermittently, limiting their use to periods or activities associated with troublesome leakage. However, some use products permanently, either following treatment that has not been (completely) successful or depending on their frailty, severity of symptoms and personal priorities – they are not candidates for treatment aimed to cure.

Successful incontinence management with products is often referred to as contained incontinence, managed incontinence or social continence, in recognition of the substantial benefits it can bring to quality of life even though a cure has not been achieved (1). A complete cure is not possible for many people who may continue to rely on containment products (2).

A wide variety of continence products exists, and the choice can be confusing. In this chapter, the goal is to provide the current evidence for healthcare professionals to make informed decisions as they choose – or help product users choose - between continence product categories and the most appropriate product(s) within a category. We have also aimed to make this information directly accessible to users.

In Section B this chapter provides overall guidelines for selecting products to assist with toileting, prevent or contain leakage, or address urinary retention, as well as those for incontinence-related skin and odour problems. The key elements of patient assessment are described, and classification of people into broad groups is suggested based on sex and gender , adult or child and the nature and severity of their incontinence. Each of the major product categories is then addressed (Sections D-P), and where possible - evidence-based recommendations for product selection and use are given. When little or no published data are available, expert opinion forms the basis of recommendations. Tables are provided summarising the user characteristics, priorities and contexts that commonly favour or discourage the use of each of the major product categories available. The chapter also includes (Section C) a review of the methodological challenges of conducting continence product evaluations and interpreting the results. The literature search strategy adopted for the chapter is described in Appendix 1.

In most product categories there are numerous different product designs for which there are no published data. Many are available for purchase by consumers without input from a healthcare professional. Even products that have received regulatory approval and are available through healthcare systems may have only been assessed for manufacturing processes and/or safety, depending on regulatory body requirements. Many products are therefore available without evidence of efficacy

Overall recommendation

- Our main message is that continence is often best managed by a 'mix' of different products – often used at different times or for different activities (day/night/home/away/sport). One product is unlikely to be effective for all occasions.
- To assist this, the International Consultation on Incontinence and the International Continence Society (ICS) have collaborated to make the material more accessible via a website hosted by the ICS at http://www.continenceproductadvisor.org. This interactive website provides current evidence to healthcare professionals and users to facilitate informed choices in selecting appropriate products and accessible, evidence-based advice on how to use them to best effect

B. OVERALL GUIDELINES FOR SELECTING CONTINENCE PRODUCTS

Suitable continence products are critical for the well-being and quality of life of product users and their caregivers. Sufficient concealment enables people with incontinence to protect their public identity as a "continent person" and avoid the stigma associated with incontinence (3, 4). Failure to do so can result in limited social and professional opportunities, jeopardise relationships and detrimentally affect emotional and mental well-being (5). Importantly, caregivers need to feel confident that the person(s) they care for will not be embarrassed publicly. Good product choice / use also

reduces the care level required to maintain hygiene, skincare, and laundry (6).

The intimate and stigmatised nature of incontinence means that issues relating to self-image can affect users' preferences when selecting products. This may be marked in younger people for whom body image may be significant and for whom disruption to normal social and interpersonal development may result in isolation or lack of access to normal experiences (7) (8). A key measure of product success is the ability to conceal the problem (9), and concealment may involve compromises: at times, the added reliability of products with a larger capacity than is strictly necessary may be preferred even though they may be less discreet when worn.

The range of products available can vary enormously between and within countries, depending on the funding available, healthcare policy, and supply logistics. In publicly funded healthcare systems, some products may be provided free of charge, based on cost-sharing policy, or reimbursed by insurers, whereas, in others, no support is available, and consumers must pay out-of-pocket. Additionally, the provision of continence services is not considered a priority by health system administrators in most countries, and this is especially true in developing countries (10) (11) (12) (13). In this context, this chapter and accompanying website form a useful resource that can foster greater awareness of product choice and help clinicians and users identify products that, although not readily available locally, may be sourced elsewhere.

1. PRODUCT CATEGORIES

Apart from those for addressing incontinence-related skin and odour problems, all the products described in this chapter can be categorised as in Fig B-1, according to whether they are designed to: (i) assist with toileting; (ii) help manage urinary retention; or (iii) prevent/contain urinary or faecal incontinence.

All toileting products can be useful for dealing with urine and/ or faeces except for handheld urinals which are just for urine. Containment/control products are subdivided into three overlapping classes: for urinary retention, urinary incontinence, and faecal incontinence. For example, someone with urinary retention is most likely to benefit from one of the products in the red ellipse (Fig B-1), while someone with urinary incontinence will most likely benefit from one in the blue ellipse. A patient experiencing both problems will need two products (one from each ellipse) or one product from the intersection of the two ellipses.

2. ASSESSMENT FACTORS

Assessment of a user's physical characteristics - such as anthropometrics, level of independence, mobility and dexterity, level of cognition and the underlying nature of the incontinence - will help determine the best product(s) for them. In addition, other practical and psychosocial considerations include user participation in selection (14), provision of adequate instructions for use (15) and the need for products to fulfil their function reliably and easily (7) (15) (16). The nature of the environments in which the products will be used, and the availability of caregivers are other important factors. Table B-1 summarises the key assessment elements although no evidence-based assessment tool exists. Specific guidance on assessment is provided within the subsections of this chapter.

Personal preference is known to play a substantial role in product selection (e.g. (17) and (18)), and information on the range of products that may suit an individual is important so that appropriate choices may be made. Education of users and / or caregivers is key to ensuring product use is optimal; this may range from straightforward instruction in the effective fitting and changing of absorbent products to more in-depth training in the ongoing care of, for example, a suprapubic catheter.

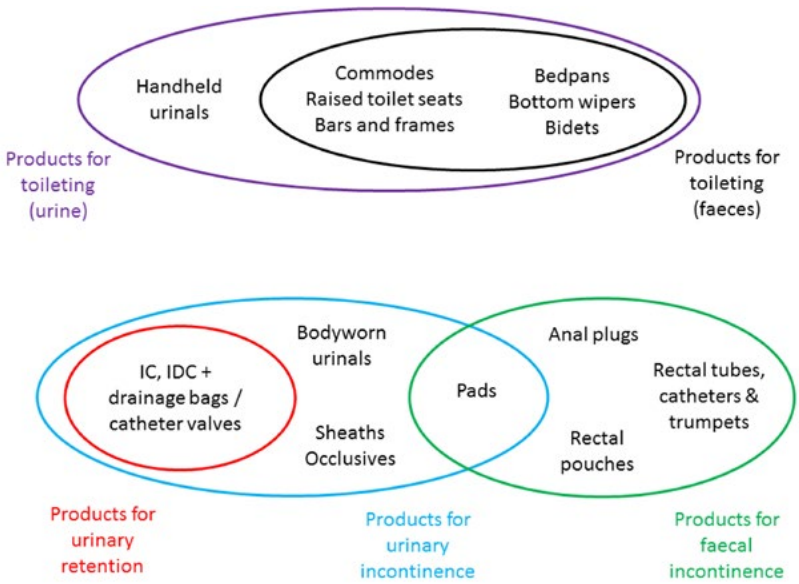


Fig B-1: Products for toileting (top) and for managing incontinence and / or urinary retention (bottom).

Table B-1: Key elements of assessing a patient and his / her environment

Element	Rationale
Nature of the continence problem	The frequency, volume, and flow rate of the incontinence influences product suitability.
Sex & Gender	Males may consider and prefer sheaths as a more masculine option to pads. Females may be attracted to products that are more feminine in design and presentation. Some 'unisex' products like absorbent pads have different designs that work better for men (or women).
Physical characteristics	Anthropometrics (e.g., height and waist, thigh, penile circumference) will influence the comfort and effectiveness of a product.
Cognition	Cognitive impairment can affect the person's ability to manage the product. Products that resemble usual underwear (e.g., some absorbents) may be easiest to manage. Products that have health implications if used incorrectly (e.g., mechanical devices or catheter valves) should be avoided if cognitive impairment is likely to preclude correct and safe use.
Mobility	Impaired mobility may make some product choices impractical or require toilet or clothing modification to use the product effectively.
Dexterity	Problems with hand or finger movement can make it challenging to use some products (e.g., taps on leg bags, straps with buttons).
Eyesight	Impaired eyesight limits effective application and management of some products
Leg abduction problems	Difficulty with abduction can make the use of some products impractical or ineffective.
Lifestyle and environment	Daily activities and environment can influence product choice; a mixture of products may provide optimum management. Different products may be most satisfactory for daytime and going out (when discreetness may be a priority) and night-time or staying in (when comfort may be a priority), for holidays (when laundry and / or large quantities of disposables may be a problem) or for use at work. The proximity and accessibility to a toilet may be key.
Independence / assistance	If a caregiver is required to apply or change the product, it may be important to involve them in selecting it and establishing their willingness and ability to use it.
Laundry facilities	Washable pads and bed linen may be very heavy when wet and take a long time to dry. It is important to check that the person doing the laundry has the ability and facilities to cope.
Disposal facilities	The ability to dispose of the selected products appropriately, safely, and discreetly needs to be considered.
Storage facilities	Some products – notably, pads for heavy incontinence – can be bulky. Adequate space to store supplies between deliveries / purchases needs to be available.
Personal preferences	Different people like different products, and where possible, patients should be given a choice of products with which to experiment to determine the most satisfactory product.
Personal priorities	Everyone wants to avoid leakage, but other factors such as discreetness may be more or less important to individuals or vary according to different contexts and activities.

3. MAIN USER GROUPS

Seven primary user groups are identified in this chapter:
- People with urinary retention.
- People who need help with toileting / toilet access.
- Females with light urinary incontinence.
- Males with light urinary incontinence.
- Females with moderate / heavy urinary incontinence.
- Males with moderate / heavy urinary incontinence.
- People with faecal incontinence.

An individual may belong to more than one group. Each group includes children and young people: their products are broadly similar to those for adults.

4. CHOOSING BETWEEN PRODUCT CATEGORIES

Tables summarising the user characteristics, priorities, and contexts that favour or discourage using each of the product categories for six of the seven user groups are available in the 6th edition of ICI (19) and a user-friendly format on the www.continenceproductadvisor.org website. Assistance with choosing appropriate products for the first group (people with urinary retention) is given in Section L - indwelling catheters and Section M - intermittent catheters.

The same product will not necessarily suit all people, even if the result of their assessment is similar. Thus, providing access to a range of products to test will help determine the most satisfactory choice. Similarly, priorities vary between users; for example, some will opt for a bulky, less discreet pad to achieve an acceptably low risk of leakage, while others will see the balance differently. Choosing between products or strategies can be complex. A product decision aid to help users and healthcare professionals choose between products has been developed (20) and incorporated into the continence product advisor website. Other relevant aids to decision-making include a support tool, developed through expert consensus, to assist non-specialist healthcare professionals to identify factors to help identify appropriate incontinence care options (19).

A mix of products drawn from more than one category may provide the best solution; for example, needs may vary between day / night or home / away.

5. SUMMARY

Continence products can play an important role in enhancing the quality of life and reducing the stigma of incontinence of those who are awaiting treatment; are waiting for treatment to take effect; elect not to pursue cure options; are unable to be fully cured and are living with an ongoing bladder / bowel problem.

6. RECOMMENDATIONS

- Users often require / prefer a mix of different products for use at different times and for different activities to achieve optimum management **Grade of recommendation C**
- Incontinence should be actively managed with products to minimise the impact of incontinence on quality of life **Grade of Recommendation C**.
- Users should be carefully assessed (and reassessed periodically) to select the most appropriate products **Grade of Recommendation C**.
- Users should be offered a range of products that are appropriate for their needs so that they can make informed choices. **Grade of Recommendation C.**

C. PRODUCT EVALUATION METHODS

This section aims to assist those planning clinical trials of products. There have been relatively few large clinical trials of continence products, and for most product categories, research evidence to guide the selection of individual products / designs / features is limited and, in some cases, absent.

Measuring the performance of continence products is challenging. Manufacturers modify and change their products regularly - in terms of both materials and designs - and this limits the long-term validity of research results. There are also complex issues regarding research questions, study design, product representation, blinding, and sample size (20), which are discussed below.

1. METHODOLOGICAL CHALLENGES

Part of the complexity of product evaluations stems from the sheer number of product categories and brands available, meaning that many different comparisons could be made. Table C-1 illustrates the problem using a hierarchy of questions relating to absorbent products. So, in this example, once the decision is made to choose an absorbent product in response to question 1, successive further questions can be used to narrow the choice to a specific product brand. Questions at any of these levels may form the basis for research projects.

In the field of absorbent products, the practitioner and / or patient wishes to know whether to use an underpad or a bodyworn product, a reusable or a disposable, a diaper or an insert (if they select a bodyworn), a diaper with internal elastication (standing gathers) or without and, finally, which of the many diaper brands is likely to suit them best. This final question is the most pertinent for the practitioner (who may already have made decisions about questions 1-4, Table C-1), but it is particularly problematic because of the high rate of product change. By the time the results of a clinical trial of product brands are known, many test products will have been modified, and the results will have limited value for selection. However, these 'single design' studies do have value in demonstrating the range of performance between the brands within a product design category, and where objective measurements can be made (for example, of leakage performance), they can allow for comparisons to be made. Single design studies are also helpful in promoting product improvement by revealing common problems experienced by patients and exposing particularly poor products or poor product features which are amenable to change by manufacturers.

Table C-1: Levels of research questions

1. Which product category (e.g. catheter, sheath, absorbent pad)?
2. Which design of product design (e.g. pull-up or diaper design of pad)?
3. Which material type (e.g. reusable or disposable)?
4. Which features (e.g. with / without elastic gathers)?
5. Which product brand?

Overall product designs, generic features and classes of materials change much less frequently and attempting to answer questions 1-4 (Table C-1) is likely to lead to more long-lasting results with value beyond the lifetime of the brands tested. Many researchers have attempted such studies, but these have frequently been confounded by problems with product representation.

The single greatest (and most frequently overlooked) threat to the validity of clinical trials of products is the selection of the brands entered into the study to represent the various designs. Evaluations of several product variants of a similar design (e.g. different brands) have shown that patient 'overall opinion' scores can vary by as much as 70 percentage points between apparently similar products (21). Accordingly, in an evaluation to compare different designs, the selection of one or more products to represent each design is crucial. Studies that have purported to compare different designs or materials have often included a small number (most often just one) of arbitrarily selected product(s). Generalising the results of such studies to whole product groups (e.g. reusable underpads, or disposable bodyworns) is meaningless and misleading. It is perfectly possible to select (either by accident or design) a particularly 'good' product from one group and a particularly 'poor' product from another. Therefore, a well-designed study will be seriously flawed if there is no clear process or pilot study to determine and justify the choice of particular brands. Even with a systematic process of product selection (or preferably a pilot study), it is unwise to select a single brand to represent a whole group of products, and selecting a small group of brands (e.g. three) is preferable. This allows for any 'within group' differences to be detected and helps to demonstrate the 'representativeness' of the products selected.

The most controlled method of testing different designs, materials or features of products is to make up experimental batches that differ only in the aspect of interest (e.g. the material or the feature), and a small number of studies have attempted this (21) (22). However, experimentally made products are not usually identical to those available on the market, limiting their product selection value.

It is common for practitioners to be asked (by their employers or companies) to do a small evaluation or trial – sometimes to 'test out' a new product and sometimes to help choose between competing brands for bulk buying. Such trials should be approached with caution; they can be very demanding, and their results may be of very limited value, even for local use. The methodological challenges identified above still apply but are compounded by the small sample size and restricted product selection. These studies are likely to be helpful only for identifying gross product shortcomings or benefits.

2. RESEARCH DESIGN

A randomised controlled trial is not possible for clinical trials of products in most categories simply because a 'control' product does not usually exist. Nor is there a 'standard or reference' product to act as a control, and comparisons with 'standard practice' (i.e. the product currently in use) are prone to bias.

Although it is methodologically simpler (and more robust) to compare only two different product groups, it is more clinically relevant to compare several competing groups using a multiple cross-over design, with valid comparisons. For example, there are four main design groups of disposable bodyworn pads for moderate / heavy incontinence (inserts, diapers, pull-ups and T-shaped). Evaluation of all four groups together is much faster (and therefore gives more long-lasting results) and more cost-effective than several serial studies. Cross-over trials are vulnerable to order effects, and randomisation of the testing order should be carried out using Latin squares (23) to ensure balance.

It is important that clinical trials of single designs of products (which aim to enable selection of particular product brands) are comprehensive (i.e. cover all the available products) because otherwise, manufacturers can justifiably claim that, although their product may be similar to one of those tested, even subtle distinctions may lead to clinically important differences.

A further problem with research design is the blinding of products. Different products have different appearances, and it is impossible to blind subjects or staff to the product in use. Products can be repackaged to assist anonymising, but this may have unwanted effects on the products and is expensive.

Previous product experience can also affect study results, particularly if a substantial proportion of subjects are currently using one of the brands included in the study. Therefore, it is important to record which products are in current use to add this data to the model used in the analysis.

2.1. Sample size and study power

Studies that include more than two products (or two small groups of products) will need to be powered to make multiple comparisons. As the number of products included in the study increases, the number of possible comparisons of pairs of products rises. This requires a corresponding reduction in the significance level (e.g., using the Bonferroni method for each pair-wise comparison to retain the overall level of significance - usually $p<0.05$). Thus as the total number of pair-wise comparisons increases, the likelihood of a type 2 error (accepting the null hypothesis when it is false) also increases.

Sample sizes, therefore, need to be calculated to allow for each pair-wise comparison. Sample size requirements rise rapidly if each subject does not test each product, and the number of products entered into a study must therefore be limited to avoid subject fatigue. As an example, a clinical trial of four product groups where the primary outcome variable will be binary (e.g. satisfactory / unsatisfactory) will require a sample size of approximately 80 subjects with an alpha of < 0.05 and d (difference) of 20%.

2.2. Outcome variables

Studies of product performance have most frequently used self-report questionnaires at the end of the product test period to assess participant ratings of product performance. Diaries of product-related events such as leakage, laundry generation and product consumption are also commonly included. Users in some absorbent pad studies have been asked to identify and prioritise aspects of product performance (24) (25) (26) to inform questionnaires, and Table C-2 shows the most common aspects of high priority to women with light urinary incontinence (25).

Outcome variables in studies designed to compare catheterisation strategies and / or catheter materials or other design features commonly encompass measures of urinary tract infection, tissue trauma and recurrent catheter encrustation leading to blockage (Section L).

Table C-2: Most common high priority items to women with light incontinence using absorbent products (25).

Daytime: % women (N=99)		**Night-time: % of women (N=81)**	
Hold urine without leaking	83.8	Hold urine without leaking	93.8
Contain smell	75.8	Stay in place	77.8
Stay in place	54.5	Contain smell	54.3
Discreetness	41.1	Comfortable when wet	54.3
Comfort when wet	40.4	To keep skin dry	48.1

Questionnaire items vary depending on the products being tested. For product groups where few studies have been carried out, it is particularly important to tailor questionnaires to user needs by asking study subjects to prioritise items and assess final questionnaires for content and face validity. One study has measured the test retest reliability of a questionnaire to assess sheath performance and found moderately good Kappa scores (around 0.7) when assessing the same sheath twice with four weeks between measurement periods (20).

Skin health, urinary tract infection, pain or discomfort are the main physical health consequences for containment products. Skin health (which can be rated by self-report or by skin inspection) has sometimes been used as the primary outcome variable (e.g. (27)). Urinary tract infection is an important outcome for invasive devices such as catheters, and it has also been used for pads (28).

Although leakage performance is frequently rated as a high priority by product users, good leakage performance is not adequate as a sole measure of patient satisfaction with performance. A single (or multiple) fatal flaw such as poor comfort, bulkiness, or poor fit may cause a product that performs well for leakage to be unacceptable to the patient for other reasons. Accordingly, aggregate measures - which assume that the overall performance of a product can be calculated using a weighted sum of the scores for specific aspects of performance (like comfort and freedom from leakage) -

are ill-advised. Therefore, patient overall opinion or satisfaction with the product should be used as the primary outcome variable (20).

Most incontinence-specific quality of life tools are designed to measure change after interventions to improve incontinence and include urinary symptoms. Therefore, these tools are likely to be insensitive to changes in the quality of life brought about by products designed to contain incontinence rather than reduce or prevent it. However, three quality of life measures have been developed specifically for trials of continence products or long-term catheters; one for absorbent products (29), one for intermittent catheters (30) and one for long-term catheters (31).

3. SUMMARY AND RECOMMENDATIONS

There is little published evidence on which to base summary and recommendations regarding methodology, and so the following summary points are all Level of Evidence 3 / **Grade of Recommendation C**.

- Evaluation of continence products is methodologically complex, and methodological weaknesses have hampered many attempts to provide robust product selection evidence.
- Product representation is critical to providing robust and generalisable data. The selection of products for inclusion in a study should be transparent and systematic. Several products should be included to represent a product group. In particular, care should be taken not to select a particularly good or a particularly poor product to represent a whole class of products.
- Multiple crossover designs are likely to be more efficient than randomised controlled trials for many products (e.g., pads), and therefore sample size estimation needs to consider the multiple comparisons that will be made.
- Outcome variables should include a patient (or caregiver) questionnaire including items that have been established as important to users.
- Diary data should be included to determine leakage performance, skin health, laundry, and product consumption.
- Incidence of urinary tract infection should be included when testing invasive devices such as catheters, but “significant” UTI/ bacteriuria must be carefully defined (Section L).
- The primary outcome variables should be patient overall opinion / satisfaction and patient preference.
- Health economics should be measured alongside product performance

4. PRIORITIES FOR RESEARCH

- The development of Quality-of-Life tools for users of continence products.
- Consistent use of a validated product assessment scale.
- Impartial product assessment that compares several products in the same category.

D. HANDHELD URINALS

Handheld urinals are portable devices designed to allow individuals to empty their bladder in circumstances where gaining access to a toilet is not possible or is inconvenient, often due to limited mobility or joint range of motion. To function effectively, handheld urinals must enable the user to empty his/her bladder comfortably, confidently, and without spillage during filling and emptying. Excessive physical effort should not be required. The main factors influencing a user’s capacity to successfully utilise a handheld urinal are listed in Table D-1.

Table D-1: The main factors influencing the capacity of a user to successfully utilise a handheld urinal.

• The position in which it will be used (e.g. lying in bed, sitting on the side of a bed, sitting back in a chair or on its front edge, standing, kneeling, crouching) together with the nature of the surface upon which the individual is being supported.
• The ability of the urinal user to move (with or without aids or assistance) into the required positions.
• Postural control in those positions, together with a hip range of motion, particularly abduction.
• The optimal direction of approach for positioning the urinal (e.g. anterior, posterior, lateral).
• Manual dexterity and strength to adjust clothing, initially position the urinal, maintain its position during voiding, remove the laden urinal post-void and empty or store it somewhere safe to avoid spillage.
• The ability to initiate a void, together with the volume typically voided.
• Cognitive functioning.
• Personal preferences and, where appropriate, the availability of assistance.

Handheld urinals are frequently made from moulded plastic, although single-use cardboard options are available. Some are equipped with handles to facilitate positioning and handling, and some are fitted with drainage bags to collect urine. Urinals designed for women are available in various shapes and sizes (some are quite small and portable), incorporating an interfacing opening that is often anatomically shaped to fit snugly against the woman’s body.

Those intended for men tend to vary less in design, typically having a narrow neck opening to accommodate the penis, and some are fitted with integral non-spill valves or adaptors to prevent the backflow of urine following use (32) (33) (34).

Some men may find that they can make their urinal by recycling household bottles or containers (33). Small, discrete, disposable and re-useable ‘travel’ handheld urinals are available for both men and women (32) (33).

As spillage is not always avoidable during the use of handheld urinals, particularly if supine, the use of absorbent pads to protect furniture, bedding and clothing can be a useful addition (35).

An example selection of products is shown in Fig D-1, Fig D-2 and Fig D-3.

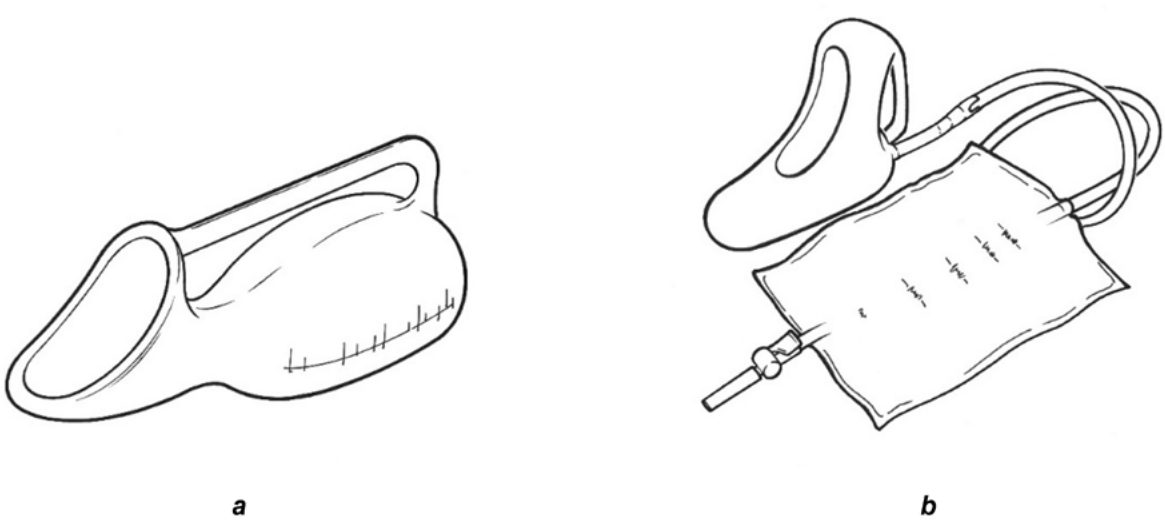


Fig D-1: Female handheld urinal (a) with drainage bag attached (b).

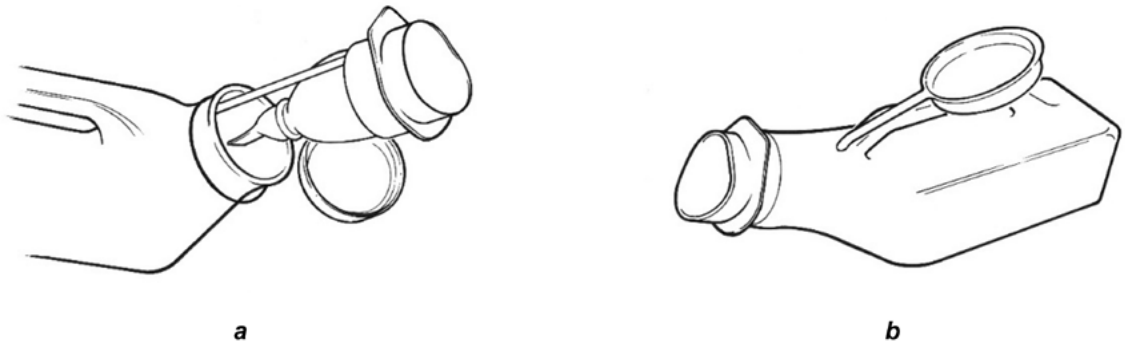


Fig D-2: Male handheld urinal with non-return (anti-spill) valve (a) and without (b).

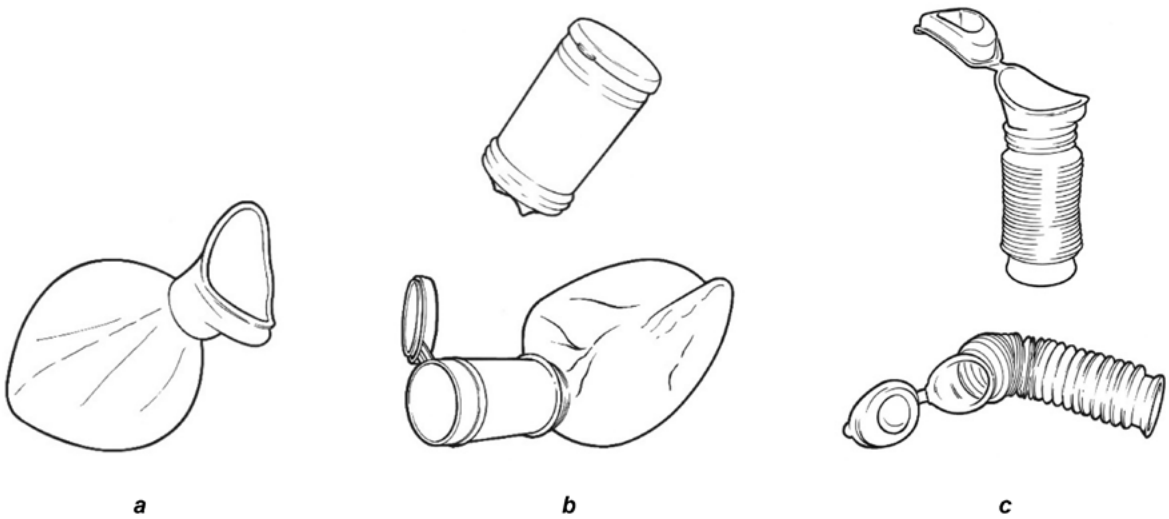


Fig D-3: Collapsible, handheld travel urinals: female (a); male (b) and unisex (c). The male and unisex designs are shown collapsed for storage (top) and ready for use (bottom).

1. EVIDENCE

The 6th International Consultation (36) highlighted a paucity of clinical trials examining the effectiveness of handheld urinals. There were no published trials of male handheld urinals at the time. The single-trial identified (37), involving a multi-centre cross-over evaluation of 13 female urinals, found that no single product suited all users. Many were successfully used when standing, crouching or seated at the edge of a bed/chair/wheelchair, but fewer were successful when seated back in a wheel/chair, and only one was identified to be reasonably effective in a lying / semi-reclined position. Of note, this study highlighted that there were fewer products to meet the needs of women with higher levels of dependence. Other work to develop and evaluate a novel, power-assisted female urinal that pumps urine into a holding reservoir highlighted mixed results in terms of reliability, size, weight, noise and aesthetics (38).

One exploratory study has been identified for inclusion in the current consultation. Farrington *et al.* (39) tested a disposable (pulpable) urinal, the 'Vernafem' with healthy volunteers (n=11), inpatients receiving palliative care on an oncology ward in hospital (n=9) and healthcare professionals (nurses or healthcare assistants) caring for inpatients receiving palliative care on an oncology ward in hospital (n=7). Data were collected through qualitative interviews to explore participant experiences of the urinal. The urinal was found to be acceptable, safe and effective, with many (but not all) participants preferring it to a conventional bedpan. Some design limitations were identified, including the urinal volume's adequacy and difficulties with correctly positioning the urinal. The authors concluded that while unlikely to be suitable for all patients, hospitals should consider offering a female urinal to patients receiving palliative care.

2. SUMMARY

- A super-absorbent polymer can be added to urinals prior to use to absorb and solidify urine (32) (35) (40) **(Level of Evidence 1).**
- Experimentation is often required to identify the optimal urinal for an individual (32) (34) (35) (37) (40) **(Level of Evidence 2).**
- Cleaning of handheld urinals is an important consideration. Cleansing with soap and water may be appropriate between episodes of use by a single individual at home. However, more robust methods that comply with the manufacturer's recommendations and local infection control policies will be necessary where users are multiple (34) (37) (40) (41) **(Level of Evidence 2)**.
- Men with a retracted penis may find that urinals developed primarily with women in mind can work well for them if they can tuck their whole penis and scrotum inside the urinal during use (33) **(Level of Evidence 3)**.
- The careful selection and adaptation of clothing can assist quick and easy use of urinals for both men and women (32) (33) (34) (35) (41) **(Level of Evidence 3)**.
- Expanding the toileting devices available to those in acute care settings to include a wider range of handheld urinals suitable for use by both men and women is recommended (35) (40) **(Level of Evidence 3)**.

3. RECOMMENDATIONS

Recommendations relating to handheld urinals are summarised in Table D-2.

Table D-2: Recommendations relating to handheld urinals.

- Handheld urinals should usefully form one of a range of options available to both men and women to manage their toileting needs, enhancing the quality of life of both the user and (where relevant) their carer(s) **(Grade of Recommendation C)**.
- Experimentation should be allowed to select the most appropriate urinal to meet individual needs and individual circumstances **(Grade of Recommendation C).**
- An individual should be offered different types of handheld urinals to manage in different situations **(Grade of Recommendation C).**

4. PRIORITIES FOR RESEARCH

- Evaluation of currently available male and female urinals to guide users, caregivers, and healthcare professionals.
- Development of the range of female urinals, particularly to meet the needs of those who are less physically able, unable to move to the edge of a bed/chair/wheelchair, and/or need to use a urinal while supine.

E. COMMODES, MOBILE SHOWER-CHAIRS AND BEDPANS

Toileting is a fundamental aspect of continence and personal care. Using conventional toileting facilities is a complex undertaking requiring, for example, core stability, balance, strength, range of movement and cognitive, sensory and perceptual skills to transfer to and from the toilet, adjust clothing, grip and manipulate toilet paper and other menstrual and bowel / bladder management products and adequate wiping or rinsing of the perineal area. Using toilets in public spaces requires locating and arriving at the facility in a timely manner. Gaining access to,and safely utilising, toileting facilities can represent a significant challenge for people with limited or impaired mobility and / or a range of other disabilities. Various strategies, assistive aids, and equipment exist to facilitate ease of access, independence in toileting and continence, and privacy and dignity. These include toilet seat raisers, toilet frames / surrounds, padded toilet seats, grab or support rails, bidets or personal cleansing/drying systems, bottom wipers, etc. (Table E-1), adaptations to clothing (e.g., use of Velcro instead of buttons), and the physical layout of toileting facilities.

Installation of these toileting aids or their latest designs may be lagging in health care facilities, however. A recent analysis of the environment of 20 contemporary nursing homes in Norway (42) revealed that their designs do not facilitate privacy and pose risks for safety; for example, the heights of toilets and sinks were not adjustable, there was inadequate space to place assistive devices such as walkers and canes, and soap, toilet paper holders, and handrails were often out of reach.

Although there is limited research examining the effectiveness of many of these assistive options for promoting continence, occupational therapists are well-positioned to offer individual assessments, including for those in the home setting (43) (44) (45) (46). Furthermore, occupational therapists can make appropriate and reliable prescriptions for the toilet and bathroom areas of patient homes

without the need for an actual home visit, using digital photographs taken by family members, clinical information about the patient, and an equipment list (47). The results of this study completed prior to the community lock-downs during the COVID-19 pandemic are timely and relevant given changes to remote home assessments that were necessary during the pandemic and may continue.

Where an individual cannot access a toilet quickly and safely, conventional, or adapted alternatives - such as commodes, mobile shower chairs and bedpans - may be appropriate. In lieu of a toilet, commodes are static or mobile pieces of equipment that comprise a chair-like frame incorporating a toilet seat under a removable pan (disposable or washable) which is positioned to receive urine and faeces. Mobile shower-chairs (sometimes called sani-chairs) are also available. These are waterproof chairs on wheels that incorporate a toilet seat and are designed to be manoeuvred over the top of a conventional toilet once an individual is seated on them (48) (49).

Previous research highlighted concerns with the stability and - therefore - safety of some commode designs and their limitations in terms of aesthetics and comfort (48) (50) (51) (52). The appearance of a commode and the invisibility of its collection container are features particularly important in a home environment (48) (52) (53). Additional considerations when using these devices in the home setting are lingering unpleasant odour and the availability/willingness of someone to empty and clean it as a caregiver, rather than the commode user, typically empties and cleans a commode used in the home (53). Odour reduction is addressed in section P.

For persons with a spinal cord injury (SCI), there is a complex array of sometimes competing factors that need to be considered when prescribing shower-chairs/commodes (54); for example, the need for large rear wheels to facilitate propulsion may complicate sliding transfers to and from the equipment. While folding frames permit portability, they are heavier than fixed frames. Additionally, commodes pose a risk of pressure injuries for these individuals (55) (56-58). Assessment for toileting assistive devices for SCI should include a review of current bowel care routines, functional capacity to undertake toileting and bowel care, postural stability and transfers to and from the shower chairs/commodes, and risk for pressure injuries skin integrity and interface pressure mapping. However, the quality of evidence about the design and performance of mobile shower-commodes used by adults with SCI is fair to poor, lacking randomised control trials (54).

Bedpans are receptacles designed to be positioned beneath an individual who needs to empty their bladder or bowels while in bed or perhaps while seated on a conventional chair. Bedpans can be broadly categorised into concave pans (rounded, triangular-shaped with a curved base and sloping front to back), cut-away pans

Table E-1: Main categories of assistive aids and equipment for toileting

Toilet seat raisers	• Contoured toilet-seat shaped extensions that fit directly onto toilet bowls once lid/ seat have been raised. • Range of heights available. • Usually fitted with brackets for secure fixing. • Some are available with integral lids.
Toilet frames/surrounds	• · Metal frames positioned around the toilet to provide armrests to assist transfers. • May incorporate a toilet seat raiser or a conventional toilet seat and lid. • May be height and width adjustable. • Freestanding or fixed to the floor.
Grab or support rails	• Fixed to an adjacent wall, floor and/and ceiling. • Wide variety of styles, including fixed and fold-away designs. • Help improve stability and confidence during transfers and adjusting clothing. • Research examining the most effective configuration of rails concluded that the use of two vertical bars resulted in the least anterior-posterior displacement (and therefore greatest stability during transfers) and was rated highly by healthy older participants as well as those living with hip replacements and strokes (54) **(Level of Evidence 3).**
Bidets and personal cleansing systems	• Combined with, or integral to, a toilet, it may enable those without sufficient hand function or balance to reach the perianal area to cleanse without the need for assistance (55) (56) **(Level of Evidence 4).**
Bottom wipers	• Grip toilet paper or wet wipes on an ‘arm’ to assist those who are unable to reach to cleanse the perianal area. • Designed to be used from the front of the toilet. • Available in various designs, including folding for discrete transportation outside the home (may include a carry case). • Some have buttons to release the paper/wipe after use.

Table E-2: The main factors influencing the appropriateness of a commode, shower-chair or bedpan as a solution for individual needs.

- The physical characteristics of the individual such as size, weight, postural stability and functional capabilities.
- The mobility of the individual (including in bed) and approach to transfers (e.g. to commode or shower-chair).
- The cognitive status of the individual (e.g. capacity to recognise the purpose of the equipment).
- Availability of and access to brakes (where appropriate).
- Likely duration of individual episodes of use of the equipment.
- The level of assistance and / or supervision required to use the equipment safely and the burden that represents to any caregiver involved.
- User access to the perianal area for cleansing.
- Comfort and need for pressure relief during use.
- The environment in which the equipment will be used and its impact on privacy and dignity.
- The proximity of the area of use to waste disposal and storage facilities.
- Cleaning and maintenance requirements, responsible person and the burden that cleaning could represent.
- Personal preferences and aesthetics, particularly where equipment is to be used at home, and especially in ‘public’ areas of the home such as a lounge room.

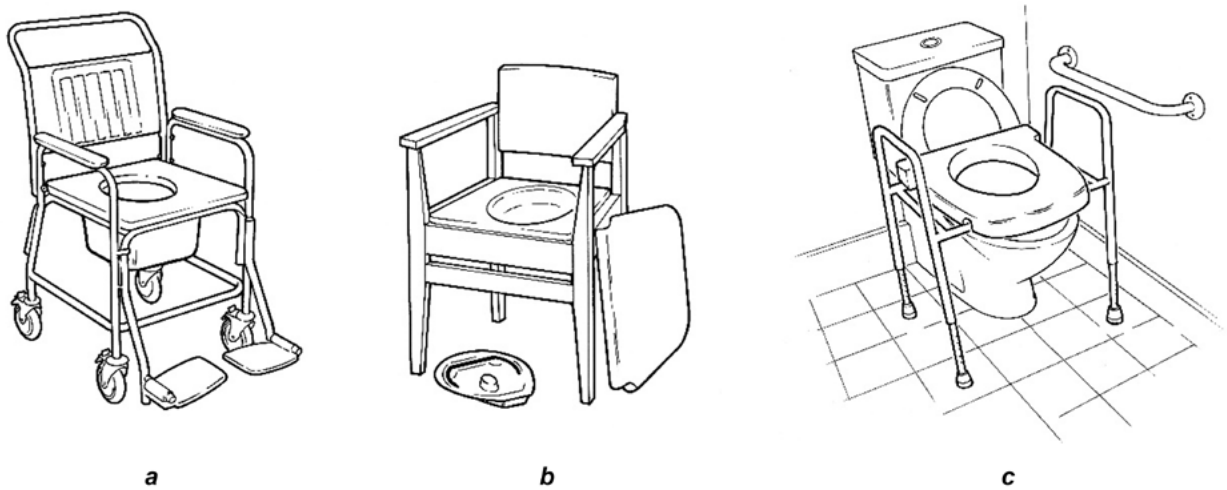


Fig E-1: Commode chair with wheels (a), chair with commode (b) and toilet frame with integral raiser and grab bar (c).

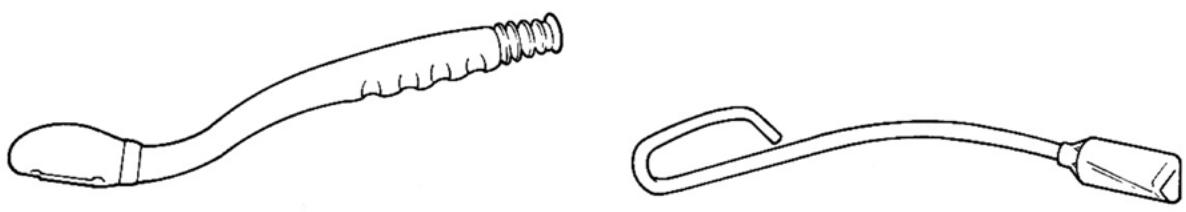


Fig E-2: Example bottom wipers.

(rounded, triangular-shaped with a flatter seat and rolled edges to provide handgrips) and shovel or 'fracture' pans (rectangular or wedge-shaped with a flattened end that is positioned beneath the individual, and with a handle at the opposite end).

Alongside issues around privacy and dignity, bedpans have other disadvantages. They do not readily permit the user to assume positions that facilitate urination or defaecation and are uncomfortable or even painful to sit on (59). Users fear missing the pan while urinating and can wait a long time for care staff to remove the pan after elimination is completed (59). Without lids, care must be taken to avoid spillage of contents when removing a bedpan from under an individual and transporting contents for disposal can be malodourous. The design of some female handheld urinals may also make them suitable (for men or women) for collecting faeces (41).

Table E-2 lists the main factors influencing the appropriateness of a commode, shower-chair or bedpan as a solution for individual needs, and Fig E-1 and Fig E-2 show examples of products in this category.

1. EVIDENCE

This review identified four studies about the design of grab bars to assist toileting (60) (61) (62) (63), one study about the design of an iToilet (64), and one study about signs used to identify the location of public toilets (65). Kennedy *et al.* (60) compared different designs and positions of grab bars installed near toilets. Using two vertical grab bars, compared to one vertical bar, a horizontal bar, a diagonal bar, or no bars, was preferred and more effective for persons who toilet independently. Vertical bars also had the lowest centre of pressure displacement during toilet transfers, decreasing the risk of falls. For those in nursing homes needing toileting assistance, grab bars that fold-down/swing-away on both sides of a toilet were preferred and required less limb muscle effort than standard grab bar configurations (61) (62).

A device named "Safe Embrace", consisting of a hinged U-shaped stainless-steel bar, has been developed to prevent falling off a toilet (63). The device is mounted behind the toilet and is pulled down over an individual's head to rest around the front of their trunk and on which they can rest their arms.

Panek (64) described a prototype design of an iToilet. The iToilet project, funded by the European Union, aims to develop an information and communication technology (ICT) enhanced modular toilet system to support the autonomy, dignity and safety of older persons living at home. The iToilet will be a motorised chair with bilateral arms/attached grab bars and adjustable height and tilt, which fits over a toilet. The iToilet controls will be available on a remote control integrated into the grab bars or by voice command (in English, German and Hungarian languages). The iToilet will contain a 3D sensor aimed at recognising and alerting falls. The iToilet's components will be modular and can be selected according to individual needs and preferences.

Signage is an important factor for identifying the location of public toilet facilities. Knowing the location of public toilets is a common self-management strategy of individuals with incontinence (66). In many cases, signs of these facilities contain graphics (icon of a man or woman) and text. An analysis of how factors such as graphics, text, and colours of the background, graphics or text of toilet signs affect recognition resulted in the hypothesis that when a sign is designed in accordance with a population's stereotypes and familiarity, reaction time to identify the sign will be shorter. (65)

Recognition of a men's or women's toilet was measured by the reaction time of Taiwanese university students and staff (50 men and 50 women) to press a key on a computer keyboard. Six levels of sign-presentation styles were randomly shown on a screen: graphics for men's and women's toilets, men's and women's toilets in Chinese text (characters), and men's and women's toilets in English letters. The sign-presentation styles had three colour levels: blue, red, or black graphics or text on a white background or white text and graphics on a coloured background.

Results showed that participants had faster reaction times for toilet signs using Chinese text rather than graphics and English text. Using non-stereotypical colours, i.e., red for men and blue for women's toilet signs, prolonged reaction times. However, when the same colours were used as the background of the sign, the reaction times remained unaffected. There were some differences by sex; for example, men required more time for identifying women's toilet signs. Using red for women's toilet signs resulted in shorter reaction times for women than when using blue.

2. SUMMARY

- A conventional or suitably adapted flush toilet is preferable to using a commode or bedpan wherever it is safely possible to do so (67) (68) (69) **(Level of Evidence 3).**
- Commodes or shower chairs (where an individual can safely use them) are preferable to bedpans. Bedpans may position users poorly to urinate or defaecate and may cause pain (59) **(Level of Evidence 3).**
- Commode (and shower chair) designs offer limited trunk support, which, combined with long periods of unsupervised use, may increase the risk of falls (68) **(Level of Evidence 3).**
- Shower chairs may be preferable to static commodes in terms of facilitating access to a toilet, preserving privacy, dignity and the management of noise and odour (67) (68) (**Level of Evidence 3)**.
- A shower-chair or commode stability must be assessed to ensure it is safe and appropriate for individual needs (34) (52) (50) (51) (48) (54) **(Level of Evidence 3).**
- Grab bars installed near toilets are used to reduce the risk of falls and facilitate transfer onto the toilet seat. Those who can toilet independently prefer bilateral vertical grab bars while those who need toileting assistance prefer bilateral fold-down grab bars compared to one grab bar or other positions (60) (61) (62) **(Level of Evidence 3).**
- A U-shaped stainless-steel bar that can be positioned in front of a person on the toilet is available to decrease the risk of falling off a toilet (63) **(Level of Evidence 4).**
- Assessment for toileting assistive devices for those with SCI should include a review of functional capacity to undertake toileting and bowel care, postural stability and transfers to and from the shower chairs/commodes, risk for pressure injuries, skin integrity, and interface pressure mapping (54) **(Level of Evidence 3).**
- Signs identifying the location of toilets using graphics, text, and colours that are familiar and normative to local users promote recognition (65) **(Level of Evidence 3).**

Table E-3: Recommendations relating to com-modes, mobile shower-chairs and bedpans.

- Privacy and dignity should be considered during toileting, including the management of associated noise and odours **(Grade of Recommendation C)**.
- Wherever safely possible, access to a conventional or adapted toilet should be considered to preserve the user's safety and modesty during transportation **(Grade of Recommendation C).**
- The use of bedpans should be minimised to the greatest extent possible without unnecessarily resorting to invasive options such as catheterisation **(Grade of Recommendation C).**
- Full and careful assessment of individual needs, including mobility, transfers, postural stability, skin integrity, access to the perianal area, and safety must be undertaken before equipment is prescribed or used, and should be followed by regular reviews to assess ongoing suitability **(Grade of Recommendation C).**
- Regardless of the equipment employed, users must have ready access to toilet paper and/or moist wipes and hand washing or sanitising supplies, and/or appropriate adaptive devices or assistance to help them when toileting **(Grade of Recommendation C)**.
- People should have safe and easy access to a direct method of calling for assistance when left alone on a toilet on any type of toileting equipment. People should be transferred off a toilet, commode, shower chair or bedpan in a timely manner after completion of elimination to reduce skin injuries and fall risk **(Grade of Recommendation C)**.
- Regular evaluation and ongoing maintenance of toileting equipment should be ensured in any environment **(Grade of Recommendation C).**

3. RECOMMENDATIONS

Recommendations relating to commodes, mobile shower-chairs and bedpans are summarised in Table E-3.

4. PRIORITIES FOR RESEARCH

- Evaluative studies of toilet seat raisers, toilet frames/surrounds, padded toilet seats, grab and support rails, bidets or personal cleansing/drying systems, bottom wipers, etc., for ease of use, the effectiveness of promoting continence, and safety.

.• Validated and standardised clinical assessment tools and outcome measures to guide the selection and determine the success of shower chairs/commodes for those with long-term needs, particularly adults with SCI (54).
- Development and testing of ICT-enhanced toileting assistive devices (64).
- Signs identifying the location of toilets should use graphics, text, and colours that are familiar and normal to local users and those following international standards to promote timely recognition (65).

F. ABSORBENT PRODUCTS

There is little new work on absorbent products to add to that discussed in the 6th consultation (36). There have been three new studies on the effective use of disposable bodyworn absorbent products for moderate-heavy incontinence (70) (71) (72) and an attempt to develop a new international standard to measure their leakage performance (73). A further study (74) compared washable pull-on pads with disposable pads for managing mild to moderate UI. Also published have been a new patient-reported outcome measure for absorbent product users (75), a new ICS standard providing recommended nomenclature for disposable bodyworn absorbent products (76), a novel method designed to measure the usability of absorbent products from caregiver's perspectives (77) and a study on the environmental impact of disposable absorbent incontinence products (78). Most significantly, Gray *et al.* (79) have published the outcomes of a project in which the US Wound, Ostomy and Continence Nurses (WOCN) Society charged a task force with creating evidence-based recommendations for assessing, selecting, using, and evaluating body-worn absorbent products for adults with urinary and/or faecal incontinence. The task force completed a scoping literature review to identify recommendations supported by adequate research to qualify as evidence-based, and then convened a panel of experts to develop consensus statements. Finally, these consensus-based statements underwent a second round of content validation using a modified Delphi technique using a different panel of clinicians with relevant expertise. The conclusions for this project have been folded into the following text.

General guidelines on patient assessment for product selection are discussed in Section B. Aspects of assessment that are particularly important regarding absorbent products are frequency / severity and time of day (day and/or night) of leakage; user's sex / gender (some products work better for some than others); ability to change products independently / need for carer assistance; product changing position (standing / lying); laundry / drying facilities available; individual priorities (e.g. need for discreetness); personal preference for design / materials (e.g. disposable versus washable designs); and lifestyle / living environment (at home / travel / work etc.). There is an international standard (ISO 15621:2017) which provides useful guidelines for evaluating absorbent incontinence products, covering these factors.

The key aspects of absorbent product performance have been identified and prioritised by interviewing men and women taking part in a series of clinical trials (25). There was notable consistency across patient groups (light / heavy incontinence, men / women), with all indicating that their top priority was - unsurprisingly -the ability of a

product to hold urine without leakage. Other important factors were: discreetness, containment of odour, the ability of a product to stay in place, comfort when wet and the ability to keep skin dry.

Since the 6th consultation (36), Yearwood-Martin et al. have developed a patient-reported outcome measure (PadPROM) to help with user evaluations of absorbent products (75), but it has yet to be used in any published studies. A novel method designed to discriminate between the usability of products from a carer perspective, evaluating product fit, workload and satisfaction has been developed in a simulated environment and requires real-world testing (77).

Incidental findings from product evaluations indicate that, although it is almost always an important factor, absorption capacity alone does not determine whether a user will choose to use a product. Some users may have frequent, small volume, low flow-rate losses of urine ("dribble"), whilst others may be dry for days but then have a higher volume, higher flow-rate incident ("gush" or "flooding"). Both may prefer to use products intended for light incontinence. Mobile and independent community-dwelling women with all levels of incontinence are reported to generally prefer small products, and they are often willing to change them frequently rather than use larger products and change them less often (80). Conversely, dependent, immobile individuals may prefer the security of larger products despite relatively low volumes of urine loss due to their dependence on others for product changing.

The mass of urine in an individual wearer's products can vary enormously, and studies that have collected and weighed used products have found overlap between the quantities recorded for different sub-groups of users. For example, in a study of absorbent products for moderate-heavy incontinence used by older people in residential care, around 15% of weighed products had less than 100g of urine in them, even though it was usually much more (81) while, in a study of older women with light incontinence living in the community, about 10% of used products had more than 100g of urine in them, even though it was usually much less (82).

Although the number of products used per day might be a good measure of the degree of urinary incontinence, this has not been found to be the case in nursing home residents in Norway (28). Absorbent products (of unspecified design) used by residents in six homes were collected and weighed, and a poor correlation was found between the number of products used over 48 hours and the total mass of urine in them. Caregivers tending to change products at routine times was the likely explanation.

Some studies have focused on the use of absorbent products by men. Teunnissen and Lagro-Jansson (83) interviewed 56 men with UI of which only nine used absorbent products. They concluded that men use them less frequently than women, have little knowledge about purpose-built products, are more likely to construct their products out of absorbent materials such as towels, and are less satisfied with absorbent products than women. Furthermore, men may prefer other available devices such as urinary sheaths (84) (Section G).

However, the findings of these studies about male and female product use and preferences may not be generalisable to all countries and cultures. In some countries, only limited ranges of absorbent products are available (predominantly all-in-ones), with products for light incontinence less frequently available. Since the sixth consultation (36), Teerawattananon et al. have reported a significant improvement in health-related quality of life and independence in activities of daily living when patients with chronic UI or FI in two Thai rehabilitation centres were provided with an adequate supply of disposable all-in-ones, having previously used not more than two per week (72).

All-in-ones are widely sold in supermarkets, prominently displayed, and may be viewed with less embarrassment than in countries supplied primarily through healthcare systems or pharmacies. In comparison, sheath systems may be harder to access and relatively more expensive. Climate (and consequently customary mode of dress) can affect the acceptability of sheaths and their attendant drainage bags.

1. ABSORBENT PRODUCT CATEGORIES

Most absorbent products are bodyworn but some (underpads) are designed to be placed beneath the user, and products in either category may be disposable (discarded after a single use) or washable (laundered and reused multiple times). Although each category encompasses many brands, all products fall into one of just a small number of generic designs (Table F-1), which further divide into those intended for men, women (or both) or children. However, the names used to describe these generic designs can vary considerably among - and even within – countries and cultures, and there is a confusing plethora of synonyms in use in the clinical and academic literature and in the information provided by product suppliers. This makes it difficult to review the literature and draw on it for advice on selecting products and using them effectively.

Since the 6th consultation (36), the International Continence Society has begun addressing this problem by publishing consensus-based recommendations for nomenclature relating to disposable bodyworn absorbent products (76), and its recommendations have been used in the classification that follows. Similar guidance is not yet available for underpads or for washable products of any design, but the nomenclature used below has been chosen for consistency with the ICS guidelines for disposable bodyworns where possible. The International Standards Organisation is also working on nomenclature for absorbent products, but its findings are not yet available.

Bodyworn absorbent products for UI fall into the seven design groups shown in Table F-1 and Figs F-1 to F-11, each having the defining and main variant features described in Tables F-2 to F-8. Products come in a wide range of absorbencies for managing light through to very heavy UI, but it is useful to divide them into two main sub-groups: those intended for light UI (usually smaller products) and those for moderate-heavy losses (usually larger products). Furthermore, designs relying on a close fit around the wearer's body are often supplied in a range of sizes to fit, for example, small, medium or large users. It does not necessarily follow, however, that a product designed to fit a large body has a higher absorbency than one intended for a small person.

Table F-1: Classification of absorbent products for incontinence. Terms in brackets are acceptable alter-natives to the preferred (unbracketed) terms. (76).

Design categories:	Bodyworns	Underpads
Design groups	Pads Unbacked pads Male pads Male pouches Pull-on pads (Protective underwear) All-in-ones (Wrap-around pads, Adult briefs) Belted pads (Belted products)	Bed pads Chair pads

Table F-2: The defining features and main variant features of pads (See Figs F-1 to F-4)

Defining features	A waterproof-backed absorbent product that is held in place using separate, close-fitting (regular or specially designed) underwear.
Main variant features	• Products may be disposable or reusable. • Products may be used by either sex, but some are intended (by their colour, style, shape, or the placing of absorbent material, for example) just for men or just for women. Some variants are intended for children. • Products come with different absorption capacities. • Longitudinal elastic side barriers and leg cuffs on either side of the crotch may be included to improve fit, comfort and prevent leakage. • Disposable variants may have an adhesive strip on the back or adhesive wings to the sides to help secure them in underwear; Washable variants may have hook-and-loop patches or other means of securing. • Disposable variants may have a wetness indicator. • Products may or may not be suitable for containing FI as well as UI.

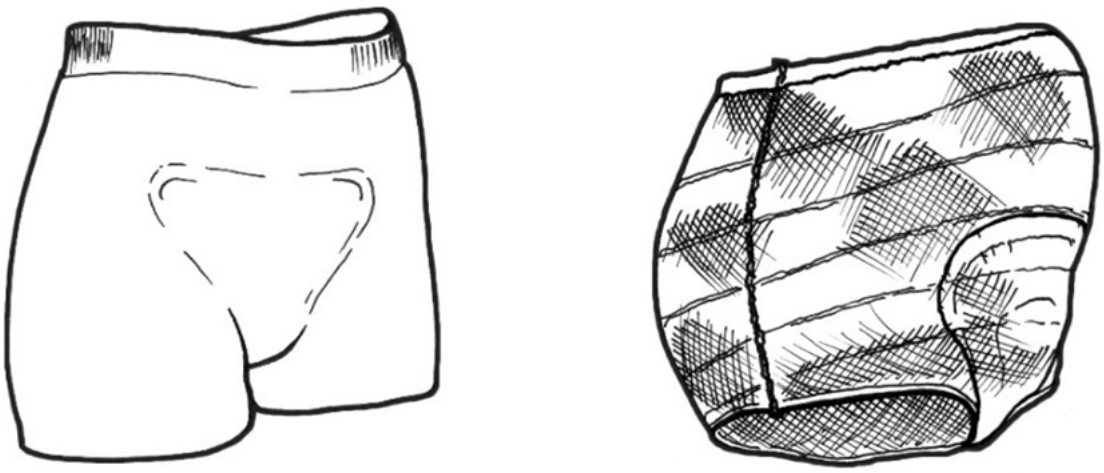


Fig F-1: Mesh briefs with (a) and without (b) legs for supporting disposable bodyworn pads.

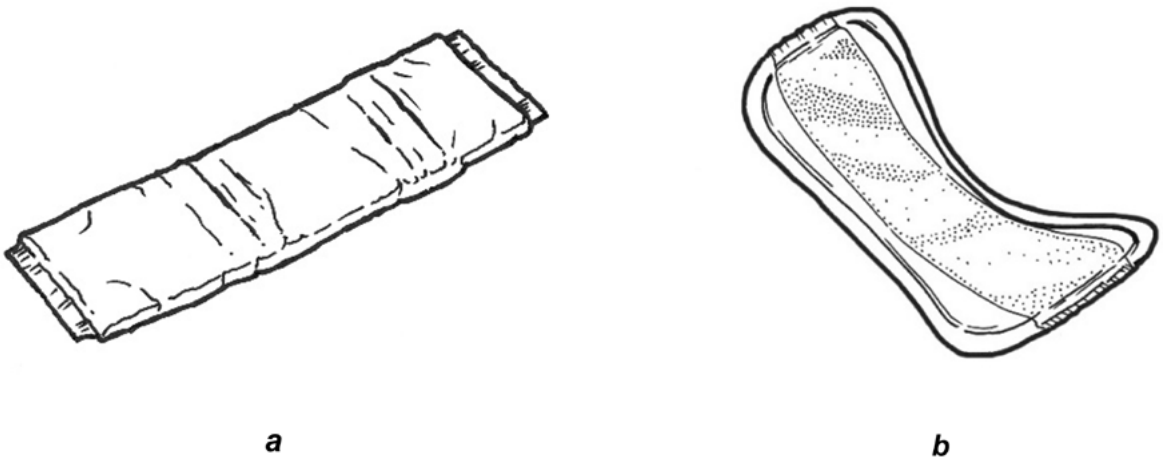


Fig F-2: Small, disposable, unshaped (a) and shaped (b) insert pads for light incontinence.

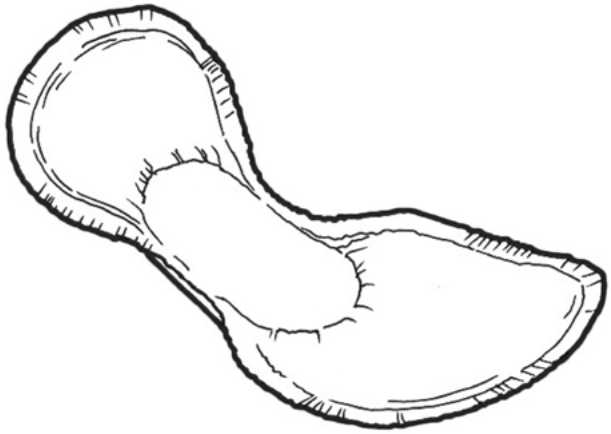


Fig F-3: Large, disposable, shaped insert pads for moderate / heavy incontinence.

Table F-3: The defining features and main variant features of unbacked pads. (Unbacked pads are simi-lar in appearance to those shown in Fig F-2, but without the waterproof backing.)

Defining features	An absorbent product without a waterproof backing used either (i) inside another product such as a category 6 product to supplement its absorption capacity or to reduce the frequency with which it needs to be changed (the unbacked pad may be changed with relative ease, without necessarily needing to also change the outer product), or (ii) on its own, secured using separate, close-fitting, underwear which itself includes waterproofing in the pad area.
Main variant features	• Products may be used by either sex. • Products may be rectangular or contoured to better fit the wearer. • Products come with different absorption capacities. • Products may or may not be suitable for containing FI as well as UI.

Table F-4: The defining features and main variant features of male pads. (See Fig F-6b)

Defining features	A waterproof-backed absorbent product for men that is designed to cover the penis and scrotum and is held in place using separate, close-fitting (regular or specially designed) underwear.
Main variant features	• Products come with different absorption capacities. • Longitudinal elastic side barriers and leg cuffs at the sides may be included to im-prove fit and comfort and prevent leakage. • Products may have an adhesive strip on the back to help secure them in underwear

Table F-5: The defining features and main variant features of male pouches. (See Fig F-6a)

Defining features	A waterproof-backed absorbent product for men, fashioned into a pocket into which the penis, and sometimes the scro-tumis placed. They are held in place using separate, close-fitting (regular or specially designed) underwear.
Main variant features	• Products come with different absorption capacities. • Products may have an adhesive strip on the back to help secure them in underwear. • Products may have a hook and loop fastening system or adhesive tape to secure the product around the penis

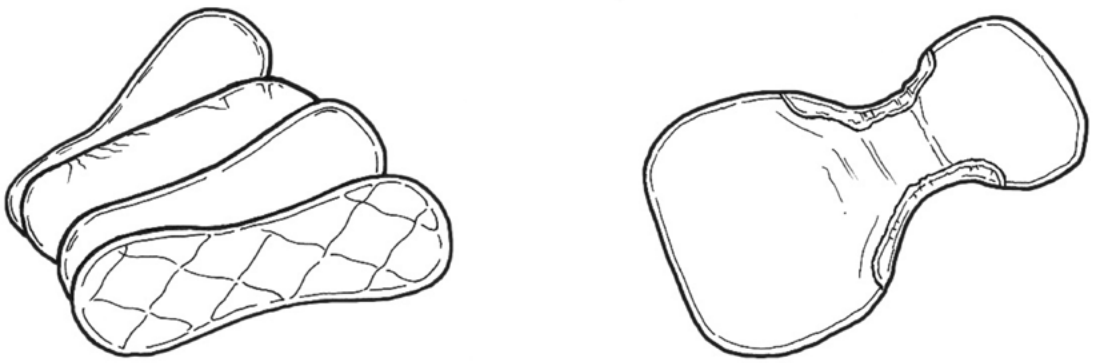


Fig F-4: Washable, shaped insert pads for light (a) and moderate / heavy (b) incontinence.

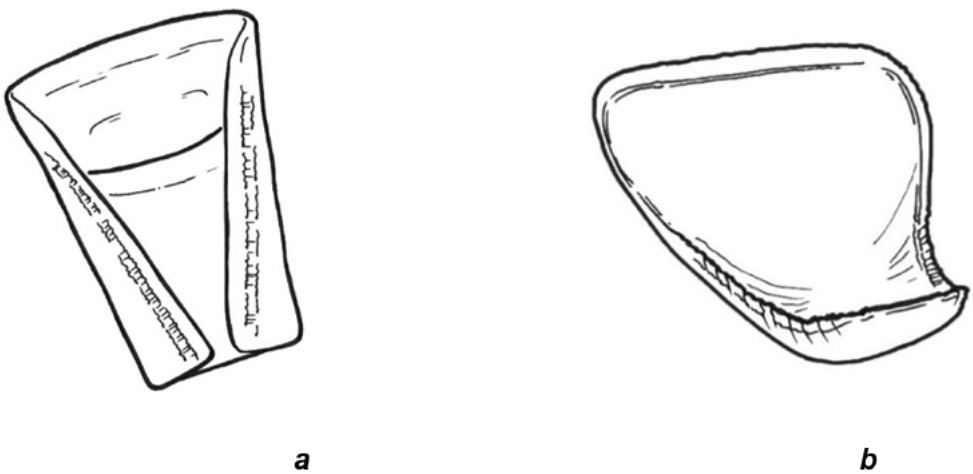
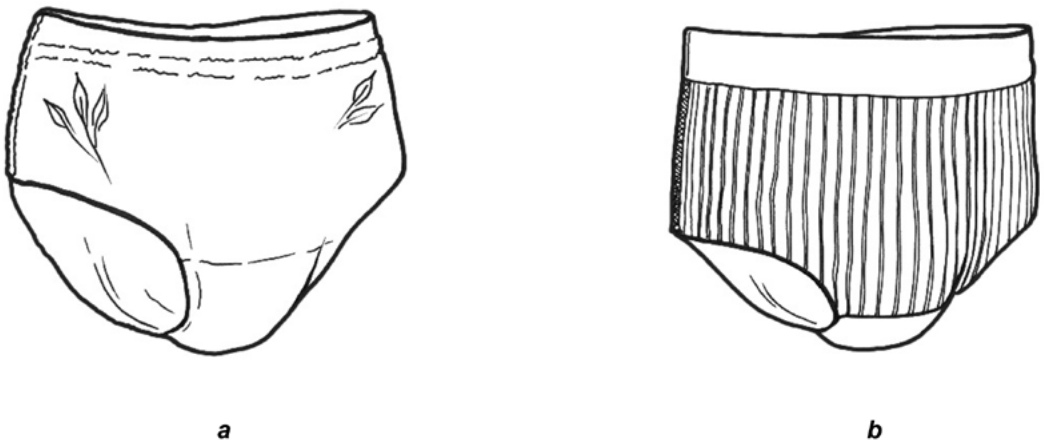


Fig F-5: (a) A male pouch and (b) and a male pad. Both come in disposable and washable variants.

Table F-6: The defining features and main variant features of pull-on pads (protective underwear).

Defining features	A product in which the absorbent core, waterproof backing and the means to hold it in place are combined in a single design resembling regular underwear. Elastic linings around the waist and hips help give a close fit.
Main variant features	• Products may be used by either sex, but some are intended (by their colour, style or the placing of absorbent material, for example) just for men or just for women. • Products come with different absorption capacities and to fit different body sizes. • Longitudinal elastic side barriers and leg cuffs on either side of the crotch may be in-cluded to improve fit and comfort and prevent leakage. • In some designs, side seams can be torn away for easy removal. • Products may have wetness indicators. • Products may or may not be suitable for containing FI as well as UI.



a *b*

Fig F-6: Disposable pull-on pads for moderate / heavy incontinence for women (a), and for men (b).

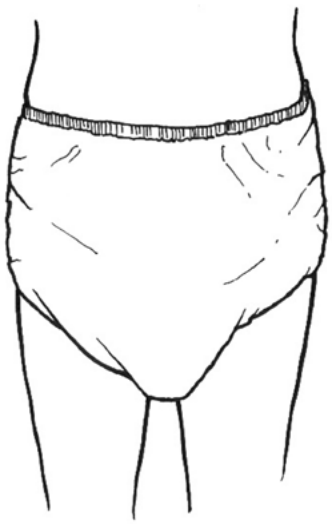


Fig F-7: Washable pull-on pads for moderate / heavy incontinence (unisex).

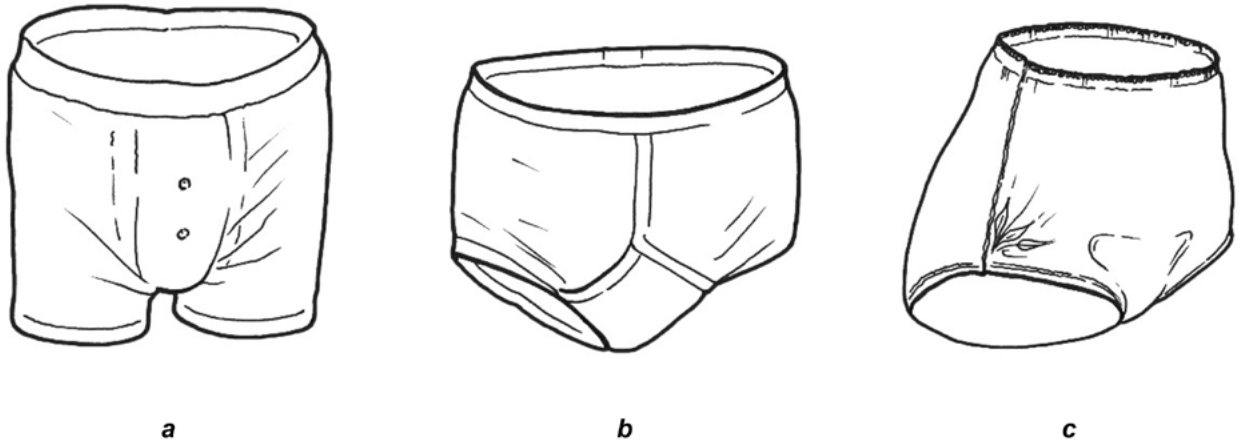


Fig F-8: Washable pull-on pads for light incontinence: boxer style for men (a), y-front style for men (b), and for women (c).

Table F-7: The defining features and main variant features of all-in-ones (wrap-around pads, adult briefs).

Defining features	A one-piece product in which the absorbent core and the means to hold it in place are combined in a single design, secured using adjustable adhesive tabs or a hook and loop fastening system at the sides.
Main variant features	• Products may be used by either sex, but some are intended (by their colour, style, or the placing of absorbent material, for example) just for men or just for women. • Products come with different absorption capacities and to fit different body sizes. • Longitudinal elastic side barriers and leg cuffs on either side of the crotch may be in-cluded to improve fit and comfort and prevent leakage. • Products may have wetness indicators. • Products may or may not be suitable for containing FI as well as UI.

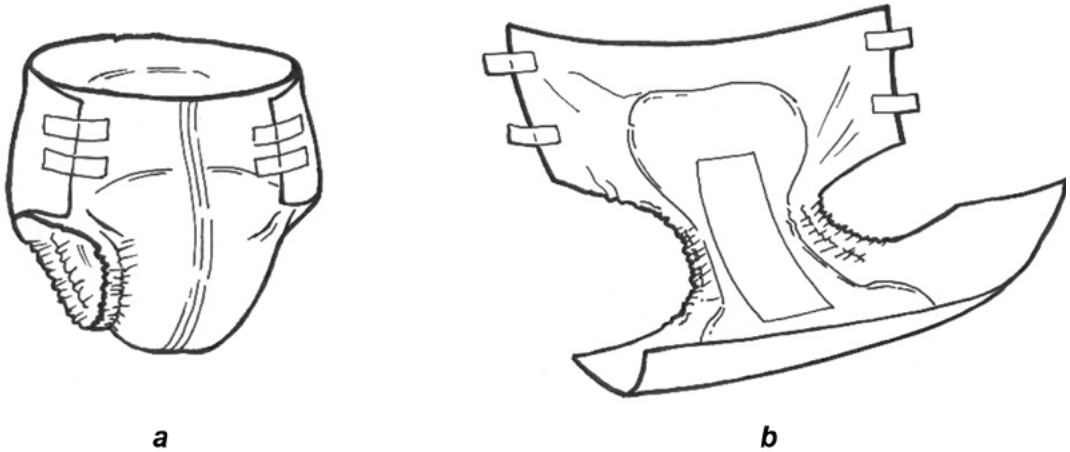


Fig F-9: Disposable all-in-ones, closed (a) and open (b).

Fig F-10: Washable all-in-ones.

Table F-8: The defining features and main variant features of belted pads (belted products).

Defining features	A one-piece product in which the absorbent core, waterproof backing, and the means to hold it in place are combined in a single design, secured by means of an adjustable belt with adhesive tabs or a hook and loop fastening system.
Main variant features	• Products may be used by either sex, but some are intended (by their colour, style or the placing of absorbent material, for example) just for men or just for women. • Products come with different absorption capacities and to fit different body sizes. • Longitudinal elastic side barriers and leg cuffs on either side of the crotch may be in-cluded to improve fit and comfort and prevent leakage. • Products may have wetness indicators. • Products may or may not be suitable for containing FI as well as UI.

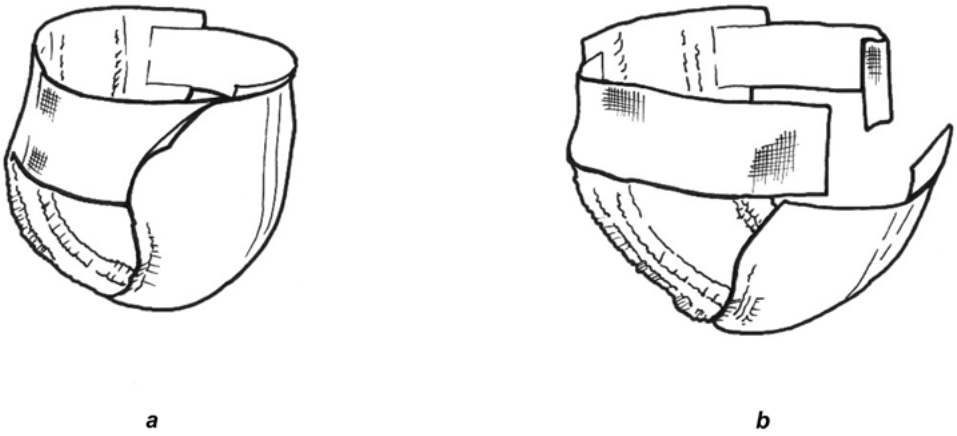


Fig F-11: Disposable belted, closed (a) and open b)

Very few products are designed specifically to contain faeces, but those intended (primarily) for UI are commonly used to manage FI, too.

Sometimes people make their own products, typically folding terry-towelling squares into briefs, fastening with pins and using plastic pants as a waterproof barrier. Such pants may also be worn over more conventional designs in an attempt to reduce leakage and / or odour.

“Body” garments (like vests which have a crotch section that opens and closes with snap fasteners, much like those manufactured for babies) may be useful to help hold products in place and may reduce any rustling noise from the plastic backing material on absorbent products.

Underpads are usually simple rectangles of different sizes to be used on the bed (bed pads) or chair (chair pads). Washable underpads may have a high friction backing or – with bed pads - have ‘wings’ for tucking beneath the mattress to help keep them in place. Underpads vary widely in absorbency, with less absorbent products being used as ‘back-up’ along with bodyworn products and more absorbent bed pad variants being used as sole protection on the bed at night.

Availability of products will necessarily affect choice. However, even where only a single product type (e.g. all-in-ones) is readily available, within that product type, particular brands and / or absorbencies may work better for some users or circumstances than others. Clinicians and users are likely to manage incontinence more successfully if they familiarise themselves with the advantages and limitations of different designs and brands. For example, cheaper products may be less reliable but adequate for use at home when more frequent changing is possible. Conversely, the high priority of achieving reliable protection when away from home may justify using more expensive products then. Similarly, more absorbent products intended for night-time use may provide extra valued security during the day when travelling.

2. ABSORBENT PRODUCT MATERIALS

Absorbent products – disposable or washable – usually comprise three main layers: an absorbent core sandwiched between a waterproof backsheet beneath and a water-permeable topsheet next to the wearer’s skin.

The main component in disposable absorbent cores is invariably fluffed wood pulp, but most also contain powdered superabsorbent polymer, usually concentrated in the crotch region where it is most likely to get wet. Superabsorbent polymers hold much more urine – weight for weight – than fluffed wood pulp and retain it far more tenaciously under pressure. They are usually based on cross-linked salts of polyacrylic acid whose chemistry can be varied according to the balance of properties such as absorption capacity and absorption speed desired. It is increasingly common for absorbent cores to comprise two or more layers, each designed to perform a different function. For example, an upper layer might comprise low absorbency fibres engineered to receive and distribute urine efficiently and maintain a dry layer next to the skin, while lower layers provide absorption capacity. Some disposable products have ‘breathable’ plastic backings designed to reduce skin occlusion.

The absorbent core of washable bodyworn products is usually made from cotton terry-towelling or from a needlefelt or knitted fabric comprising rayon and / or polyester fibres. A variety of polymers are used for waterproofing. In general, the thicker, stiffer materials are more durable (the durability of the plastic backing often determines the lifetime of the product) but less comfortable. Topsheets are usually made from either cotton – which is hydrophilic and intended to have good dry comfort – or polyester – which is hydrophobic and intended to have good wet comfort. Traditional, washable fabric squares – folded into shape and secured using waterproof pants – are usually made from cotton terry-towelling.

Concern for the environment and for controlling costs has led to an increase in the number of washable products available on the market. An important consideration in the comparison of washable and disposable designs is their relative environmental impacts. Since the 6th consultation (36), Willskytt & Tillman (78) have published a useful case study on the environmental costs associated with absorbent incontinence products. They identified a number of ways to reduce environmental impact through more efficient use of resource materials, reuse of some product components, and effective recycling and quantified the potential gains.

3. ABSORBENT PRODUCT CAPACITY AND USER REQUIREMENTS

Absorbent products come in a range of absorbencies for different levels of incontinence, and understandably purchasers wish to know how much urine they will hold. However, there is no simple answer: no product has a simple absorption capacity; that is, a volume of urine below which it is guaranteed not to leak. Rather, the probability of a product not leaking decreases as the urine volume increases. The mark of a more absorbent product is that – for a given urine volume – it is less likely to leak than a less absorbent alternative.

This is a complex concept to communicate in sales literature and product packaging and so companies commonly quote a simple absorption capacity figure, even though it is based on a misconception. Some use the volume of fluid a product will hold in a laboratory test - usually international standard ISO 11948-1 (78) - but this figure can be very misleading. Although it correlates well with leakage performance for some groups of users), the volume of urine that a product will hold when tested with ISO 11948-1 is enormous compared with how much it will hold in real use. For this reason, some companies prefer to quote a “working capacity”, which might be calculated as some proportion of its capacity under laboratory test. However, this is still misleading as it implies that the product will not leak until the working capacity is exceeded. A simple, valid and widely accepted solution to this problem has yet to be devised.

It is equally difficult to determine user needs concerning the volume of urine their products need to hold. Not only can different users leak widely differing volumes from each other, but an individual user may also leak widely differing volumes on different occasions. This means that, like product performance, users’ needs cannot be easily quantified. For the purposes of this review, the evidence is divided into that relating to light UI and that relating to moderate-heavy UI. Published data describing users as ‘lightly incontinent’ place the median and 90th percentile urine volumes in their used products at around 15ml and 100ml, respectively (85). Similarly, those with

Table F-9 Bodyworn absorbent products for women with light urinary incontinence

	Disposable	Washable
Design groups	Inserts (Fig F-2)	Inserts (Fig F-4a)
	Pull-ups i.e., pants with integral pad	Pull-ups i.e., pants with integral pad (Fig F-8c)
	Menstrual pads	

moderate-heavy UI have yielded corresponding figures of about 250ml and 600ml (85).

4. BODYWORN ABSORBENT PRODUCTS FOR WOMEN WITH LIGHT URINARY INCONTINENCE

There are four main product designs for women with light incontinence (Table F-9). In addition, menstrual pads are known to be frequently used for light urinary incontinence. The disposable pull-ups are relatively expensive, single-use items and seldom-used for light incontinence except as 'emergency' items. Underpads are not commonly used for light incontinence.

4.1. Evidence

A small number of robust comparative evaluations and one Cochrane review of absorbent products for women with light incontinence have been published, (86). Most studies are now rather old (2004 or earlier) and relate to products no longer available (22) (24) (87) (88). There has been one published study of pads for women with light incontinence since the 6th consultation (36) and that compared a disposable pad with a washable pull-on pad (74).

In the most recent substantial study (2008), Fader *et al.* (85) used a crossover randomised design to compare the most common product designs: disposable pads, menstrual pads, washable pull-on pads, and washable pads for women with light UI. Three product brands were selected to represent each design, and each brand was tested for one week (three weeks for each design block, a total of 12 weeks). Product performance was characterised using a validated questionnaire to evaluate product performance (leakage, discreetness etc.) with a five-point scale (very good – very poor) at the end of each week of product testing. A product change and leakage diary were used to record the severity of leakage from products (three-point scale: a lot, a little, or no leakage), and numbers of laundry items and products used were recorded to estimate costs. Skin health changes were recorded weekly. At a final interview, preferences were ranked (with and without costs), acceptability of the design recorded (highly acceptable – totally unacceptable) and overall opinion marked on a visual analogue scale (VAS) of 0-100 points (worst design – best design). The VAS score was used to estimate cost-effectiveness.

Eighty-five women (mean age 60) completed the study and 8691 used pads were weighed. The disposable pad was significantly better than the other designs on most variables except for discreetness. For leakage prevention, overall acceptability and preference, disposable pads were significantly better than menstrual pads, which were better than washable pull-on pads, which were better than washable pads. There was no clear benefit for skin health using either washable or disposable designs. Most women preferred the disposable pads but some preferred the other cheaper designs (6/85 preferred menstrual pads; 13/85 preferred washable pull-on pads, both of which were >50% cheaper to use than disposable pads). Washable pads were significantly worse than the other designs (72/85 found them unacceptable). Overall, there were generally more practical problems with washables, particularly when away from home (Level of Evidence 1).

The authors concluded that allowing women to choose their preferred product design (or different designs for different circumstances) would be more cost-effective and provide better patient satisfaction than the provision of disposable pads (the most expensive product) alone.

More recently, in a controlled cross over trial, Alam and colleagues (74) asked 70 women with mild to moderate urinary incontinence (defined as a response of "small" or "moderate" amount to the ICIQ-SF question "How much do you leak?" (89) to compare a disposable pad with a washable pull-on pad. Each woman used each of the products for a period of two days. Outcome measures were responses to the I-QOL Incontinence Quality of Life Instrument (90) and a product performance questionnaire for each product. Fifty-two women completed the study. There was no significant difference between the two products for I-QOL total scores or I-QOL sub scores concerning avoidance and limiting behaviours, psychosocial impacts or social embarrassment. However, the washable product scored significantly better on the product performance questionnaire regarding the overall impression, discreteness, comfort when dry, comfort when wet, ability to keep skin dry, and kindness to skin. There was no difference between the products in their ability to hold urine without leaking.

4.2. Summary

- Disposable pads are generally more effective in terms of leakage and more acceptable than menstrual pads, washable pull-on pads, and washable pads **(Level of Evidence 1)**.
- Menstrual pads are cheaper and washable pull-on pads cheaper still (on a per-use basis) than disposable pads and they are acceptable to many, particularly those with lighter incontinence and particularly when used at home. They may also be more readily available in some regions than disposable pads designed specifically for incontinence. **(Level of Evidence 1).**
- Washable pads are not acceptable to most women with light urinary incontinence. (**Level of Evidence 1)**.

4.3. Recommendations

Recommendations relating to bodyworn absorbent products for women with light urinary incontinence are listed in Table F-10, while Table F-11 describes the user characteristics, priorities and contexts which favour or discourage the use of the different product designs.

Table F-10: Recommendations relating to body-worn absorbent products for women with light urinary incontinence.

- Disposable pads should be recommended as the most effective and preferred absorbent product for women with light UI **(Grade of Recommendation B).**
- Menstrual pads or washable pull-on pads may be considered sufficient for some patients with very light urinary in-continence and are cheaper **(Grade of Recommendation B).**
- Washable pads are not recommended for women with light UI **(Grade of Rec-ommendation B).**
- Combinations / mixes of designs for different situations (e.g. disposable pads for going out, washable pull-on pads for staying at home) are likely to provide optimum management in terms of patient needs and cost-effectiveness, and product advice and provision (where purchased by institutions / services) should reflect this **(Grade of Recom-mendation B).**

See also the general recommendations relating to absorbent product selection in Table F-20 and to washable products in Table F-21.

4.4. Priorities for research

- Because the performance of washables is generally poor (particularly for leakage) compared to disposables, the development of better washable products for women with light urinary incontinence is a priority.
- The strategy of women using different designs for different situations (e.g., when at home, away, at work) needs to be evaluated.

5. BODYWORN ABSORBENT PRODUCTS FOR MEN WITH LIGHT URINARY INCONTINENCE

There are five main bodyworn absorbent product designs for men with light UI (Table F-12). However, disposable and washable pads are often unappealing to men as they are frequently marketed as specifically for women and bear a strong resemblance to menstrual pads. Anatomical differences are also likely to mean that they are less effective for men. Male pouches and male pads (Fig F-5) are designed to be more suitable for men by containing or covering the penis.

5.1. Evidence

Only one randomised trial evaluating absorbent products for men with light UI has been published (91). Six male pouches (all disposable), six male pads (5 disposable, 1 washable), one unisex disposable pad, and one washable pull-on pad were chosen to represent the four main designs available in the UK in 2003 and evaluated. Seventy men with light UI completed the study, evaluating each product for a week in turn and recording their views with product performance questionnaires, both after testing each product and having tested all the products in a given design category. They also filled out product leakage diaries and saved used

Table F-11: User characteristics, priorities and contexts which favour or discourage the use of the dif-ferent bodyworn absorbent product designs for females with light UI.

Product Type	More likely to suit you if...	Less likely to suit you if...
Disposable pads	• You are most concerned about reliably containing.	• Low cost is a priority for you. • Discretion is a priority for you.
Menstrual pads	• Low cost is a priority for you.	• Your leakage is at the heavier end of light leakage.
Washable pull-on pads	• Low cost is a priority for you • Your leakage is very light.	• You do not have adequate laundry facilities. • You are unwilling to use washable products. • You are not prepared to carry used products when out. • Your leakage is at the heavier end of light leakage.
Washable pads	• Low cost is a priority for you. • Your leakage is very light.	• You do not have adequate laundry facilities. • You are unwilling to use washable products. • You are not prepared to carry used products when out. • Your leakage is at the heavier end of light leakage.
NB The content of this table is based on the referenced evidence cited in the chapter, but the unrefer-enced version provided for the lay public on the accompanying website (www.continenceproductadvisor.org) is reproduced here.		

products for weighing. 'Overall opinion' was used as the primary outcome variable.

Results showed:

- The performance of male pouch designs was significantly worse than that of the male pad and unisex pad designs. The most common problems with male pouches were staying in place and difficulties re-inserting the penis in it once it was wet.
- The unisex disposable pad was effective at containing leakage and was substantially cheaper than the male pad designs.
- Male pads had the best leakage scores, but one product was significantly better than the others. It was leaf-shaped (approximately triangular and slightly elasticated along two edges to give shaping / cupping).
- The washable male pad was less successful than the five disposable male pads.
- The washable pull-on pad attracted polarised overall opinion scores (loved or hated). It scored well for staying place but poorly for leakage.

In a later trial (92) the performance of three continence devices (sheath drainage system, body-worn urinal (BWU), penile clamp) and disposable absorbent products was assessed by 56 men with persistent UI (>1 year) post radical prostatectomy. Each product was tested for three weeks. The results for the non-absorbent products are reported in other sections (G, I and K). Absorbent products were judged to be good for everyday activities and best for night-time use, most easy to use, comfortable when dry but most likely to leak and most uncomfortable when wet. However, there was a preference for having a mixture of products to meet daytime needs; around two-thirds of the men elected to use different products in different contexts. They reported that absorbent products and other

Table F-12: Bodyworn absorbent products for men with light urinary incontinence

	Disposable	**Washable**
Design groups	Male pads (Fig F-5b)	Male pads (Fig-5b)
	Male pouches (Fig F-5a)	Male pouch (Fig 5a)
		Pull-up pads (Fig F-8a & F-8b)

Table F-13: Recommendations relating to bodyworn absorbent products for men with light UI.

- **Disposable male pads (especially leaf-shaped) are recommended as the most acceptable and effective design for men with light incontinence, but some men prefer other designs which should be considered as alternatives (Grade of Recommendation B).**
- **Simple unisex pads are cheaper and may be acceptable to some men with light UI (Grade of Recommendation B).**
- **Washable pull-on pads are likely to be most suitable for men with very light incontinence who have difficulties keeping a (male) pad or male pouch in place (Grade of Recommendation B).**
- **Disposable absorbent products- as opposed to male devices - are recommended for night-time users with post-prostatectomy incontinence (Grade of Recommendation B).**

See also the general recommendations relating to absorbent product selection in Table F-20 and to washable absorbent products in Table F-21.

Table F-14: User characteristics, priorities and contexts which favour or discourage the use of the dif-ferent absorbent product designs for males with light UI.

Product Type	**More likely to suit you if...**	**Less likely to suit you if...**
Disposable male pouches	• Discretion is a priority for you • Using a specifically male product is important to you.	• You have penile retraction. • Your leakage is at the heavier end of light leakage.
Disposable male pads	• Actually, they suit most men.	
Unisex disposable pads	• Low cost is a priority for you. • You are happy to use a unisex product.	
Washable pull-on pads	• Your leakage is very light. • Low cost is a priority for you. • You are mobile and active.	• You do not have adequate laundry facilities. • You are unwilling to use washable products. • You are not prepared to carry used products when out. • Your leakage is at the heavier end of light leakage.
NB The content of this table is based on the referenced evidence cited in the chapter, but the unreferenced version provided for the lay public on the accompanying website (www.continenceproductadvisor.org) is reproduced here.		

devices have different strengths and limitations which suit them to different circumstances and activities.

5.2. Recommendations

Recommendations relating to bodyworn absorbent products for men with light UI are listed in Table F-13, while Table F-14 describes the user characteristics, priorities and contexts that favour or discourage the use of the different product designs.

5.3. Priorities for research

Although the performance of washable products was generally poor (particularly for leakage) compared to disposables, some men would like to use washables. The development of better washable products is, therefore, a priority for men with light UI.

6. BODYWORN ABSORBENT PRODUCTS FOR MEN AND WOMEN WITH MODERATE-HEAVY URINARY INCONTINENCE

There are at least 12 absorbent product designs for men and women with moderate-heavy UI (Table F-15). Most bodyworn products are disposable but washable variants of most designs are available, too.

Disposable and washable bed pads and chair pads may be used as sole protection or as “back up” to a bodyworn product (See Sections F7 and F8).

6.1. Evidence

Although reported in the 5th International Consultation (92) two clinical studies of absorbent products for moderate-heavy incontinence conducted by Fader *et al.* (85) - one community based, the other in nursing homes - remain the most recent studies of reasonable size. In the community-based trial, 85 moderate / heavily incontinent adults (urinary or urinary / faecal) living in their own homes (49 men and 36 women) were enrolled and tested three (or two) products from each of five design categories (total of 14 test products): disposable pads (with mesh pants); disposable all-in-ones; disposable pull-on pads; disposable belted pads; and washable products (variety of bodyworn designs). All products were provided in a daytime and a (mostly more absorbent) night-time variant. Products were selected based on having similar scores for absorbency across the designs (Rothwell scores (93), see section F6) and performance data from pilot studies. In the nursing-home-based trial, 100 moderate / heavily incontinent adults (UI or UI and FI) living in a total of 10 nursing homes (27 men and 73 women) evaluated one product from each of the four disposable design categories above. Products were selected on the basis of their performance in the community-based trial and again, day and night-time variants were provided.

Product performance was characterised using validated questionnaires that asked the participants or carers to evaluate product performance (leakage, ease of putting on, discreetness etc.) using a five-point scale (very good – very poor) at the end of each test period. Used products were individually weighed and the perceived severity of leakage from them was recorded on a three-point scale (none, a little, a lot). The numbers of laundry items and products used were recorded to estimate costs, and skin health changes were recorded by the participant or by the researchers. At the end of testing, participants (or their carers) were interviewed and asked to rank their preferences (with and without costs), state the acceptability of each design (highly acceptable – totally unacceptable) and record their overall opinion on a visual analogue scale (VAS) of 0-100 points (worst – best design). A product changing experiment was conducted with 12 women from the nursing home based trial to determine any differences between product designs. Under idealised conditions, products of the different designs were applied (by the same carers) in random order for each patient, and product change times were recorded with a stopwatch.

Results (Community):

- Disposable pads had worse leakage performance than the other disposable designs for day and night use.
- Disposable pull-on pads were preferred over disposable pads for the daytime.
- Disposable belted pads were not better overall than traditional all-in-ones.
- Performance and preference findings differed between men and women, probably due - in part – to the larger leakage volumes experienced by the men.
- Disposable pull-on pads (the most expensive design) were better overall than the other designs for women during the day or night
- Disposable all-in-ones were better for leakage than disposable pads (the cheapest), but women did not prefer them; for men, disposable all-in-one pads were better, both overall and for leakage and were the most cost-effective design.
- A washable product with a felt absorbent core and an integral plastic backing fixed by poppers performed significantly worse for leakage than the other two washables and was not included with them in the analysis comparing designs.
- Washable cotton terry-toweling (2 designs): one, a simple square, folded and pinned in an all-in-one shape and, the other, an all-in-one-like design (both worn with plastic pants) were better for leakage at night than the disposable designs but were less popular overall for daytime use. Only 25% of women found them acceptable, but over 60% of men found them highly acceptable at night.

Table F-15: Absorbent products for adults with moderate-heavy UI

	Disposable (single use)		**Washable (reusable)**	
Type	Bodyworns	Underpads	Bodyworns	Underpads
Design groups	Pads (Figs F-1 and F-3) All-in-ones (Fig F-9) Belted pads (Fig F-11) Pull-on pads (Fig F-9)	Bed pads Chair pads	Pads (Figs F-1 and F-4a) All-in-ones (Fig F-10) Belted pads Pull-on pads (Fig F-7)	Bed pads Chair pads

- There were many practical problems dealing with washable products, particularly when out of the house. But they were more acceptable at home.
- No firm conclusions could be drawn about the performance of designs for faecal incontinence, and there was no firm evidence that there were differences in skin health problems between designs **(Level of Evidence 1).**

Results (Nursing home):
- Disposable belted pads were not easier or quicker to change than disposable all-in-ones.
- Carers found disposable pull-on pads and disposable pads significantly easier and quicker to apply than the other designs (in the standing position).
- The ability to stand was associated with the carer preference for disposable pull-on pads or disposable pads.
- Various older studies (2004 or older) have involved user trials of washable bodyworn products alone (94); disposable bodyworn products alone (95) (96); comparisons between disposable and washable bodyworn products (97) (98) (99) (100) (101) (102) (103) (104) (105); or between disposable and washable bed pads and bodyworns (27) (106) (107). The results from these studies are of limited value because of the many new products that have superseded them, but they do yield useful insights that apply to generic designs.

In 2014 Fader *et al.* published a study that used a "shopping experiment" to investigate the preferences of community-dwelling UK women and men with moderate-to-heavy urinary incontinence for four different designs of disposable absorbent products (pads, all-in-ones, belted pads and pull-on pads) and towelling washable / reusable products, day and night (108). Participants tested each design and selected products they would prefer, given a range of different budgets. Disposable pads (the design most frequently supplied by the UK National Health Service) were ranked second to disposable pull-on pads by women and lowest by men. When faced with budget constraints, up to 40% of participants opted for 'mix-and-match designs. Over 15 different combinations of products were selected by participants in this shopping experiment. Most (91%) stated a willingness to 'top-up' assigned budgets from their own income to secure preferred designs. Participants displayed diverse preferences, and Fader *et al.* concluded that enabling user choice of absorbent product design through individual budgets could improve the satisfaction of consumers and efficiency of allocation of limited resources.

In new studies since the 6th consultation (36), Bitencourt and colleagues (70) and Fernando and Wagg (109) investigated the use of disposable absorbent products by hospitalised adults. In a study aimed at discovering the reasons why patients were using absorbent incontinence products at all (disposable all-in-ones), Bitencourt *et al.* (70) recruited 105 adults (61% female, 39% male; 52% aged 20-60, 48% over 60) from surgical wards in a Brazilian hospital. They found that only 15% of patients had UI or diarrhoea. For a further 38%, there was no recorded reason for wearing absorbent products, while mobility impairment and / or cognitive impairment were the declared reasons for the balance. The authors proposed the adoption of an "Evaluation Scale for Diapers Use in Adults" to assist care staff in determining when the use of absorbent products was appropriate, and to monitor their use.

Fernando and Wagg (109) set out to establish the views of wearers and carers on acceptable wait times before soiled absorbent products for incontinence (of unspecified design) are changed. They recruited 50 patients (84% female, 16% male; mean age 79 years, all over 65) from a tertiary acute care hospital in Canada. They found statistically significant differences in patients versus care providers for daytime UI, with patients mostly intolerant of wait times more than 1 hour after an episode of UI, while carers considered longer wait times acceptable. Both patients and care providers reported that products soiled by FI required changing within 15 minutes both during the day and at night. The actual wait times experienced by patients were longer than the times deemed acceptable by patients or care providers. The study highlighted the importance of appreciating patient perspectives in promoting person-centred care.

6.1.1. Disposable, bodyworn absorbent products for urinary incontinence: development of international standards.

Because clinical evaluations are expensive and time-consuming, laboratory evaluation of absorbent products – particularly in support of purchasing decisions and marketing – is widespread. Few laboratory methods have been clinically validated, but there is a clinically-validated International Standard (ISO 11948-1) relating to the leakage performance of disposable bodyworn pads and all-in-ones for adults with moderate-heavy UI in institutions (93). It describes a simple method for measuring the absorption capacity of products in the laboratory that was shown to correlate well with the leakage performance of 18 different products evaluated in an international multi-centre clinical study involving 112 heavily incontinent adults (110). The strength of the correlation between technical and clinical data depended on the exact parameters being compared, but typically r = 0.9 **(Level of Evidence 2)**. This laboratory test (the Rothwell method) is now in common use in the UK, Sweden and other countries and provides a basis for selecting similar products with which to make direct comparisons (for cost purposes) or to select promising products for inclusion in clinical trials.

The ability of ISO 11948-1 to predict the leakage performance of more recent products (138 all-in-one and pad designs) for heavy UI was investigated by Cottenden *et al.* (111). Correlations were poorer than in the original 1993 study but still strong enough to make the method useful.

The Rothwell method merely measures the absorption capacity of the material in a product and would be blind to any enhancement to leakage performance that might be achieved by distributing the material optimally or by such product features as elastication. Since the 6th consultation (36), a study has been published (73) that compared the Rothwell method with a manikin method thought to hold potential as a new international standard. It achieved slightly higher correlations with user test data than the Rothwell method and, unlike Rothwell, was able to detect the benefits of elastication. However, its poor reproducibility (between laboratories) subsequently led to its abandonment as a candidate for a new international standard, although it has been published as a national standard in some countries. The need for a validated and widely accepted replacement for Rothwell persists.

Although leakage performance is a very important measure of product effectiveness, other factors are of course important too. Accordingly, it is helpful for users to systematically evaluate several products with similar leakage performance, as they may differ in other important variables such as fit and comfort.

Table F-16: Recommendations relating to bodyworn absorbent products for men and women with moderate-heavy UI.

- Sex (and gender) should be considered when products are prescribed / purchased for users. As men often have substantially higher incontinent urine volumes than women, men may require more products and / or more absorbent products than women (Grade of Recommendation B).
- Sex (and gender) should also be considered when products are prescribed / purchased for users because men and women are likely to prefer different designs. Men generally prefer disposable all-in-ones to pads (Grade of Recommendation B).
- Recommend disposable pads to women as an acceptable cost-effective alternative to pull on pads (Grade of Recommendation B).
- Caution is recommended if washable designs are being considered. Heavy bulk confines their use mainly to the night-time (where they may be particularly useful for users who lie on their side). They are unacceptable for most people during the daytime and for most women at any time. For this reason, a blanket policy of health services providing washables alone is not recommended. If washables are being considered, refer to Table F-21 (Grades of Recommendation B).
- Freedom from leakage: Where possible, international standard laboratory tests should be used to rank the likely leakage performance of disposable pads and disposable all-in-ones for moderate-heavy UI (Grade of Recommendation B). In general, all-in-ones should be selected in preference to pads to minimise leakage (Grade of Recommendation B).
- Carer application: When products are applied by a carer to a patient who can stand for product changing, disposable pads or pull-on pads should be used as they are easier and quicker to change than all-in-ones or belted pads. If the patient is lying down (e.g. at night), pull-on pads should be avoided (Grade of Recommendation B).
- Combinations of designs for different situations (e.g. disposable pads for staying in, disposable pull-on pads for going out, washable all-in-ones at night) are recommended to provide optimum management in terms of patient needs and cost-effectiveness (Grade of Recommendation B).

See also the general recommendations relating to product selection in Table F-20 and to washable products in Table F-21.

Table F-17: User characteristics, priorities and contexts which favour or discourage the use of the dif-ferent pad designs for adults with moderate-heavy UI.

Product Type	More likely to suit you if...	Less likely to suit you if...
Disposable pads	• You are female. • Discretion is a priority for you. • You want a product that is easy to put on. • You can stand up (with assistance if necessary) but can't change your own product.	• Your leakage is very heavy. • You are mobile and active.
Disposable pull-on pads	• You are female. • Discretion is a priority for you. • You want a product that is easy to put on. • You can stand up (with assistance if necessary) but can't change your own product. • You are most concerned about reliably containing leakage.	• You find the removal of clothing for changing the product difficult. • Low cost is a priority for you. • You need a product for use at night and need help with product changing.
All-in-ones	• You are male. • Your leakage is very heavy. • You are unable to stand to change the product.	• Discretion is a priority for you.
Belted pads	• You are male. • You are most concerned about reliably containing leakage.	
Washable pads	• You are male. • Your leakage is very heavy, particularly at night.	• You do not have adequate laundry facilities. • You are unwilling to use washable products. • You are not prepared to carry used products when out • Discreetness and appearance are priorities for you.
NB The content of this table is based on the referenced evidence cited in the chapter, but the unreferenced version provided for the lay public on the accompanying website (www.continenceproductadvisor.org) is reproduced here.		

6.2. Summary

- There is no single best product design (i.e., one design that is significantly better than all other designs for all users) **(Level of Evidence 1).**
- Different designs are better for men and women. In particular, men generally leak substantially higher volumes of urine than women **(Level of Evidence 1)**.
- For men, disposable pull-on pads or disposable belted pad designs are not better overall than the cheaper disposable all-in-ones, indicating that the latter is the most cost-effective design for men. For women, pull-on pads are better overall than the other designs (except for night-use for those living in nursing homes) **(Level of Evidence 1)**.
- Unlike men, women in the community do not favour disposable all-in-ones over disposable pads, and of these cheaper designs, pads may be preferred by women **(Level of Evidence 1)**.
- The leakage performance of disposable pads and disposable all-in-ones for heavy incontinence can be predicted with reasonable precision using an ISO laboratory test **(Level of evidence 2)**.
- Washable products are vof variable design, materials, and performance. Terry-towelling products (used with plastic pants) have good leakage performance but limited acceptability - confined mainly to some men at night **(Level of Evidence 2).**
- The leakage performance of disposable pads is worse than other disposable designs, but they leak significantly less if they are held in place by mesh rather than ordinary pants **(Level of Evidence 3)**.
- There is no firm evidence regarding the performance of different designs for faecal incontinence and no firm evidence that any design or type of material (washable or disposable) is better or worse for skin health **(Level of Evidence 4)**.

6.3. Recommendations

Recommendations relating to bodyworn absorbent products for men and women with moderate-heavy urinary incontinence are summarised in Table F-16, while Table F-17 describes the user characteristics, priorities and contexts that favour or discourage the use of the different product designs.

6.4. Priorities for research

- Comparison of absorbent products (disposable and washable) when used by caregiver-dependent users in the community.
- Development of more effective and acceptable disposable designs specifically for men.
- Development of more effective and aesthetically acceptable washable products, particularly for night-time use and for women.
- Development of a new international standard to replace or complement ISO 11948-1 (Rothwell method), which can detect any benefits of such features as elastication.

7. DISPOSABLE UNDERPADS

The most recent publications on the use of bed pads were in 1994 (27) (106), which probably reflects their diminished and limited role in the long-term management of incontinence. The presence of a disposable underpad on a chair discloses the fact that the user is incontinent. The use of bed pads for sole protection requires clothes to be pulled up (or absent), which poses a threat to a person's dignity. Disposable bed pads easily become displaced, folded and creased inhibiting both performance and comfort, and possibly threatening skin health. Large disposable bed pads with wings to tuck under the mattress may have a role as bed protection 'back-up' to bodyworn absorbent products. The main use of disposable underpads should be confined to temporary bed or chair protection such as during clinical procedures (e.g. enemata) or when using a urinal.

Trials comparing different disposable bed pads are few (27) (112) (113), and it is not possible to draw firm conclusions from them on the effectiveness of different product design features and materials.

Bed pads are generally supplied as non-sterile items, and some case reports published between 1985 and 1997 suggest that recycled paper in bed pads could be a potential source of infection (114) (115) (116) (117). However, there are no recent studies and risk to patients appears to be minimal when products are used as directed.

7.1. Summary

No robust data are available on the effectiveness of current disposable chair pads or bed pads or of their various design features or constituent materials. There is a possible risk of infection from bed pads made from recycled paper for immunocompromised users **(Level of evidence 4).**

7.2. Recommendations

Recommendations relating to disposable underpads are summarised in Table F-18.

Table F-18: Recommendations relating to disposable underpads.

- Disposable underpads should not be used for long-term management of UI or FI but have a useful role as temporary protection for chairs and beds during clinical procedures (Grade of Recommendation C).
- Immunocompromised people should not use bed pads made from recycled paper because of the risk of infection (Grade of Recommendation B).

7.3. Priorities for research

Disposable underpads have a limited role in continence management but are known to be widely used. An exploration of patient views regarding their use may help demonstrate their limitations, particularly regarding skin health.

8. WASHABLE UNDERPADS

Aspects of assessment that are important regarding washable underpads are patient acceptability and preference, particularly with regard to willingness to be naked below the waist (if the product is to be the primary means of protection, rather than acting as back up to a bodyworn product) and availability of laundry and drying facilities.

Some evaluations have found significant differences between products relating to leakage performance, and skin health but none of the products evaluated are now available (118) (119). Compared products always differed from one another in too many respects for it to be possible to extract reliable generic conclusions that can be related to current products. However, the choice of topsheet material and the presence or absence of features like tuck-in flaps and

integral water-proofing appear to be, primarily, matters of personal preference.

In institutional settings, washable bed pads are commonly used by multiple patients and questions are often asked about the risk of cross-infection. Cottenden *et al.* (120) assessed the risk by determining the microbial content of 145 bed pads of five different designs after a night's use by incontinent adults, followed by laundering using a standard foul wash procedure which included heat disinfection at 71°C for three minutes. Laundering destroyed all known pathogenic organisms, although some commensal flora were isolated in small numbers. It was concluded that foul wash laundry left bed pads safe for multiple patient reuse with no demonstrable risk of cross-infection.

8.1. Summary

The literature contains insufficient robust data on which to base guidelines for choosing between washable bed pads. Choice of topsheet material and the presence / absence of design features like tuck-in flaps and integral/separate water-proof backing appear to be, primarily, matters of personal preference **(Level of evidence 3).** Provided an approved foul wash procedure is used, the risk of cross-infection between different users of a bed pads is very low **(Level of Evidence 2).**

8.2. Recommendations

Recommendations relating to washable underpads are summarised in Table F-19.

Table F-19: Recommendations relating to washable underpads.

- If considering using washable under-pads for sole use (i.e. without a body-worn product), the patient will need to be naked below the waist. This needs patient consultation and approval (Grade of Recommendation C).
- Personal preferences of users with regard to topsheet material, tuck-in flaps and integral waterproof backing should be considered in making product selections (Grade of Recommendation C).
- An adequate foul laundry wash cycle should be used, so the risk of cross-infection between successive users of washable bed pads is low and not a contraindication for their use (Grade of Recommendation B).

8.3. Priorities for research

Research on these products is not seen as a high priority.

9. ABSORBENT PRODUCTS FOR CHILDREN WITH URINARY AND / OR FAECAL INCONTINENCE

Most children are expected to achieve daytime dryness by the age of three (121). However, some boys take longer to become dry and some (e.g. children with learning and physical disabilities) may never do so. These children usually require absorbent products to contain leakage.

Aspects of assessment that are particularly important regarding bodyworn products for children are the presence of faecal incontinence, day / night incontinence, level of independence with toileting, and use of aids such as callipers.

No studies of absorbent products have been published since the 5th consultation (92). The existing study was a comparison of all-in-one and pull-on pad designs (26).

Findings indicated that, generally, the all-in-one and pull-on pad products performed similarly. Overall, all-in-ones were preferred for night-time use by the majority of parents. By contrast, 40% of parents preferred pull-on pads for daytime use, and these were found to be particularly appropriate for older children and those who were attempting independent toileting, provided they did not have faecal incontinence. All-in-ones were more suitable for children who were dependent on carers and / or had faecal incontinence and wore callipers or adapted footwear. The authors recommended that both all-in-ones and pull-on pads should be supplied for children, with pull-on pads (which are about 50% more expensive than all-in-ones) being provided for selected children during the daytime.

9.1. Summary and recommendations

All-in-ones and pull-on pads meet different needs, and both should be made available to children with disabilities, dependent on assessment **(Level of Evidence 3 / Grade of Recommendation C)**.

9.2. Priorities for research

- Comparison of washable and disposable bodyworn absorbent products.
- What are the problems faced by parents / caregivers and children in managing continence with different product designs and materials?

10. ABSORBENT PRODUCTS FOR FAECAL INCONTINENCE

Very few absorbent products specifically designed to contain FI are available and no studies comparing different products were found. Most absorbent products used by people with FI were designed primarily to address UI.

Bliss *et al.* (122) have reported preliminary findings of a survey of the use, evaluation and suggested modifications of absorbent products for faecal incontinence, based on a study with 188 community-living persons with the problem. Forty-five per cent of persons used an absorbent product for FI. Ninety-eight percent of those with UI and FI used the same type of product for both. Suggested improvements in product designs included having better odour control, fit, and ability to stay in place; a clearer distinction between the front and back of a pantiliner or pad; adding wings for greater absorbency, and making them flushable, cooler feeling, wider and longer in the rear and more absorbent but less bulky. For mild faecal incontinence, especially when faeces remain between the buttocks without soiling underwear, persons have used a small disposable gauze surgical dressing placed between the buttocks (Fig F-12). This product was more acceptable than a pantyliner or pad to some men (122) **(Level of Evidence 2)**.

Recent work on odour relating to absorbent product usage for FI is described in Section P, while management of FI using products other than absorbent ones is described in Section N.

10.1. Recommendations

- A disposable gauze dressing that can be placed between the buttocks should be considered and may be acceptable for men with light faecal incontinence **(Level of Recommendation C).**

10.2. Research priorities

- Better designs of absorbent products are needed for light and moderate FI (with and without UI).

11. BROADER RECOMMENDATIONS

General recommendations on absorbent product selection and recommendations relating to washable products, in particular, are summarised in Tables F-20 and F-21, respectively.

Table F-20: General recommendations on pad selection

- **Individuality:** No one product works best for all users: needs and priorities vary. Accordingly, users should be advised to try a variety of products when possible **(Grade of Recommendation B).**
- **Brand differences: People should be advised that** individual product brands within a design group often exhibit a wide range of performance and acceptability for individuals, and it cannot, therefore, be assumed that products of different brands but the broadly similar design will be equally acceptable or effective **(Grade of Recommendation B).**
- **Combinations of designs:** Absorbent products vary greatly in price and performance, and suitability for individual needs. Users should be advised that they may find combinations of designs preferable and cost-effective. For example, women might use disposable pull-on pads (expensive but discreet and good for leakage) for going out and disposable pads (cheap, less good for leakage) for staying at home. Men might use disposable all-in-ones for daytime and washable terry-towelling products for nighttime **(Grade of Recommendation B).**
- **Freedom from leakage:** Nobody wants their product to leak, but compromises have to be made. If it is a priority for a product to successfully contain a person's most severe accident, it may need to be substantially more bulky and expensive than is needed most of the time. Advise users that they may choose to tolerate a higher risk of product leakage in exchange for being able to use cheaper, smaller, more discrete products. Priorities for a given user should be investigated in making product selections **(Grade of Recommendation C).**
- **Comfort and skin health:** In general, products containing superabsorber should be selected in preference to those without (Grade of Recommendation B). Shaped pads should usually be selected in preference to unshaped **(Grade of Recommendation C).**
- **Staying in place:** No product is effective if it slips from the position. Pads should be used with stretch (e.g. cotton / lycra) underwear or mesh pants **(Grade of Recommendation B)**. Shaped pads should be used in preference to rectangular pads **(Grade of Recommendation C).**
- **Ease of putting on and taking off:** The ease of putting products on and taking them off should be considered, especially for caregivers and for incontinent users with reduced mobility or dexterity **(Grade of Recommendation C).**
- **Aesthetics and discretion:** A possible preference for small, more discrete products (even if they are more likely to leak) should be considered, especially for those wishing to wear close-fitting clothing **(Grade of Recommendation C).** The possibility of plastic backing materials rustling noisily should be taken into account in selection**(Grade of Recommendation C).**
- **Independence and lifestyle:** The ability of a user to change his / her own product should be considered **(Grade of Recommendation C):** those able to change their own product can often manage with a smaller (less absorbent) one than those reliant on a caregiver. Users who travel should consider in their choice of product(s) the practicalities of carrying a supply, disposing of used ones, and dealing with laundry **(Grade of Recommendation C)**.
- **Costs:** Cost issues should be approached with caution **(Grade of Recommendation C)**. Expensive products do not necessarily work better than cheaper ones. Cheaper products do not necessarily save money. If they leak more, they may have to be changed more frequently and / or lead to higher laundry costs. More product changes will mean increased caregiver workload. However, more absorbent products will not necessarily reduce product consumption rates: products are often changed according to the nursing unit or personal routine.

Table F-21: Recommendations relating to washable pads.

- **Laundry issues:** Access to good, reliable washing and drying facilities should be checked before washable products are introduced **(Grade of Recommendation B).** Laundry – especially of bed pads – can be heavy work, beyond the capability of frail incontinent people or their caregivers. The number of washable products needed per user depends on laundry turn-around times. Drying times for washables can be long and expensive, especially for bodyworns for heavy incontinence and for bed pads.
- **Personal preferences:** Personal preferences (of both users and caregivers) with regard to choosing between washable and disposable products should be carefully taken into account **(Grade of Recommendation C).** Some users prefer the chore of laundering washables to anxiety over when their next consignment of disposables will be delivered. Washables generally require less storage space than disposables. Discreet disposal of disposables can be a challenge. The possibility of using a mix of disposable and washable products should be considered **(Grade of Recommendation C)**. Some users who choose disposables when at home prefer washables when travelling because of the space that disposables occupy in luggage and the possible inconvenience of disposal. Others use washables at home and disposables when away as they see the balance of disadvantages and advantages differently.
- **Personalisation of products:** In institutions, the chore of personalizing washable products and sorting them after each laundry cycle should be considered before they are introduced **(Grade of Recommendation C).** Washable bodyworns are often personalised to particular users. In institutions, this means marking products with users' names and sorting them after laundry, an extra task for caregivers. Washable bed pads are not usually personalised.
- **Staining:** Washable products should not usually be used by those with faecal incontinence – beyond occasional light smearing – because of staining **(Grade of Recommendation C)**. Skin sprays and ointments may also stain washables.
- **Costs:** Cost comparisons between washable and disposable products should be made with caution **(Grade of Recommendation C).** Key factors are local arrangements (mostly laundry and transport costs), the durability of the products (which depends on how carefully they are used and the criteria for deciding when they should be replaced); the costs of ordering, transporting and disposing of disposables; and product purchase costs. Much of the cost of washables is encountered with the initial capital outlay for stock. This also represents a commitment to use the products for an extended period, and so expensive mistakes can be made if it transpires that a better product was / has become available. It will usually be wise to experiment with samples of a variety of alternative products before committing to major purchases.

G. EXTERNAL URINE COLLECTION DEVICES

External urine collection devices are primarily available for men.

Close-fitting penile sheaths (sometimes called condom catheters, uridomes, Texas catheters or external catheters) are male incontinence devices (no practical equivalent is currently available for women). The sheath fits over the penis much like a contraceptive condom and collects urine as it leaves the body. The sheath is normally connected at its outer end to a tube that leads to a urine drainage bag. Urine drains into the bag, which is usually worn on the thigh or calf and is collected there until emptying is convenient. Sheaths come with a variety of design features and the main ones are listed in Table G-1 and illustrated in Fig G-1.

The main factors that make sheaths (un)suitable for men are summarised in Table G-2.

An effective urinary sheath is one that stays securely in place for an acceptable period, is leak-free, comfortable to wear, easy to apply and remove, avoids skin damage and channels the urine effectively into a urine drainage bag. Correct sizing and fastening are critical to product success. Users indicate that the foremost important quality of a penile sheath is security from leakage, followed by comfort and ease of application and removal.

Table G-2: The main factors that make sheaths (un)suitable for men.

Sheaths are suitable for men with:
• Moderate to heavy urine loss.
• Urinary frequency and / or urgency.
• Limited Mobility
(Sheaths can be used in combination with intermittent catheterisation.)
Sheaths are not advised for men with:
• Confusion or psychological vulnerability. Sensation through spinal cord injury or neuropathy (111) (112) (113).
• A retracted or very small penis (alternative products are available).

Table G-1: The main design features of sheaths.

- **Materials:** latex, silicone rubber or other synthetic polymers.
- **Size:** range of diameters (about 20-40 mm, in 5-10 mm increments) and lengths; most companies supply a measuring tool to ensure the best fit; guide is placed at the widest point of the penis, typically about 20 mm from the base **(110).**
- **Adhesive:** may be integral to the sheath (one-piece systems) or be a separate strip or spray (two-piece systems).
- **Applicator:** some sheaths are provided with an applicator with the aim of making application easier or reducing manual contact with the penis.
- **Anti-kinking / twisting features:** these are intended to improve drainage by aiming to prevent the sheath from kinking or twisting at the distal end near the connection to the drainage bag tube.
- **Anti-blow-off:** some designs aim to reduce the likelihood of the sheath blowing off at high urine flow rates, as at the beginning of a void; for example, the distal end of the sheath may be thickened and bulbous to stop the internal walls from sticking to one another between voids.
- **Connections to the drainage bag:** some designs aim to increase the ease and security of drainage bag connection, for example, a push ring or ridge at the end of the outlet tubing.
- **Retracted penis:** some sheaths are designed with or without specific features in order to accommodate a retracted penis, for example, a shorter sheath or a wider adhesive seal.
- **Durability:** varies according to the manufacturer. 24 hours is a common recommendation, but some are intended for extended wear.
- **Transparency:** some sheaths are made from transparent materials (e.g. silicone), which can allow for observation of penile skin condition along the shaft and glans.

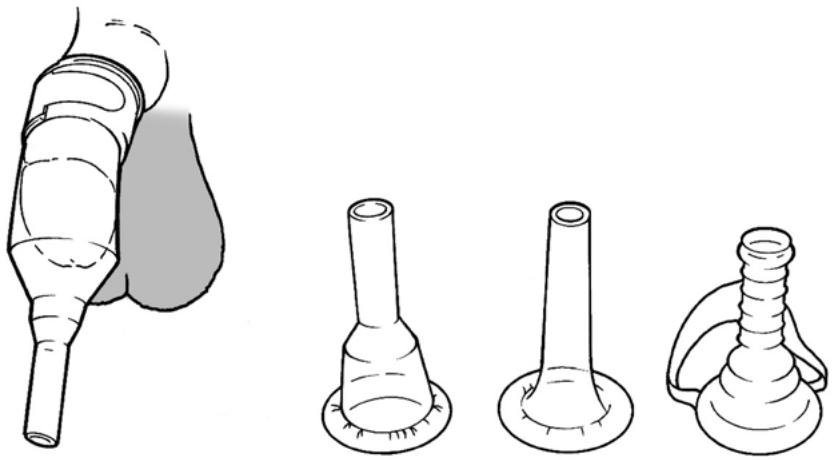


Fig G-1: Sheath without integral adhesive, secured with external fixation (a), and a variety of sheaths showing anti-blow-off features and applicator (b).

1. EVIDENCE

The 6th International Consultation (36) identified trials in which a sheath system was compared to alternative continence products: indwelling catheters (123), pads (84) or one sheath versus another (124) (125) (126) and the results from these studies are included in the summary section, below.

Since the last consultation, two studies have been published (18) (127). Saint and colleagues compared UTIs, pain, discomfort and other complications between two otherwise similar groups of men who received either a sheath or an indwelling catheter for short-term urinary management during hospitalisation (n=80) (127). The two device types were similar in terms of the proportions of men experiencing UTIs and other non-infectious complications. Pain, discomfort, bleeding, or other trauma were experienced by signif-

Table G-3: Reported complications associated with sheath use.

Complication	Prevention/Treatment
Contact dermatitis or allergy; balanitis, oedema (131) skin maceration from wet exposure (132)	Allergy to latex can develop over time; change the product to silicone base; routinely check skin; ensure skin is dry before application of sheath and skin barrier; ensure sheath is the correct size.
Compression, tourniquet effect; (133) (134) (135).	Use sheaths with caution in individuals with no penile sensation; avoid adhesive straps or use straps with stretch to allow for penis expansion/ contraction; correct size is critical.
Skin irritation (136).	Ensure sheath does not become twisted near the distal end to avoid stagnation of urine and extended urine contact with penile skin; good genital hygiene.
Glans irritation/pressure ulcer	Ensure adequate space at the end of the sheath to prevent pressure on the glans.
UTI – range 40-63% (137) (138).	Ensure consistent drainage – if sheath twists, it will block urine flow; at-risk individuals – those with poor hygiene, cognitively impairment who may tug/twist sheath drainage tubing.
Hydronephrosis (139) (140).	Detrusor over activity risk factor for vesicoureteral reflux; may require antimuscarinics & intermittent catheterisation in addition to sheath drainage; warn users of the risks of acute urinary retention (AUR) when consuming large amounts of alcohol in a short time – individuals should be taught signs of AUR & teaching of intermittent catheterisation if engaged in high fluid intake or recreational drugs.
Fibro-epithelial penile polyps (141) (142) (143).	Close skin observation by user or caregiver; good user education to aid in proactive skin health
Isolated gangrene (144).	Immunocompromised individuals are at high risk for infection related to condom use.

icantly fewer men being fitted with a sheath than with an indwelling catheter. However, the two devices were comparable on removal.

Da Silva and colleagues reported that amongst thirty hospitalised men using sheaths, poor fitting of the devices by nurses was common, skin damage occurred in one third, and that the majority of patients received no guidance on sheath use (128).

There is a need for greater education of health professionals, lay-carers and users about sheaths. An expert panel noted resistance to the introduction of external collection devices, including sheaths, in hospital settings and the need for education on their application, effectiveness and possible complications. The importance of education of patients and lay-carers in ambulatory care about safe and effective device application was also noted (129). Half of the men included in one trial comparing sheaths with pads, bodyworn urinals and penile clamps had previously tried a penile sheath system but only one of these had received assistance from a healthcare professional for fitting and follow-up (18).

A sheath product which is secured to the glans is available. Manufacturer information suggests that the product is useful for men with a short or retracted penis for whom a standard sheath system is unsatisfactory. Apart from testimonials, there are as yet no published data evaluating the product and only one paper (130) that suggested the product could be a useful alternative to a conventional sheath.

Although many men use sheaths successfully, several case studies attest to the potential problems (Table G-3). It is of note that most such problems are preventable with proper sizing, continuous drainage, routine changing and appropriate skin care.

A review of findings relating to odour associated with sheath use is given in Section P.I.4.

2. SUMMARY

- Sheaths are more comfortable than indwelling catheters, and UTI incidence is similar (84) or somewhat lower in sheath users without dementia (123) **(Level of Evidence 2)**.
- Men with moderate incontinence using a sheath rank QOL better with a sheath than when using an absorbent product (84) **(Level of Evidence 2)**.
- Sheaths with integrated adhesive are preferred over those with an adhesive strip or applicator (124) (126) **(Level of Evidence 2).**
- Silicone sheaths are preferred over latex (124) **(Level of Evidence 2).**
- Men prefer a choice of continence products (pads, sheath, clamp) depending on activities and lifestyle (18) **(Level of Evidence 2).**

3. RECOMMENDATIONS

Recommendations regarding urinary sheaths are summarised in Table G-4.

Table G-4: Recommendations relating to urinary sheaths.

- Product differences mean that men should try different products before making a final selection **(Grade of Recommendation B)**.
- Offer men access to a combination of continence products (sheath, pads, clamps), depending on activity **(Grade of Recommendation B)**
- Advice men that key performance characteristics are security (i.e. ability to keep a leak-proof seal and channel urine to the drainage bag without leakage) and ease of application and removal of the sheath **(Grade of Recommendation B).**
- Advise men that sheath applicators may not make sheath application easier **(Grade of Recommendation B).**
- Sheaths with integral adhesive (one-piece systems) \should be offered over (two-piece systems) **(Grade of Recommendation C).**
- Sheath users should be monitored for latex or adhesive allergies, skin health, tissue damage and UTI **(Grade of Recommendation C).**
- Advise men then when possible, the external sheath rather than the indwelling urethral catheter should be the urinary collection device of choice. **(Grade of recommendation B).**

4. PRIORITIES FOR RESEARCH

- Evaluation of leg bag and sheath design features claimed to reduce twisting and kinking at the drainage bag connection site.
- Evaluation of products advertised as suitable for men with a retracted penis.
- Studies to generate and validate procedures to help identify the type of sheath most likely to suit an individual.

H. URINE DRAINAGE BAGS AND ACCESSORIES

Urine drainage bags fall into two main categories. Bodyworn bags generally have a lower capacity (less than 500 ml) and are designed to be worn under clothing on the leg (often called leg-bags) or around the waist. They aim to provide discreet storage of urine and can be attached to either a catheter or a sheath. They are mainly used during the day and are secured to the leg or waist in a convenient position using a range of straps or other support devices. The popularity (or otherwise) of many features is generally a matter of personal preference.

Second, there are large capacity bags - commonly called night bags – which are designed to provide additional drainage capacity overnight or for people who are permanently in bed. They are usually held in a position away from the body on either a floor-stand or a hanger that hooks onto the bed or chair frame. They may also be connected to a bodyworn bag to form a link system for overnight use.

Expert opinion found in best practice guidelines recommends positioning drainage bags so that they are off the floor, but data are insufficient to establish whether this practice reduces the incidence of bacteriuria. (145) (146) (147)

To prevent cross contamination, a closed drainage system is standard and, in the home, it is common to use vinegar, household detergent or diluted bleach (148) (149) (150) (151) (152) to clean drainage bags.

The main design features and variants of urine drainage bags are described in Table H-1 and illustrated in Fig H-1, and Fig H-2 shows a variety of tap designs

Urine drainage bags are suitable for those with:

Table H-1: Drainage bag features

	Leg bag	Night bag
Capacity	350-900 (usual 500 ml)	2000-4000 ml
Material	Transparent PVC (polyvinyl chloride), PVDF (polyvinylidene fluoride (less noise from rustling)), or polyethylene or rubber / latex.	As with leg bags.
Wear position	On thigh or calf; on the abdomen.	Situated below bladder with tubing distributed to prevent low hanging/dependent loops.
Attachment	Latex or cloth elastic straps.	Separate frame/stand or hooked on bed or wheelchair.
Connecting tube	Various lengths; can be cut to meet individual needs.	One length only; intended to maintain a closed link system.
Drainage tap	Flip valve, separate cap, screw cap.	As per leg bags.
Sampling port	If present, located in drainage tubing.	Located in drainage tubing.
Comfort	Cloth backed prevents skin irritation.	No specific comfort features.
Discretion	Internal welds reduce bulging and the sound of urine on movement.	None are discreet; may be covered with a cloth bag to disguise bag.
Anti-kinking	Connecting the tube reduces kinking and twisting, so that urine drainage is not obstructed.	Sturdy plastic tubing does not allow twisting at the catheter site but may kink along drainage tubing.
Anti-reflux valve	Non-return flap valve to prevent urine reflux if the bag is raised above bladder; may reduce risk of CAUTI.	As with leg bags.
Linkage system	Allows attachment of leg bag to night bag so maintain a closed system; may reduce risk of cross-infection.	

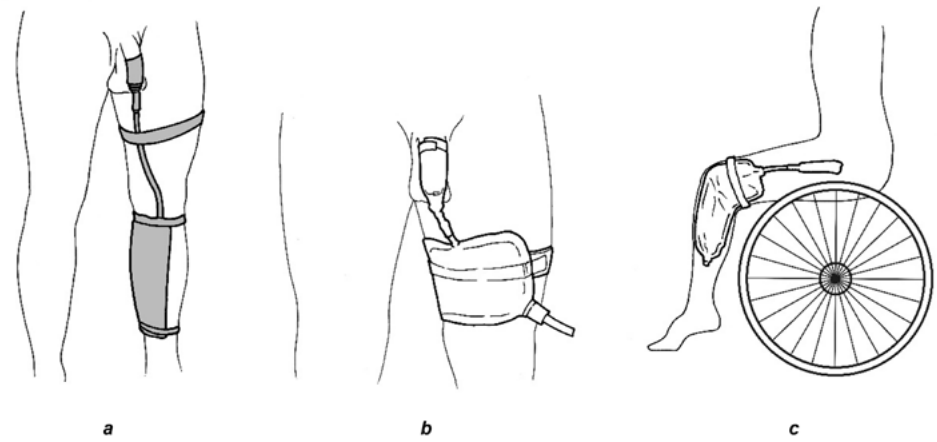


Fig H-1: A urine drainage bag shown worn on the calf (a), a discreet thigh urine drainage bag (b) and a shaped urine drainage bag for wheelchair use (c).

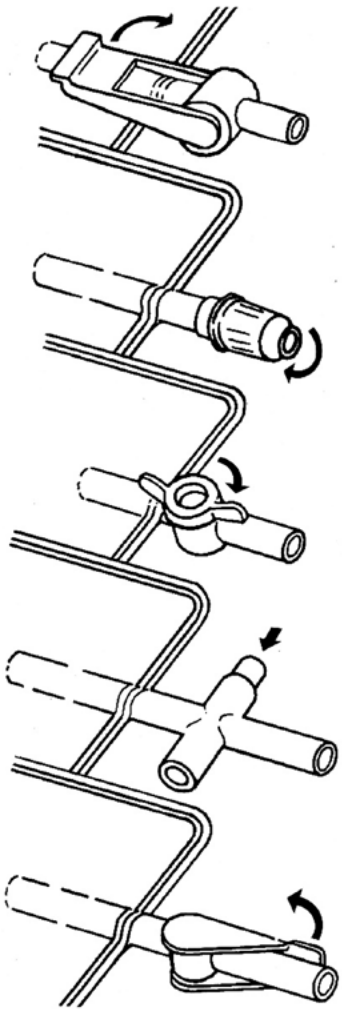


Fig H-2: A variety of urine drainage bag tap designs. The arrows indicate the action needed to open and close each valve.

- The visual acuity to see the tap / spigot and the manual dexterity to open and shut it (153) (154).
- The ability to assess skin condition where straps and drainage bag contact the leg.

1. EVIDENCE

The last consultation (36) identified three new trials addressing dependent drainage tubing loops (or airlocks) (155), specimen collection technique (156) and catheter securement (157), two dependent loop prevalence studies (158) (156) and two best practice surveys (159) (157).

Since the last consultation (36), there have been no clinical trials addressing this topic. However, one study used computational models to examine the influence of tubing design on urodynamics and explored its potential to influence biofilm formation and encrustation. Results indicated that tubing diameters could be reduced by 40%-50% and still meet flow rate standards for leg bags. The authors proposed that this might also reduce tube kinking (160).

2. SUMMARY

- Taps are sometimes difficult to open and may leak onto the fingers when the bag is emptied (161) (162) **(Level of Evidence 2)**.
- Chafing between bag and skin is often reported (161) (162) **(Level of Evidence 2).**
- Bags with tubing that is flexible and can be cut to length to suit the individual are appreciated (161) **(Level of Evidence 2).**
- Discreet bags (that are not readily visible beneath clothing) are appreciated (161) **(Level of Evidence 2)**.
- Designs in which the tap and outlet spouts are widely separated are most effective at preventing contamination of the hands with urine (163) (164) **(Level of Evidence 2).**
- There is insufficient evidence that pre-connected products reduce the incidence of bacteriuria (147) (Level of Evidence 2).
- There is no evidence that the addition of antiseptic agents to drainage bags prevents the onset of bacteriuria (165) **(Level of Evidence 2)**.

- Comfort and ease of applying straps to the leg is key to successful wear (154) (166) (167) **(Level of Evidence 2)**.
- If there are dependent loops in the drainage tube, airlocks can compromise efficient bladder emptying (155) (156) **(Level of Evidence 3)**.
- Most drainage bags (bodyworn and night bags) have an integrated anti-reflux valve, but it is unclear whether they reduce the incidence of CAUTI (147) (168) **(Level of Evidence 3)**.
- There is inadequate evidence to state that single-use (147) or daily change of leg bags or drainage bags reduces bacteriuria or CAUTI. In practice, drainage bag changes ranged from every 3 days to more than 20 days (169) (170) (171) **(Level of Evidence 3)**.
- An abdominal 'belly bag' drainage system may be more convenient, comfortable and less likely to cause discomfort than leg and night bags (172) **(Level of Evidence 3)**.

Table H-2: Recommendations relating to urine drainage bags and accessories.

- Practitioners should recommend taps which are easy to open and should not leak onto the fingers when the bag is emptied **(Grade of Recommendation B).**
- Care should be taken to avoid chafing between bag and skin **(Grade of Recommendation B).**
- Individual needs and personal preferPences should determine the use of leg / suspension / attachments and position of where the bag is worn (166) **(Grade of Recommendation C).**
- An abdominal drainage bag ('Belly Bag') may be considered as a convenient, comfortable option to a leg secured bag (172) **(Grade of Recommendation C).**
- A closed urinary drainage bag system where the system is only broken to change the sterile bag according to the manufacturer's directions should be consider. This may reduce the onset of bacteriuria **(Grade of Recommendation A).**
- Drainage systems for night bags should be positioned off the floor to reduce the risk of cross-infection (145) (146) (173) **(Grade of Recommendation C).**
- All facilities should enforce regular monitoring of practice to ensure adherence to evidence-based guidelines on catheter/drainage bag management **(Grade of Recommendation C)**.
- Catheter securement devices should be in place on the thigh or abdomen for all indwelling catheters **(Grade of Recommendation C).**
- Dependent catheter loops should be minimised to allow optimum urine drainage **(Grade of Recommendation C).**

3. RECOMMENDATIONS

Recommendations relating to urine drainage bags and accessories are summarised in Table H-2.

4. PRIORITIES FOR RESEARCH

- Evaluation of a linked system with night bag/leg bag and the onset of bacteriuria compared to changing from day to night bag.
- Reviewing practice in home settings: is a closed catheter drainage system more effective at preventing symptomatic UTI than reusable non-sterile urinary drainage?
- Most effective and acceptable cleaning methods for non-sterile urinary drainage systems.
- Development of catheter tubing that prevents the formation of dependent loops.

I. MALE BODYWORN URINALS AND DRIBBLE CONTAINERS

Products such as bodyworn urinals (BWU) and dribble containers (penile pouches) are an alternative to a sheath system (Fig I-1). They usually comprise a ring-shaped opening or cone-shaped component which is worn around the penis (and held firmly against the pubis by means of a belt and straps) and channels urine to an integral collection bag. There are two main designs: one-piece with the cone and flange as a single combined unit, or two-piece, where the cone and flange are separate and connect when in use. BWUs are more substantial collection devices than sheaths. They are designed to be washed and reused multiple times and to be worn over extended periods. They are less frequently used than sheaths but may be a good option for those with a retracted penis or who do not wish to wear a sheath. Dribble containers (penile pouches) involve holding a drainage bag or other container over the penis using a much lighter structure than the flanges used in bodyworn urinals. They are often disposable.

The more substantial designs should be fitted by a specialist: a good fit is crucial for comfort and to avoid leakage. It is also important that the wearer / carer understands how to use the device and the importance of skin care. The wearer / caregiver will need good manual dexterity to manage the device. Several urinals will be needed to use in rotation, allowing each to be properly washed and dried between periods of use.

The main factors that make bodyworn urinals (un)suitable for men, and the challenges to be addressed in using them effectively are summarised in Table I-1.

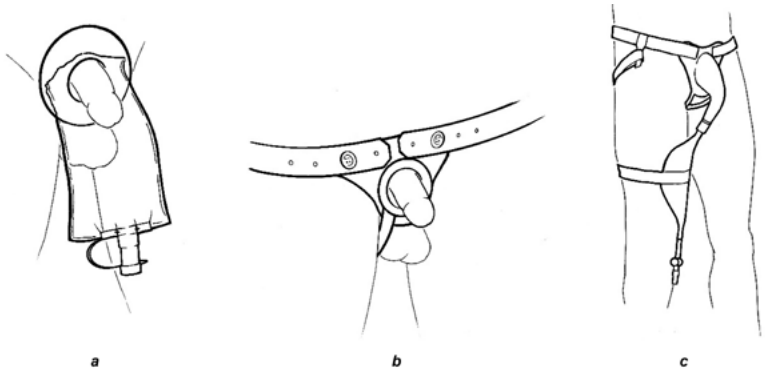


Fig I-1: A disposable penile pouch (a), a pubic pressure flange (with the cone removed) (b), and a bod-yworn urinal with leg bag (c).

Table I-1: The main factors that make bodyworn urinals (un)suitable for men, and the challenges to be addressed in using them effectively.

BWUs are suitable for men with: • A small or retracted penis that will fit into and stay in the flange. • Moderate to heavy urine loss. • Urinary frequency and / or urgency. • A preference to use a bodyworn urinal rather than absorbent products during the day. • The ability to walk but chair / bed-bound during the day.
BWUs are not suitable for men with: • Confusion. • Poor manual dexterity and who are unable to connect the straps. • Impaired mobility who spend large amounts of time lying most of the day (device tends to slip out of position). • Confusion or psychological vulnerability. • Decreased sensation through spinal cord injury or neuropathy (153) (174) (175). • A retracted or very small penis (alternative products are available).
Particular challenges related to BWU use are: • Maintaining a secure fit to prevent the penis from slipping out of the cone resulting in leakage. • Kinking or twisting of the tubing at the junction of the cone. • Risk of skin damage or allergy from the chafing of the leg straps or from the flange against the pubis.
To be effective, the user / carer must: • Understand how to use the device and the importance of skin care. • Have good manual dexterity to manage the device. • Have fitting done by a specialist to ensure the best leak-proof fit. • Moderate to heavy urine loss. • Urinary frequency and / or urgency. • Limited mobility.

1. EVIDENCE

At the time of the 6th International Consultation (36), only one trial evaluated bodyworn urinals or dribble containers. Macaulay *et al.* (18) conducted a randomised controlled trial that included BWUs. Fifty-six men compared (day and night, and for three weeks each): a BWU, sheath drainage, a penile clamp (daytime only), and the absorbent product they had regularly used before the trial. Outcome measures were *overall opinion* (rated on a 10-point visual analogue scale) for day or night use; *product acceptability* (not acceptable / poor / acceptable / good); *advantages and disadvantages* of the test products; *revealed preferences* (which products men used three months after the test).

The BWU was rated as "acceptable" by 48% of participants for daytime use at home, more comfortable when wet than pads, but worse than pads, sheaths or clamp in all other aspects, including self-image. It was also described as leaking in certain postures, particularly when sitting, as the penis can slip out of the flange. No significant differences in quality of life (measured by the King's Health Questionnaire) were noted at the three months follow up. At the conclusion of the study, men were more informed on product choices and, although most (58%) were using a mix of products at the three-month follow-up, few (22%) included a BWU in their mix.

2. RECOMMENDATION

Expert fitting and careful user selection should be ensured to ensure the effective and appropriate use of bodyworn urinals **(Grade of Recommendation B).**

3. PRIORITIES FOR RESEARCH

- Development and evaluation of leak-free, comfortable, and aesthetically acceptable BWUs for men.
- Development and validation of a reliable instrument to measure the performance of different BWU designs and the impact on the quality of life of users.

J. MECHANICAL DEVICES FOR WOMEN WITH UI

Mechanical devices for women are designed (primarily or in part) to prevent urinary leakage. There are three main categories:

External urethral devices: products that are applied over the urethra at the opening.

Internal urethral devices: products that are placed inside the urethra.

Internal vaginal devices: products that are inserted into the vagina.

The main factors that make mechanical devices (un)suitable for women are summarised in Table J-1

Table J-1: The main factors that make mechanical devices (un)suitable for women.

Mechanical devices may be suitable for women with:
• Stress urinary incontinence.
• Good hand control.
• Good memory and cognitive function.
• The ability to understand how to use them.
• A preference for preventing leakage over containing it.
They may be used in combination with other con-servative management approaches such as PFMT.
Mechanical devices may not be suitable for women with:
• Urinary urgency, frequency syndrome / OAB.
• Urinary tract infections.

1. EVIDENCE FROM THE 6TH INTERNATIONAL CONSULTATION (2016)

The published evidence on mechanical devices for women with UI is best introduced by reviewing each device category in turn.

1.1. External urethral devices

There are two different urethral inserts currently on the market.

The Femsoft (Fig J 1A) is a urethral insert made up of a short silicon tube encapsulated by a fluid-filled silicone sheath with a tip designed to conform to and seal the bladder beck and proximal urethra. It is intended for daytime use during physical exercise and is self-inserted (using a separate insertion probe) and removed at user discretion. It is available in two lengths (3.5 cm and 4.5 cm). Before insertion, the proximal end of the cylinder is distended relative to the distal end but, as the user pushes the device (guided by the insertion probe) into the urethra, fluid transfers temporarily to the distal end, returning once the device is in place, so securing it. One study found that device use led to a significant decrease in overall daily incontinence episodes and a higher quality of life. Women with severe SUI had a greater reduction of incontinence episodes per day than those with mild or moderate SUI (176). Positive results have also been reported with women who have a complex medical history having undergone surgical repair of obstetric vesicovaginal fistula. A retrospective study found 76% of women reported being dry, although no significant results were able to be made given a lack of evaluable data recorded. Further evaluation is required to test the acceptability and safety of the device in this population (177). Side effects can include bacteriuria (38.7%), UTI (41.3%), device migration into the bladder (1.3-3.3%) and device rupture (1.1%) (176) (177). A small study found that the device significantly decreased SUI during supervised and unsupervised exercises compared to not using the device. Out of six women participating, there were two cases of dysuria and one case of haematuria, although the haematuria and one case of dysuria resolved despite further device use (178).

The InFlow is an intraurethral valve pump intended for women with a chronic acontractile bladder who would otherwise use intermittent or indwelling catheterisation. The device consists of a short silicone urethral available in various lengths for specific fitting under local anaesthetic. It is maintained in position by distal proximal flanges. When the bladder is full, an inner turbine-like valve is activated by a handheld magnetic device and allows bladder emptying. When the handheld device is removed, the valve closes, maintaining continence. For selected women dissatisfied with catheterisation, the device may provide an alternative to self or indwelling cathe-

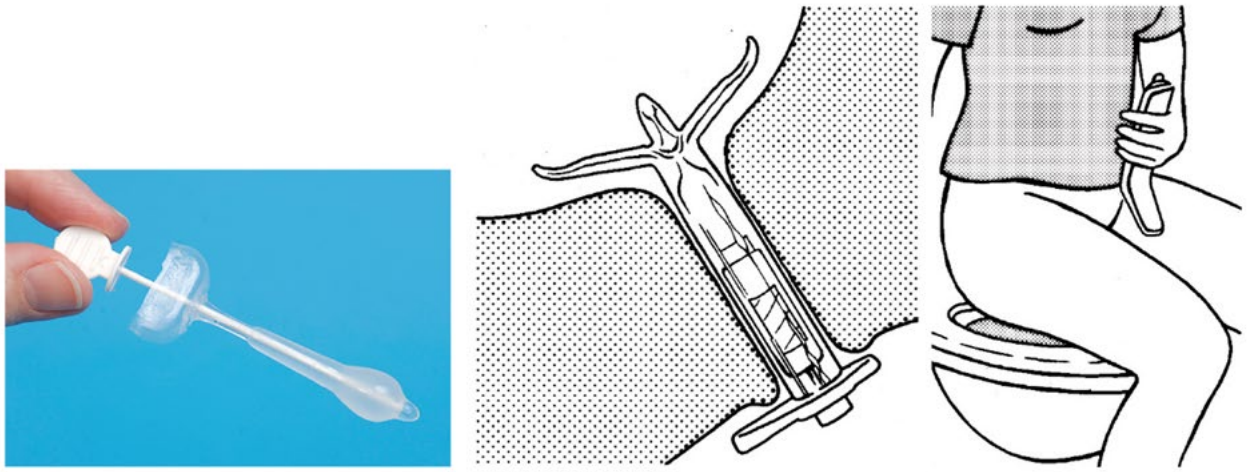


Fig J-1: Intra-urethral devices for women: the Femsoft, with separate insertion probe (white) in place (a); and the InFlow Intraurethral Valve-Pump, in position (b) and with the handheld magnetic activation device in position (c).

terisation and improve quality of life (179). Chen and colleagues found that patients who were successfully able to use the device in a trial period to assess tolerance and regular support were more likely to benefit from device use. High levels of device-related adverse events include UTI (10-50%), device expulsion (5-43%) and asymptomatic bacteriuria (56%) (133-135). Discontinuation rates were also high in two studies (50-62%) with key reasons being discomfort (27-30%), unexpected leakage (7-21%) and spontaneous expulsion (5%) (134-135). To date, no long-term research is available on the adherence to the device nor the effects that it may have on bladder / urethral mucosa (180).

1.2. Internal vaginal devices

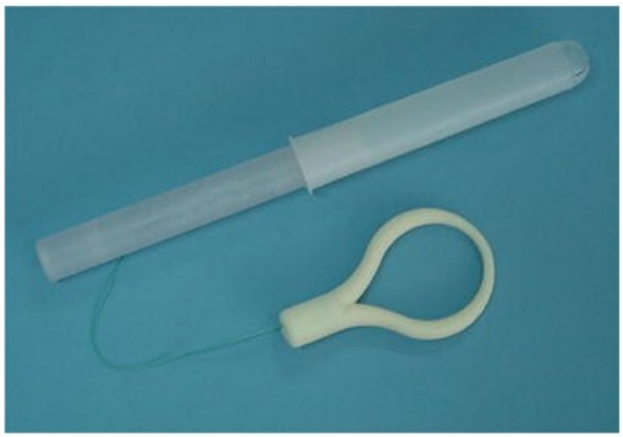


Fig J-2: Vaginal device to support the bladder neck: the Diveen, with applicator.

Intra-vaginal devices aim to correct urinary stress incontinence and have achieved varying success utilising traditional tampons, pessaries, contraceptive diaphragms, and intravaginal devices. Follow up and patient teaching are important. Side effects of vaginal devices can include UTI, discomfort (during insertion, removal or wearing of the device, device being too large or discomfort of genital tract) and vaginal symptoms include spotting and irritation. One study found there was no consensus on the frequency of pessary changes. However, a health professional survey found that the majority of replacements, washings and reinsertions of vaginal pessaries occur every 6 months after the initial insertion (181). Several designs of intravaginal devices are available and those with associated evidence are listed below.

1) Tampon compared to pessaries

Both tampon and pessary may provide protection against activity-induced incontinence (171)

1) Diaphragm / pessaries

Diaphragms (177) and pessaries (182) (183) (184) (185) have all been used with some success and may be an alternative to surgery or whilst awaiting surgery for some women **(Level of Evidence 1).** One study on pessary use has found mixed results with improvements in urgency incontinence, SUI and voiding difficulty in more than half of patients but six (14.3%) developed new-onset urinary incontinence (186). Another study found that pessary use was associated with decreased pelvic organ prolapse symptoms, frequency of urination but resulted in higher levels of new-onset SUI than SUI improvement (187).

Pessaries and behavioural therapy

Kenton *et al.* (188) Schaffer *et al.* (189) both performed a planned secondary analysis of a multi-centre randomised trial from the original ATLAS trial (190). Schaffer *et al.* (189) found the level of education, incontinence severity and post-menopausal status were predictors of success regardless of whether participants were in the continence pessary, behavioural therapy or combination therapy group. Kenton *et al.* (188) observed no changes in pelvic floor symptom bother and HRQOL between pessary and behavioural therapy groups. Therefore, individual preferences should be considered in the approach to the non-surgical treatment of SUI.

1) Vaginal devices designed specifically to support the bladder neck

One device which aims to specifically support the bladder neck (marketed as Diveen; Fig J-2) may be effective in improving incontinence symptoms (191, 192).

The 75NC007 device is designed to automatically situate itself beneath the urethra and bladder to support the former and the bladder neck. It has been found to be effective in decreasing the number of stress urinary incontinence episodes with minimal adverse events: one case of UTI and one case of metrorrhagia among 46 women who used the device. The authors concluded that despite the small sample size, the device is a safe and effective non-invasive treatment for women with SUI (193).

1) Reusable vaginal hollow tampon

A hollow tampon-like device has been made to sit behind the pubic bone, support the urethra during episodes of increased intra-abdominal pressure. One study of 59 women with SUI found a significant reduction (72% median) in urine loss in women with moderate and severe incontinence (>30g/day) on a 24-hour pad weight test but no significant benefit for women with mild symptoms (<30g/day) after three weeks of device use (194). Another study of 52 women of similar age showed significant reductions in a 24-hour pad weight test from a median 6.6g urine loss pre-insertion to 2.2g after four weeks of device use (195). Five percent of participants experienced acute bacterial cystitis, 7% had difficulty inserting and/or removing the device and 7% required out of hours attendance due to difficulty removing the device (194) (195).

1) Disposable vaginal devices

A single-use, disposable intravaginal device (Poise Impressa) Fig J-3 has a resin core with support ‘poles’ covered with a soft nylon mesh that stretches between the arms of the poles to act as a sub urethral sling. Based on two short-term studies, the use of the device has resulted in significant decreases in SUI episodes compared to baseline. 92% of women reported feeling dry and significant improvements in self-reported quality of life (196) (197). In one study, 28% of women experienced spotting and 8% asymptomatic bacteriuria as adverse events (185), but the percentage of specific types of adverse events were undefined in the second study (196) (197).

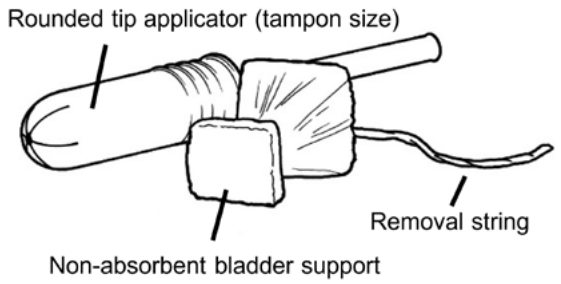


Fig J-3: The Poise) / Impressa (Kimberly Clark, USA) intravaginal device.

Systematic reviews

Lipp *et al.*'s Cochrane review for mechanical devices (198) currently confirms that there is little evidence from randomised controlled trials to judge device effectiveness against no treatment, and large well-conducted trials are required for clarification. There was also insufficient evidence to favour one device over another and little evidence to compare mechanical devices with other forms of treatment.

The European Association of Urology (EAU) summarises evidence from its full guidelines on assessment, diagnosis and nonsurgical treatment of urinary incontinence. It presents limited evidence for the use of mechanical devices for urinary incontinence. It recommends that physicians should not routinely offer intravaginal devices as a treatment for incontinence *(Grade Brecommendation)* (199).

Intravesical devices

- An intravesical attenuation device was evaluated in a randomised controlled trial for the treatment of SUI. The device involves having a balloon inserted into the bladder, inflated then sealing the device. It then acts as a sponge that focuses on reducing the spikes in intravesical pressure due to higher levels of abdominal pressure. Participants were randomised to treatment or sham procedure (no balloon insertion). Key issues were device malfunction, patient discomfort and invasive procedures resulting in a high withdrawal rate (200). Further studies have taken place on this device and are outlined in the next section.

2. NEW EVIDENCE FOR THE CURRENT CONSULTATION

New research studies conducted since the last consultation have enhanced our knowledge of mechanical devices for female urinary incontinence. Five new randomised controlled trials and one systematic review have been reported since the last consultation (36). Scarabelot and Colleagues (2018) conducted a systematic review that assessed the use of a pessary in the treatment of pelvic floor dysfunctions including urinary incontinence (201). Three trials follow up on the Rovner *et al.* (200) study on the effectiveness of the novel intravesical attenuation device on stress urinary incontinence (202, 203) (204). Four further studies, including one randomised controlled trial and three prospective single cohort studies, assess the efficacy of pessaries on women living with pelvic organ prolapse and stress urinary incontinence (205-208). Finally, one study assesses a new, single-use, one-size-fits-all device and its capacity to reduce stress urinary incontinence during a pad weight test (209).

McCammon *et al.* (202), Wyndaele *et al.* (204) and Winkler *et al.* (203) all studied the treatment effects of the intravesical attenuation device product on women with stress urinary incontinence. All three studies followed a prospective, randomised, single-blind, sham-controlled multi-centre design. All three share the same two primary outcome : at least a 50% reduction in a provocative pad weight test and at least a 10-point increase in their Incontinence Quality of Life (I-QOL) questionnaire survey after three months from baseline. Only Wyndaele *et al*. were able to achieve this dual primary measure after 3 months while McCammon *et al.* only achieved the outcome measure related to pad weight, although similar results between both groups were attained for the I-QOL survey. All three intravesical attenuation device trials highlight significant issues with the device and procedural tolerability. The rates of study withdrawal were 25.5%, 17.4% and 40.7% in the McCammon *et al*., Wyndaele *et al.* & Winkler *et al.* studies respectively. The main reasons for the high withdrawal rates were device and procedure intolerability, bladder irritation, and device-related adverse events. Adverse events were also high in each study, with 85.9%, 67% and 43.9% of participants experiencing them during the Winkler *et al.*, McCammon *et al.* and Wyndaele *et al.* studies respectively. The most commonly occurring adverse events were dysuria, urinary urgency, and gross haematuria. All adverse events in each of the McCammon *et al.* and Winkler *et al.* trials and all tolerability issues in the Wyndaele *et al.* study resolved fully after device removal. These three studies point to existing issues with device tolerability and a high level of adverse events as a result. The tested intravesical device is not currently commercially available.

Dueñas & Miceli (205) examined the efficacy of a ring pessary in 94 postmenopausal women with advanced pelvic organ prolapse (stages III and IV). The pessaries were not removed or replaced periodically unless there were adverse events associated with them and were kept in place until the end of the study (minimum 18 months follow up). At baseline, 55% of patients reported voiding difficulty, 37% reported stress urinary incontinence and 47% reported urge urinary incontinence. After one month of pessary use, 92% of participants with voiding difficulties found improved symptoms, as did 77% with stress urinary incontinence and 75% with urge urinary incontinence. A more recent study utilised a similar research method evaluating pessary use on another cohort of 123 women with advanced pelvic organ prolapse found it reduced voiding difficulty, stress urinary incontinence and urge urinary incontinence symptoms in 94%, 69% and 74% of participants respectively after 1 month of pessary use as compared to baseline (207). Both studies also showed 11-12% developed new onset stress urinary incontinence after 1 month. Overall, the results showed that participants with advanced stage pelvic organ prolapse could continue pessary use to address urinary incontinence without having to self-manage it. This practice could have financial implications by reducing the economic costs associated with regular pessary change.

Ring pessaries have also been shown to increase the quality of life of women with pelvic organ prolapse experiencing incontinence. Mendes and Colleagues have found that pessary use showed a significant improvement in quality-of-life domains, including perceived health status, UI impact, daily limitation, social limitation and severity measures (208).

Lovatsis *et al.* (206) examined the effectiveness of a bell-shaped pessary. It has a bell-shaped lower end which allows it to be seated just above the introitus at the level of the urethra providing support at the time of stress. Women with SUI were divided equally into treatment and placebo groups, with the latter receiving a silastic ring in place of the pessary. Participants did not self-insert the de-

vice, and a drape was placed so that participants were unaware of which device had been inserted. Upon placement of the device, two-thirds of the treatment group achieved a significant result of at least a 50% reduction in a provocative pad weight test (held pre- and post-placement) compared to 22.2% in the placebo group. No adverse events were documented, nor was there any significant discomfort with device placement. Despite the success, long-term trials will be required to test overall efficacy and real-world effectiveness.

A new intravaginal device has been evaluated for its effectiveness in reducing stress urinary incontinence in 26 women as part of a prospective, single cohort study. The device is single-use, one size fits all and utilises increased intra-abdominal pressure to apply pressure on the urethra only when there is a risk of urine leak. A modified 1-hour pad weight gain test was conducted pre-insertion, with participants drinking 250-500ml of water before inserting the device. With the device, pad weight gain was 79.4% lower on average than without the device, with a range of 0-23.6g pad weight increase. No adverse events were reported during the study. However, the length of assessment (1 hour) and tasks completed do not lend themselves to real-life applicability and long-term studies need to be conducted to validate device efficacy (209).

Scarabelot *et al*. (201) conducted a systematic review on the use of pessaries on pelvic floor dysfunction including treatment of urinary incontinence. Five trials were included in the review, of which two evaluated pessary use on UI and recruited women with SUI and overactive bladder. The reviewed articles demonstrate that the use of vaginal pessaries can be effective in the treatment of both urinary incontinence and pelvic organ prolapse. The authors noted that there is still a lack of long-term studies assessing pessary use, and the outcomes have often been narrowed to quality of life and satisfaction with device usage.

3. SUMMARY

Some mechanical devices may be effective and relatively non-invasive (with the exception of intraurethral or intravesical devices); however, there is a lack of randomised controlled trials and long term follow up for most products. The choice and use of mechanical devices should be made in consultation with experienced clinicians who can monitor product use regularly for adverse events and provide information and education to women who have been assessed as appropriate for the device. Specifically:

- Pessaries may be effective in SUI management and represent an alternative or complementary non-surgical approach although long term evidence is lacking. **(Level of Evidence 1).**
- Improved continence is possible for women with SUI with intravaginal devices. However, product evaluation has been limited and varies across a range of products **(Level of Evidence 3).**
- There is not enough evidence to compare the efficacy between products and severity and improvement in SUI. Comparison between device efficacy and severity of incontinence was only reflected in two studies **(Level of Evidence 3).** Relatively high drop-out rates in monitored studies may contribute to limitations in product efficacy, difficulties in the application or other factors such as discomfort **(Level of Evidence 3)**.
- Device efficacy and individual needs can be used as a guide to determine acceptability and choice of product. **(Level of Evidence 3)**.

4. RECOMMENDATIONS

Recommendations relating to mechanical devices for women with UI are summarised in Table J-2.

Table J-2: Recommendations relating to mechanical devices for women with UI.

- Internal vaginal support devices may be option when treating women with SUI, dependent upon the availability of the product, ease of insertion / removal, acceptance and cost **(Grade of Recommendation C).**
- Internal urethral devices are invasive, costly and have had a limited evaluation. However, they may be considered for intermittent and occasional use (such as during vigorous exercise) **(Grade of Recommendation C).**

No recommendations can be made on internal bladder devices pending ongoing trials. Studies have shown a significant level of adverse events for participants when they use the device (which mostly resolve after device removal). There is a high level of withdrawal rates for study participants and studies have not been conducted by researchers independent of the manufacturer.

5. PRIORITIES FOR RESEARCH

New devices - particularly invasive products– must be evaluated by randomised controlled trials, including long-term follow-up.

Evaluate the long-term effects of existing mechanical devices for urinary incontinence on the urethra and / or bladder to determine their real value and safety.

Comparison studies to other forms or like-forms of mechanical devices, conservative therapy, surgery and / or containment options are required.

Health economic assessment including cost-effectiveness and effects on quality of life be included when evaluating mechanical device use.

K. MECHANICAL DEVICES FOR MEN WITH UI

Male mechanical devices (also called penile clamps or penile compression devices) are designed to prevent urine leakage by compressing the penile urethra using a clamp design or a peri-penile strap (Fig K-1).

For some men, mechanical devices offer a cost-effective and convenient option for continence compared with a sheath and drainage bag or absorbent pads or for those who do not wish to undergo invasive incontinence surgery. However, there is potential for tissue damage and penile ischaemia, and these devices should be used with caution. The clinical opinion is that the device should be released at least every two hours and is unsuitable for use overnight or when sleeping (18). Careful assessment is necessary and they should be fitted by a trained health professional and re-evaluated on a regular basis. The availability of online products means that men can purchase devices without assessment -- healthcare pro-

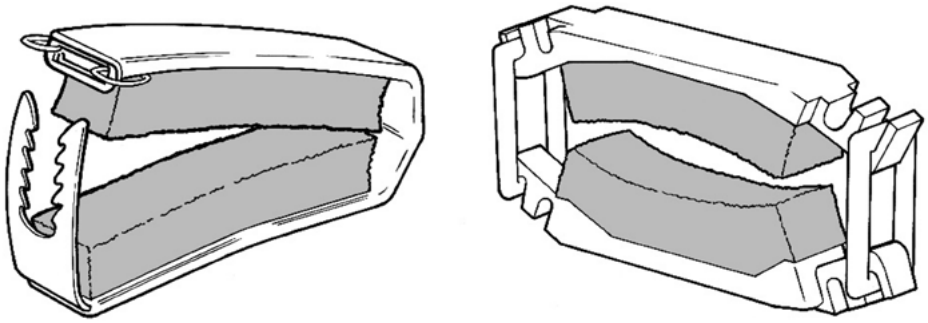


Fig K-1: Mechanical devices for men

fessionals should be alert to the need for education of men on the safe use of these mechanical devices.

A penile compression device should be comfortable, easy to apply and remove and cause no untoward effects on skin or penile vessels. It should not be used for urgency incontinence. The main factors that may make mechanical devices (un)suitable for men are summarised in Table K-1.

Table K-1: The main factors that make mechanical devices (un)suitable for men.

Mechanical devices may be suitable for men with:
• Sufficient bladder capacity to allow about 2 h wear before needing to release the device.
• Mainly stress urinary incontinence.
• Cognitive ability to remember to release the device at regular intervals.
• Adequate hand function that the device can easily be opened and closed.
• Penile length to allow comfortable placement of the device on the shaft and not the glans.
Mechanical devices are not be suitable for men with:
• Poor memory or impaired cognitive function.
• Overactive bladder / urgency inconti-nence.
• Penile skin irritation/dermatitis.
• No penile sensation or sensation of bladder fullness.

1. EVIDENCE

Although a range of devices is available, there has been little research on their safety and efficacy.

Three trials (18, 210, 211) were identified for the last consultation (36). The first evaluated the effect of three penile compression devices on mean urine loss, subjective opinion and cavernosal artery blood flow (210). The Cunningham clamp was the most successful device in terms of continence, ease of application and comfort but was also associated with the highest reduction of penile blood flow, indicating a potential for ischaemia if the device was placed too tightly. When the clamp was placed in a comfortable position and tightness, it controlled leakage well but did not eliminate it so that participants still wore a small continence pad.

The second was a randomised, controlled trial (18) of 56 men with persistent incontinence post prostate cancer treatment. Men tested, for 3 weeks each, the Cunningham penile clamp, penile sheath and bodyworn urinal (BWU) and compared these to their usual product of continence pads. Significant differences in acceptability, comfort, effectiveness ease of use were found between products: the Cunningham clamp was good for short, vigorous activities that increased abdominal pressure such as golf or swimming and was the least likely to leak. However, nearly all mean found the clamp uncomfortable or painful. Other products – sheath, pads, and bodyworn urinal – were also rated. Participants rated the sheath as effective for dryness and 'good' for extended use such as travel; the bodyworn urinal received the least positive reviews and did not stay in place well, particularly when the user was seated. Pads were positively rated for most activities and best for night-time use. Overall, participants indicated a preference for having a mixture of products to meet daytime needs. This is an important trial as it is the first to systematically compare several different continence products for men.

A third trial with 16 men measured IIQ-7 scores pre and post use of the penile compression device (Dribblestop™) as well as subjective impressions of ease of use, comfort, activity levels and overall satisfaction (211). There was a significant improvement in the IIQ-7 score; 14/16 participants found the device easy to use, allowing them to be more active and more confident and would recommend the device to others.

Since the 6th consultation, there have been two relevant studieswere found. A computational model identified design characteristics that provide the safest mechanical conditions in the penis to minimise tissue damage with the purpose of designing a safer clamp; these were envelopment, adaptability and durability (212). Another evaluated tissue response to applied loading with four different designs of clamp, all of which indicated tissue and blood flow compromise during device application but recovery within 40 minutes of removal indicating that the application of a clamp for one hour is likely to be safe (213).

2. SUMMARY

- Penile compression devices may be a valuable continence option for some men, particularly where activity may not only exacerbate incontinence but also preclude the use of bulky and / or absorbent products. **(Level of Evidence 1).**
- Men who used a compression device ranked them as easy to use and effective. **(Level of Evidence 1).**
- Some men found the Cunningham clamp uncomfortable or painful. **(Level of Evidence 1)**.
- Male mechanical devices can partially control urinary leakage, but they may not eliminate it at comfortable levels of compression. However, they are likely to lead to reduced cavernosal artery blood flow and therefore, care must be taken to ensure regular removal or release **(Level of Evidence 2).**

3. RECOMMENDATIONS TABLE

Recommendations relating to mechanical devices for men with UI are summarised in Table K-2.

Table K-2: Recommendations relating to mechanical devices for men with UI.

- Male mechanical devices should be be considered for men with stress urinary incontinence who are cognitively intact and aware of bladder filling, have normal genital sensation, intact penile skin and sufficient manual dexterity to open and close the device **(Grade of Rec-ommendation B)**
- Devices should be fitted by a trained health professional and reviewed regularly **(Grade of Recommendation C)**.
- Mechanical devices should be consid-ered as an option for short-term use when undertaking sport or other activities and as an adjunct to management with other continence products **(Grade of Recommendation C).**

4. PRIORITIES FOR RESEARCH

Further research is necessary on the length of time a device can remain in place, the amount of compression that is safe for penile vessels, and the effect on skin health and comfort when using the device. It is possible that one penile compression device will not meet the needs of all men, and further design considerations may be warranted.

L. INDWELLING CATHETERS

Indwelling urinary catheters (Fig L-1a) are inserted into the bladder urethrally (UC) (Fig L-1b) or suprapubically (SPC). Table L-1 lists the contexts in which long-term catheterisation (> 30 days) is most commonly used.

Table L-1: The contexts in which long-term in-dwelling catheterisation (> 30 days) is most com-monly used.

- Bladder outlet obstruction (BOO) where patients are unsuitable for - or waiting for - surgical or medical relief.
- Chronic retention that is causing incon-tinence, infection, renal dysfunction or substantial patient discomfort and when intermittent catheterisation is not feasi-ble.
- Continence care for comatose patients.
- Pressure ulcers at risk of urine contami-nation or non-healing incontinence as-sociated dermatitis where non-invasive methods (e.g., urinary sheath) are not feasible or have been unsuccessful.
- Intractable urinary incontinence where catheterisation enhances the patient's quality of life when alternative non-invasive approaches are unsatisfactory or unsuccessful.

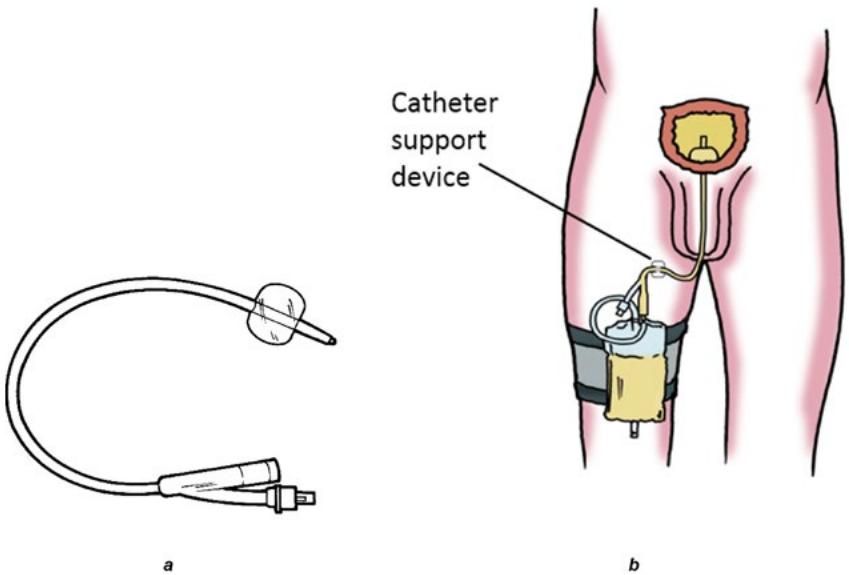


Fig L-1: An indwelling catheter with balloon inflated (a) and in position in the urethra / bladder.

The older hospitalised person is at particular risk of having an unnecessary catheter or one remaining in situ for a prolonged period and/or being discharged without instruction for catheter care or date for removal (197, 198). Common risk factors for catheters unnecessarily remaining in situ are listed in Table L-2.

Table L-2: Common risk factors for indwelling catheters unnecessarily remaining in situ.

- Absent or poor documentation on the reason for catheter insertion.
- Extended hospital stays.
- Transfer from one clinical setting to another **(214)**.
- No documented care plan for catheter removal **(214) (215)**.
- Immobility, confusion / decline in function **(216)**

Several prevalence studies have indicated that about 9% of nursing home residents have a long-term indwelling catheter (range 7%-38%) (217) (218) (219) (220) (221) (222) (216). Duration of use can be for many years - in one US-based study, mean use was 11.7 years (ranging in months from 1-589; median 8.8 years) (170) (223) (224).

Catheters should not be inserted as a continence measure until all other reasonable continence management/treatment strategies have been ruled out such as toileting, containment products and/or medication (213). In the evidence reviewed below, the primary focus is on the research related to long-term indwelling catheters (remaining in situ > 30 days).

The characteristics of the ideal catheter and ideal catheter material – according to expert opinion – are summarised in Table L-3, while Table L-4 outlines suitable materials, balloon size, catheter gauge and catheter length for different situations.

Table L-3 Characteristics of the ideal catheter and catheter material.

An effective indwelling catheter should have the following design characteristics:

- Be retained in the bladder effectively yet easily removable without trauma to the tissue.
- Have a soft 'tip' within the bladder to avoid pressure damage to the mucosa.
- Achieve effective drainage while minimising the risk of bladder mucosa being 'sucked' into the drainage channel.
- Conform to the shape of the urethra.

The ideal catheter material should:

- Be soft / flexible for comfort.
- Cause minimal tissue reaction or friction.
- Be sufficiently firm for easy insertion and maintenance of lumen patency in situ.
- Have elastic recoil so that an inflated balloon can deflate to almost its original size.
- Be resistant to colonisation by micro-organisms and to encrustation by mineral deposits.

Table L-4: Suitable catheter materials, balloon size, catheter gauge and catheter length for different situations.

	Short term	Long term	Comments
Material	Latex or plastic PTFE-coated latex.	Silicone elastomer-coated latex. Hydrophilic polymer-coated latex. All silicone.	Latex catheters: avoid where possible -- urethral discomfort due to high surface friction, risk of rapid encrustation by mineral deposits; risk of latex allergic reactions (225) (226) (227) (228) (229) (230) or anaphylaxis (231). Coated catheters cause the least friction and tissue reaction (232). Silicone catheters are stiffer & have thinner walls and slightly larger lumen compared to same size non-silicone-coated catheter; less likely to kink/bend (233); not affected by topical creams used for skin excoriation compared with coated latex catheters (234).
Balloon size	10 ml; larger balloon (30ml) only for post-op haemorrhage control.	10 ml	Large balloon contraindicated unless surgically required because of the risk of irreparable bladder neck erosion. Silicone catheter balloons may have water loss over time, with the catheter falling out (235) (236); fill the balloon with sterile water and replace fluid periodically, knowing that 1/4 to 1/2 could be lost over time (235).
Gauge	Adult 14-16 Fr; post-op procedures with haematuria/clots larger lumen 18-24 Fr.	Adult 14-16 Fr; smallest size to maintain good drainage (237) (238) (239).	Large diameter: Potential blockage of para-urethral glands and urethral injury.
Length	Male/female 41-45 cm	Male 41-145 cm; female option 25 cm.	

1. EVIDENCE

Few randomised controlled trials have been conducted on either long or short term catheterisation since the last consultation (36). The trials that have been undertaken are typically small, with sample heterogeneity, imprecise outcomes and short term follow up. Most data are of **Level of Evidence 4**, based on clinical experience and expert opinion. Two new Cochrane reviews relating to long-term catheter use add to existing reviews to attest to the lack of evidence which precludes drawing robust conclusions (See Appendix 2 for a listing).

Studies can be usefully reviewed under the following headings:
- Catheter characteristics and materials.
- Catheter coatings and CAUTI.
- Meatal cleansing.
- Catheter encrustation.
- Bladder calculi.
- Catheter-related pain.
- CAUTI.
- Bladder cancer.
- Management strategies.
- Education of health care professionals.
- Quality of life.
- Cost.
- Urinary catheters versus other strategies.

Catheter characteristics and materials

Feneley and colleagues wrote in 2012 “in an era that has witnessed outstanding technological advances in medical practice, it is difficult to understand why we are still unable to perform the relatively simple task of draining urine from the bladder without producing infection and a range of associated complications” (240). Efforts to improve the traditional Foley design include a novel balloon shape (241), drainage tubing designed to optimise flow (160) and additional eyeholes (242). Clinical testing is still awaited.

Catheter coatings and CAUTI

Considerable work has been committed to finding a catheter coating that will prevent CAUTI or delay the onset in both acute and long-term care. To date, and despite dedicated attempts to find options, there are no coated/impregnated catheters that will delay the onset of CAUTI in the long-term user. There may be a modest benefit for those catheterised seven days or fewer.
- **Silver:** Two new trials comparing CAUTI with silver alloy versus standard catheter were found. One RCT compared silver SPCs and standard SPCs with 288 urogynaecology patients and found no clinically meaningful difference in rates of UTI at six weeks (243). The other RCT compared silver alloy-coated UCs with standard among 489 spinal cord injury patients for a minimum of seven days and found no difference in UTI rates (244). Other randomised trials conclude that silver alloy catheters do not significantly reduce the incidence of CAUTI in acute care (245) (246) (247).
- **Antibiotic/antiseptic impregnated catheters:** Earlier catheter studies on the effect of nitrofurazone (248-251); minocycline and rifampicin (252); chlorhexidine, silver sulfadiazine, triclosan (253-257) have suggested benefit, but outcome measures of bacteriuria vs CAUTI, heterogeneous patient populations and small samples have limited the clinical impact of these findings. The largest randomised trial to date comparing nitrofural silicone, silver alloy-coated latex or a PTFE standard catheter (n=7102 acute care, short term catheter subjects) found that the nitrofural catheters had a small and not clinically meaningful decrease in CAUTI and were more uncomfortable than silver alloy or PTFE catheters. No significant decreases in symptomatic CAUTI occurred with silver alloy catheters compared to control (235). One large pilot RCT compared nitrofurazone coated catheters with non-impregnated with 214 subjects and found no improvement in the incidence of UTIs (250). Laboratory work continues to show promise in antibiotic and antimicrobial catheters (258) (259-264) but clinical testing is required.
- Other coatings or treatment undergoing laboratory testing: Zwitterionic molecules (in an anti-fouling coating) decreased biofilm development by 80% over seven days as compared with untreated catheters (265) (266). Laboratory testing also includes nanoparticle coatings on catheters (267) (268) coating with antimicrobial enzymes (269) (270), polydopamine peptide coating (271), the addition of plant extracts (272), the release of salicylic acid (273), interference with bacterial signalling (274) (275), the use of bacteriophages to control colonising mixed-species biofilms (276) (277) (278) and the application of low electrical currents to dislodge mature biofilms (279). Future opportunities for CAUTI control are promising based on the sophisticated laboratory work underway.

Meatal cleansing

Since the last consultation, one large (n=1642 catheter users) multi-centre stepped wedge RCT reported that the use of chlorhexidine solution for meatal cleansing prior to catheter insertion decreased CAUTI compared with normal saline (4 CAUTI in 2338 catheter days for chlorhexidine and 13 CAUTI in 2889 catheter days for normal saline) for short-term users (280). A recent systematic review and meta-analysis of the effectiveness of antiseptic cleansing of the meatal area concluded that there is some evidence that some antiseptic solutions might be more effective than sterile water in preventing the onset of bacteriuria, but the evidence base is challenged by the diverse range of antiseptics used in trials (281). Effective handwashing by healthcare professionals, caregivers and patients, before and after handling catheters and drainage equipment, is generally accepted to be the most important component of any infection control strategy. Healthcare professionals and formal caregivers should also wear gloves.

Catheter encrustation

Catheter encrustation affects the quality of life, nursing time and healthcare costs (282). Several approaches have been tested to reduce the problem including catheter maintenance solutions (283) (284), fluid intake (285) (286) and catheter valves. Preventative strategies have largely failed, but recent laboratory research, using advanced imaging techniques, has improved the understanding of crystalline biofilm formation which may aid in the development of anti-microbial materials resistant to colonisation (287).

Catheter encrustation (Fig L-2) occurs in up to 50% of LTC users, with resultant increased costs to services and patients (221) (288) (289) (290) (291). Mineral deposits - calcium phosphates and magnesium ammonium phosphate (struvite) - precipitate from the urine under alkaline conditions and cause blockage. In one trial prevalence of catheter blockage in a two month period was 11.08 per 1000 catheter-days’ use (282). During the 12 months of another trial (292), both treatment and control groups had a reduction in blockage (4.76 and 6.04 per 1000 catheter-days, respectively) but there were no statistically significant differences between groups.

Fig L-2: Section of a catheter showing encrusta-tion and blockage.

Precipitation of different ionic species (i.e. Ca++, Mg++, and phosphates) is influenced by their ionic concentrations in the urine and by the presence of urea-splitting micro-organisms such as *Proteus mirabilis* (293) (294) (295) (296). The pH at which ions precipitate from the urine varies, not only for different ions but also between individuals and at different times (297) (298). These factors contribute, at least in part, to individual susceptibility to catheter encrustation and time to blockage. 'Blockers' experience recurrent catheter blockage within a few days to a few weeks (288), and urine from recurrent blockers tends to have a very narrow 'safety margin' between 'voided' urinary pH and the pH at which crystallisation

Table L-5: Catheter maintenance solutions.

Suby G or Solution G[1]	3.23% citric acid solution, pH 4, containing magnesium oxide to minimise tissue irritation, aimed at reducing encrustation. Used where routine catheter maintenance is required to reduce the build-up of encrustations.
Solution R[1]	6% citric acid solution, pH 2, containing magnesium carbonate, aimed at dissolving encrustations. A stronger acid than Suby G and therefore not recommended for frequent, regular use.
RenacidinR[2]	A citric acid solution, pH 3.5-4.2, containing glucono-delta-lactone to minimise tissue irritation and magnesium carbonate, aimed at reducing encrustation.
Mandelic acid 1%[1]	An acidic solution, pH 2, aimed at inhibiting the growth of urease-producers. A stronger acid which is not commonly used to reduce catheter encrustations
Saline 0.9%[1,3]	A neutral solution, pH 7, is recommended for the flushing of debris and small blood clots. Neutral pH solutions will not dissolve catheter encrustations.
Chlorhexidine 0.02%[1]	An antiseptic solution aimed at preventing or reducing bacterial growth, in particular, E. coli and Klebsiella species (but will not prevent biofilm formation on long-term catheters)

[1] Available in the UK pre-packed in a sterile delivery device designed for instillation into a urinary catheter.
[2] RenacidinR is approved in the USA for kidney stone disintegration only. Although it may be effective in certain situations for persistent catheter blockers, there are no supporting studies. [3] Saline is widely available

Table L-6: Catheter encrustations - theory and evidence

	Theory	Results	Level of Evidence
Catheter materials.	Intent to reduce/stop biofilm adherence.	To date, *no evidence* that any material (silver coated latex; hydrogel or silicone-coated latex, 100% silicone; nitrofurazone coated silicone.	1
Citrate Washout solutions (Catheter maintenance solutions): Suby G, Solution R, renacidin).	Reduction of pH; mobilisation of crystalline collections; eradicate P Mirabilis.	Citrate solutions clinical studies: *no evidence* to date.	1
		Renacidin laboratory results show promise; no clinical studies.	4
Washouts: saline, sterile catheter.	Mobilise catheter debris.	*No evidence of benefit.*	1
Urease inhibitors: Acetohydroxamic acid 1.0 mg/ml & fluorofamide 1.0 microg/ml.	Lower pH in the presence of P. mirabilis.	Laboratory studies: Reduce pH in the laboratory; in clinical studies, side effects were unacceptable.	2
Fluid Intake: Water (279); acidic fluids (lemon 60 ml/L water/lime juice), potassium citrate 6g/L	pH increases when urine concentration decreases + citrate. Citrate (orange, lemon, lime juice) concentration may change pH & mineral crystallisation.	*Weak evidence* of reduced blockage (438). No evidence that cranberry juice decreases pH in catheterised people.	2
Electron Donating surfaces or electrical current through silver electrodes attached to the catheter.	Proteus mirabilis suppression.	Laboratory results only – may inhibit growth; need clinical studies.	4
Triclosan catheter balloon fluid.	Triclosan suppresses biofilm formation.	Laboratory results only – need clinical application.	4
Proteus targeting.	P mirabilis has four adhesins that help make it stick to the bladder and catheter, a protective capsule, several secretions that promote extraction of host nutrients, quick migration capacity, and a powerful urease.	Laboratory studies of strong electron-donating surfaces; triclosan in the catheter balloon need clinical testing.	4

(or nucleation) occurs (294) (299). This margin is much wider in non-blockers (296).

Catheter maintenance solutions

Pursuit of a solution to managing catheter blockage is ongoing and several catheter maintenance solutions are marketed (Table L-5). However, there is no evidence that any are effective in preventing encrustation or blockage in the clinical setting:

- Washout / maintenance solutions (284) (300) (301).
- Catheter coating or material (291) (302) (303) (304) (305) (306) (307) (308) (309) (310) (311).
- Oral medication (312) (313).
- Balloon instillation (314) (315) (316).

Several solutions are marketed to decrease encrustations/increase catheter time in situ (Table L-5). However, to date, there is no clinical evidence that catheter maintenance solutions are effective in improving catheter drainage (317). For patients who have blocking or encrusted catheters, the key nursing procedure is to review the catheter integrity, observe for reduced flow or obvious encrustation and change the catheter before it blocks. A characteristic pattern of 'catheter life' can usually be identified with record-keeping of three or more catheter episodes (294) (299) (318). This may allow proactive strategies of care designed to change the catheter before likely blockage.

Concerns have also been raised about a potential negative effect of washouts on the urothelium (283) (294) (299) (319) (320) (321) (322) (323). There is weak evidence that citric solutions (orange, lemon or lime juice) and / or water intake may change pH and mineral crystallisation (285) (324) (325). Table L-6 summarises the theory and evidence of research efforts on encrustation.

Bladder calculi

Indwelling catheters (UC and SPC) are a known risk factor for bladder calculi formation compared to intermittent catheterisation (326) (327) (328) (329). This increased risk is independent of age, sex, level and degree of injury, and the risk increases with the duration of catheterisation so that by 5 to 10 years of continuous urethral or SP catheter use, 33% to 46%, respectively, will have been treated for a bladder calculus (330). Any foreign object, like a retained piece of fluff from gauze or pubic hair can cause a stone. Careful attention to hygiene and catheterisation techniques could prevent this complication (331).

In a prospective cohort study of 66 SCI patients in Nigeria, encrustations and P. mirabilis were predictive of bladder stones; thus, ultrasound was recommended for persons with these risks to identify and treat bladder calculi (332).

Symptoms of bladder calculi vary from unresponsive CAUTI to catheter bypassing, spasms and haematuria. Individuals who do not respond to the appropriate treatment of CAUTI should have a urological referral.

Catheter-related pain

Catheterised individuals report discomfort, pain and restricted activities because of catheter-related painful bladder spasms, the position of the catheter/tubing or catheter changes (170) (333). In a prospective observational study of 116 patients post urological surgery, the type of surgery and catheterisation history predicted moderate to severe catheter-related bladder discomfort (263). In a sample of 202 long-term indwelling catheter users, 23% reported catheter-related pain (other than during the catheterisation procedure) over the previous two months (282). Women complained about the pain because of sitting on the catheter or sores in the vaginal area. Bladder spasms, CAUTIs, blockage, and dislodgement can all contribute to catheter-associated pain, as well as insertion and removal procedures (334) (335) (336) **(Level of Evidence 3).**

If bladder spasm is the cause of pain, a low dose of an anticholinergic medication may help (337). Attention to the catheter position and tubing is needed to prevent kinks or twists, to ensure that the catheter straps are not blocking urine flow and that the individual is not sitting on the tubing (338). Other approaches include treating constipation if present, ensuring that the catheter is the smallest size to provide adequate drainage, and ensuring that the catheter is secured and the drainage bag is well supported to prevent dragging on the catheter.

Catheter-associated urinary tract infections (CAUTI).

The most common infecting organisms are Escherichia coli, Enterococcus spp, Candida, and other Gram-negative and Gram-positive isolates (339). Up to 40% of cultured specimens from long term catheters will show *Proteus mirabilis* as a key organism in biofilm production, catheter blockage and pH alteration because of urease production. Table L-7 highlights the progression of initial colonisation to adherent biofilm.

Table L-7: Biofilm production from initial coloni-sation to adherent biofilm.

Biofilms **(340) (341) (342) (343) (344) (345) (346)**.
• Rapid colonisation of micro-organisms forms a strongly adherent biofilm on catheter and drainage equipment sur-faces.
• Biofilm formation begins by deposition of a conditioning layer of proteins, electrolytes and other organic mole-cules from the urine
• Micro-organisms attach to catheter sur-faces & divide to form micro-colonies, ultimately developing a complex three-dimensional structure, including fluid-filled channels through which the bio-film members receive nutrients, diffuse away wastes and send chemical sig-nals to each other
• Microorganisms growing as a biofilm are less susceptible to antimicrobial therapies than free-living organisms and are a major source of resistant, nosocomial pathogens
• *Proteus mirabilis* is a common biofilm isolate that secretes urease causing hydrolysis of urea to free ammonia, raises urine pH and promotes precipita-tion of calcium phosphate and magne-sium ammonium phosphate (struvite) and catheter blockage.

Onset of CAUTI

- All individuals with indwelling urinary catheters will develop colonisation (asymptomatic bacteriuria) at 5-8% per day to 100% by day 30 (347) (348) (349) (237) **(Level of Evidence 1)**.
- Even short term antibiotic use in a catheterised patient may place them at risk of CAUTI (340) (350) **(Level of Evidence 2)**.
- Most catheter users developing bacteriuria will remain asymptomatic and not require treatment **(Level of Evidence 1)**.
- 24% of those developing bacteriuria will develop a symptomatic UTI without bacteraemia (351) **(Level of Evidence 1)**.

- 4% with bacteriuria will develop bacteraemia, a serious health care problem (351) **(Level of Evidence 1).**

Aetiology of CAUTI

Biofilm formation on the catheter surfaces begins as early as 24 hours after insertion. Microorganisms derive from the patient's own colonic and perineal flora or from the hands of healthcare personnel during catheter insertion or management (340) and gain access in two ways:

- Extraluminally during catheter insertion or via the periurethral space.
- Intraluminally following breaks in the closed system or contamination of urine in the drainage bag or break in a closed system (within 32-48 hours v 72-168 hours respectively) (352).

Diagnosis of CAUTI

The generally accepted CAUTI definition is outlined in the U.S. National Healthcare Safety Network (NHSN) document (225). The criteria are guidelines for practice – individual patient presentation may differ. Further work is required on the most appropriate outcome measures and the corresponding patient-reported symptoms of CAUTI, particularly in long term users.

Treatment of CAUTI

- Prophylactic antibiotics prior to re-catheterisation are not recommended (139) (347) **(Level of Evidence 1)**.
- Routine use of prophylactic antibiotics or antiseptics in LTC patients is not supported and may favour the emergence of resistant organisms (139) (242) (348) (349) **(Level of Evidence 1)**.
- Cranberry juice does not affect the incidence of CAUTI (350) **(Level of Evidence 1)**.
- Urine cultures should be obtained before initiating treatment to permit selection of specific therapy for the infecting organism; extensive use of broad-spectrum therapy should be avoided (351) **(Level of Evidence 2)**.
- The catheter should be replaced prior to collecting a urine sample for culture and sensitivity or prior to starting antibiotics in symptomatic patients (139) (352) (353) (354) **(Level of Evidence 2)**.

Reducing the risk of CAUTI

Current evidence is weak regarding all aspects of CAUTI prevention in long term catheter users. Based on the existing research, none of the following factors have been shown to reduce the incidence of CAUTI:

- Pre-connected urine drainage bags (353).
- Perineal cleansing (353).
- Suprapubic versus urethral insertion (354) (355) **(Level of Evidence 2)**.
- Silver alloy antimicrobial surfaces (356) (357).
- Catheter coatings to reduce protein absorption (358).
- Inflation of the balloon with a biocide solution, such as Triclosan (305) (314).
- Disruption of matrix or glycocalyx components with agents such as heparin (359).
- Numerous trials of oral antibiotics, antimicrobial bladder washes, drainage bag solutions and topical disinfectants all lead to the conclusion that bacteriuria and UTI may be suppressed temporarily at best, but resistant organisms are highly likely to emerge (341).

Bladder cancer

The reported incidence of bladder cancer associated with chronic indwelling catheterisation varies across studies (360, 361) (362). In a US-based study of 3,670 SCI subjects with indwelling catheters, the incidence of bladder cancer was 77/100,000 population vs 17/100,000 for the US general population (363) **(Level of Evidence 3).** Even SCI patients without an indwelling catheter may have a higher risk of bladder cancer 15 times that of the general population, and it is postulated that the neurogenic bladder may itself be a risk factor (364). The potential relationship between the duration of catheterisation and cancer development could be studied further, particularly because patients change their form of bladder drainage, which confounds the subgroup analysis in retrospective studies. Squamous cell cancer also was reported in two cases in persons with suprapubic catheters, which is believed to be uncommon and needs to be differentiated from granulomatous conditions which are common (365). Bladder calculi have been identified as an independent risk factor for bladder cancer by some authors (361).

Carcinoma within the cystostomy tract with SPC has also been reported (366) (367) (368). However, Hamid *et al*. (369) raise concerns over the interpretation of screening cystoscopy and biopsy in this population and note the importance of distinguishing between histological changes and confirmed cancers when interpreting study results. Guidelines on catheter management include a recommendation that patients with urethral catheters in place for 10 years or more should be screened annually for bladder cancer (370) **(Grade of Recommendation C)**.

Catheter management strategies

In addition to CAUTI and encrustation, catheterisation is associated with several other complications: trauma due to malposition, leakage, calculi, false passage, haematuria, dislodgement, urethral strictures, hypersensitivity or anaphylaxis related to the catheter material (371) (372) (373). In a prospective surveillance project in a U.S. Veteran's Administration hospital, genitourinary trauma was as common as CAUTI (374). In one group of 202 community-dwelling adults with long-term catheters, the authors described catheter-related problems: 31% with CAUTI, 24% blockage of the catheter, 12% accidental dislodgement, pain (23%), sediment (63%), bladder spasms (36%), or urine leakage (43%) (282). Many case reports describe catheter-related complications such as urethral injury (375) (376) (377), intraperitoneal rupture of the bladder (378) (379), fistula (380), and iatrogenic hypospadias (381). These complications consume nursing time, compromise quality of life, and are costly to the healthcare system.

Overall, complications can be reduced if systematic approaches are taken to catheter care. Guidelines and protocols for catheter-care practices have been developed by clinical experts and should be part of an institution's care mandate. Research findings on topics such as meatal cleaning, lubrication, catheter securement, pain, and encrustations are discussed below.

Suprapubic versus urethral catheter insertion: Incidence of complications such as CAUTI, bladder calculi and encrustations do not differ between urethral or SP routes, but SPCs do offer easier access to catheter site, easier recatheterisation, and may be more comfortable for individuals. Table L-8 compares the two insertion approaches.

Table L-8: Comparison of long term urethral and suprapubic catheters.

Comparisons	Urethral	Suprapubic
Insertion	Insertion by a qualified healthcare professional	The initial placement must be by urologist/expert; may require anaesthetic
Upper urinary tract complications: vesicoureteral reflux; renal dysfunction, hydronephrosis; pyelonephritis renal calculi	No difference	
Urothelial Cancer	No difference	
Lower urinary tract complications: bladder calculi	No difference (384) (385).	
Lower urinary tract complications: ASB; symptomatic UTI	No difference (327) (356) (386).	
Lower urinary tract complications: urethral	Risk of urethral stricture, urethritis, scrotal abscess	Rare; SPC protects the anterior urethra (387).
Urinary incontinence/skincare	By-passing occasionally causing perineal dermatitis; can usually be treated by medical/ nursing management	Urethral leak, especially if prior urethral/bladder neck trauma from UC; can only be treated surgically. Risk of over-granulation of stoma tract causing pain/bleeding on removal (388) (389) (390). Stoma site can be prone to IAD from urine leak or irritation from the catheter.
Access for catheter insertion	It can be difficult in patients with leg spasms, who are obese, men with retracted penis	Straightforward when track established; tract can close within hours if catheter falls out.
Not suitable if	Urethral deformity/stricture	Haematuria of unknown origin, Bladder tumour Small contracted or fibrotic bladders Obesity if pannus covers SPC site; obesity makes catheter insertion more difficult or impossible because of the trocar length. Abdominal scarring from surgery or radiation

When changing a SPC, the new catheter should be inserted as quickly as possible as a delay of only a few minutes can result in partial obliteration of the tract (382)(383) and the tract will close completely within 24 hours. It is also possible to insert the new catheter too far into the bladder, so it enters the ureter with resultant trauma with balloon inflation. Careful observation of the length of the catheter external to the abdomen and the angle of protrusion prior to catheter change can help to ensure the correct positioning of the new catheter (384). However, this is not always enough evidence to show correct positioning. A case presentation of a catheter that had “doubled-back” and showed the correct length suggests that imaging may occasionally be required to ensure correct placement. Dressings around the stoma site are not normally required unless there is excessive discharge, causing staining and / or sticking to clothing

Maintaining effective catheter drainage

The use of urinary catheters is rarely completely trouble-free. Catheter drainage can be compromised by a variety of factors from simple causes such as kinked tubing or the position of the drainage bag, to bladder spasm, the pressure of a constipated bowel on the adjacent urethra, suction of bladder mucosa into the catheter eye, or blockage by blood clots, mucus or encrustations. The algorithms in Fig L-2, Fig L-3 and Fig L-4 combine current evidence-based knowledge and expert opinion to provide some guidance on troubleshooting common problems. Further research is required to determine if dependent loops, which allow urine stasis, could contribute to CAUTI (158).

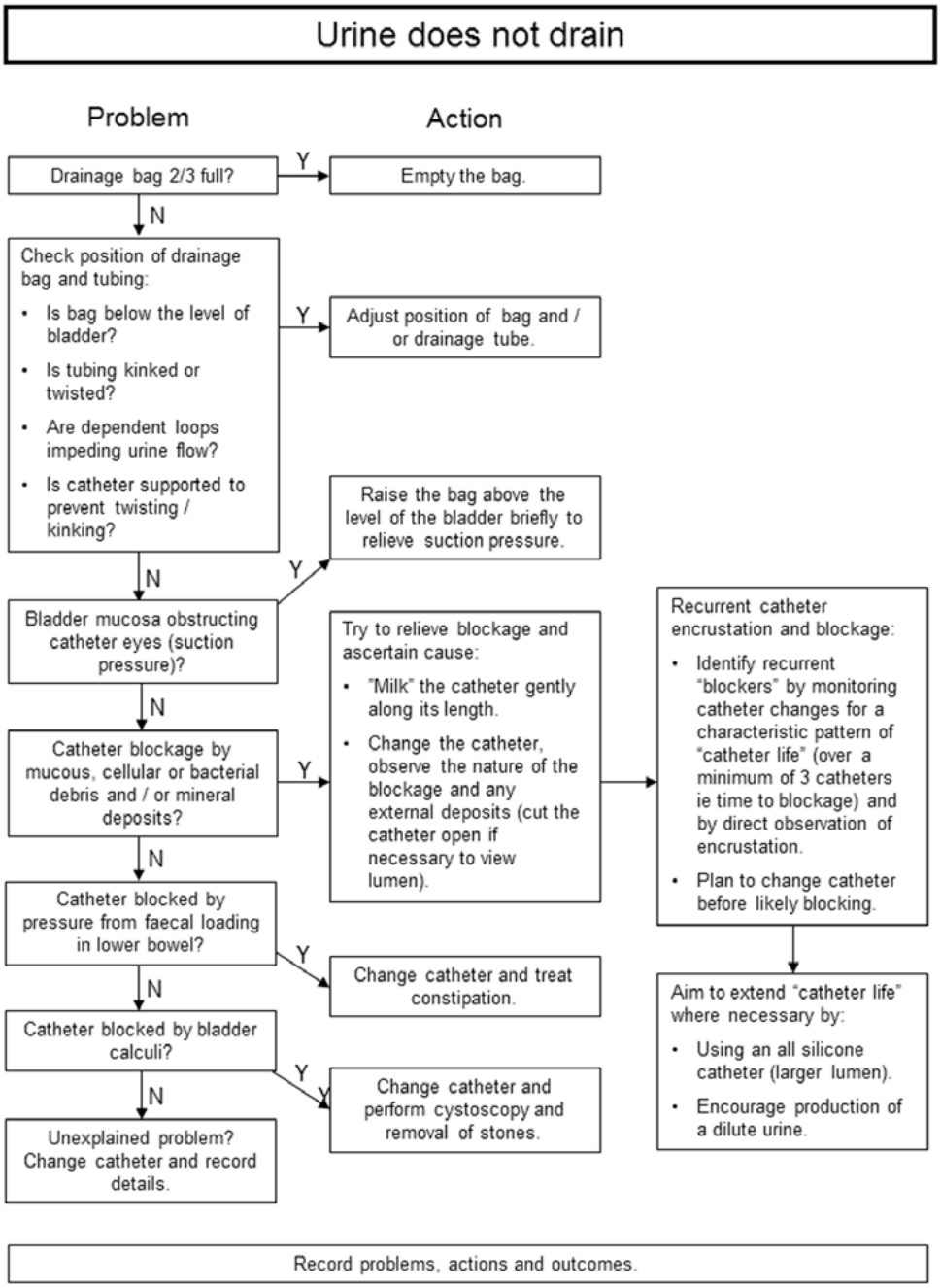


Fig L-3: Troubleshooting long-term indwelling catheter problems: urine does not drain. (N = No; Y = Yes). (Always have a spare catheter available).

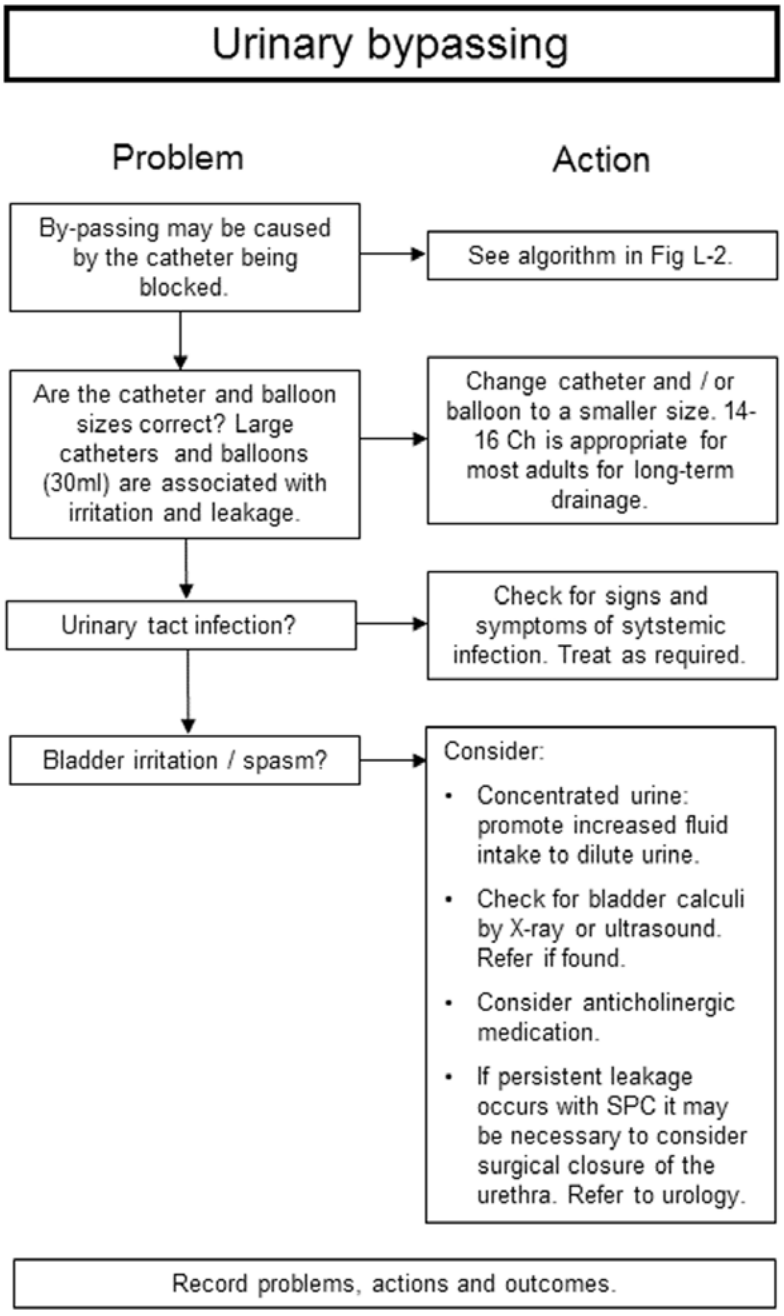


Fig L-4: Troubleshooting long-term indwelling catheter problems: urinary bypassing.

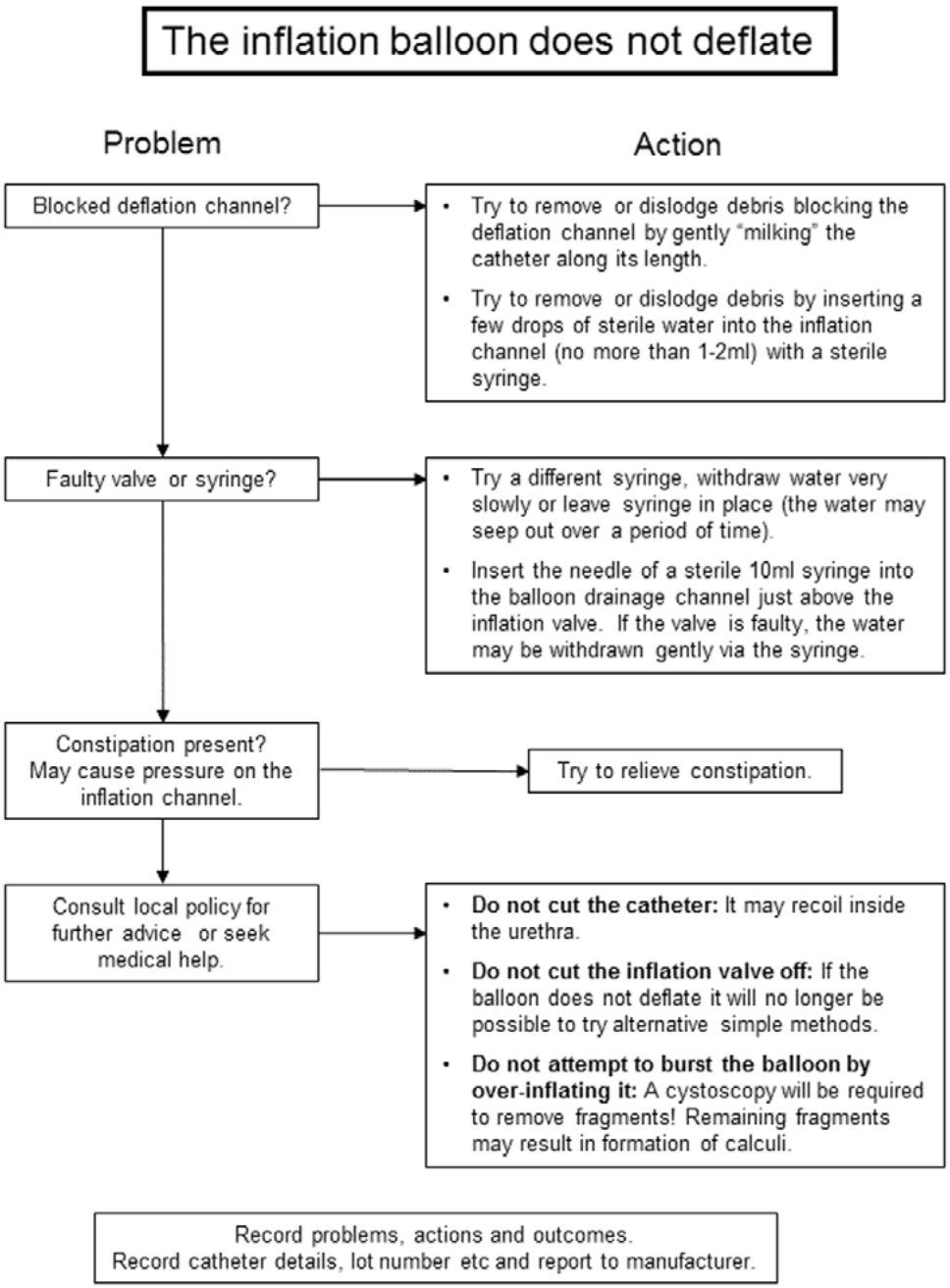


Fig L-5: Troubleshooting long-term indwelling catheter problems: the inflation balloon does not de-flate.

Catheter valves

A catheter valve is a compact device used to control urine flow and is connected to the catheter outlet in place of a bag to allow a discreet alternative to conventional urine drainage bags. Valves are available in a variety of designs (Fig L-6) ranging from simple devices used for up to a week to more complex forms which last longer, and which may permit one-handed action. Most valve designs can be attached to a drainage bag at night to allow free drainage while the patient sleeps.

- Suitable for: those who can manipulate the valve mechanism and empty the bladder regularly to avoid bladder distention and accompanying risks of reflux on the upper urinary tract.
- Not suitable for: people with poor manual dexterity, low bladder capacity, detrusor overactivity, vesicoureteric reflux, renal impairment, lack of bladder fullness sensation or cognitive impairment.

Evidence supporting the beneficial effects of catheter valves is derived from expert opinion and there is a paucity of research in this area. A lack of knowledge on valves may interfere with appropriate use; therefore, a full assessment is required to determine whether the person is a good candidate for a catheter valve using a systematic process, such as an algorithm (385).

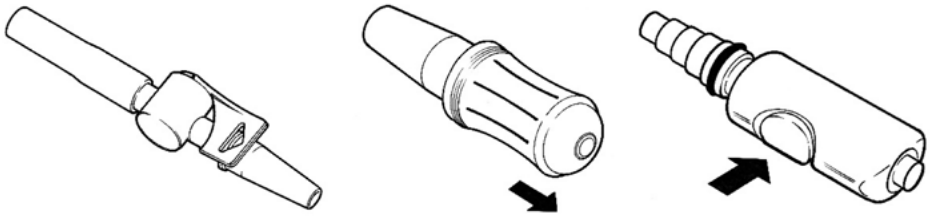


Fig L-6: A variety of catheter valves with different closure mechanisms.

There is little new research on catheter valves. Findings from studies indicate (386) (387) (388) (389) (390):

- Catheter valves provide a well-accepted system of bladder emptying for those who can manipulate the valve mechanism and empty the bladder regularly to avoid overfilling **(Level of Evidence 2)**.
- There is no evidence of increased risk of CAUTI, bladder spasms or discomfort compared to conventional drainage systems, although there may be a higher incidence of nocturnal frequency and episodes of bypassing with valves. **(Level of Evidence 2)**.
- Valves may promote maintenance of bladder tone and capacity **(Level of Evidence 4)**.
- Preferred valve design should be easy to manipulate, leak-free, and inconspicuous (399). **(Level of Evidence 3)**.
- An automatic valve system for LTC patients (400) may be helpful for patients who lack sufficient dexterity to manage a manual valve.

A catheter valve may facilitate periodic flushing, but clinical evidence is currently lacking on reduction of encrustations and prolonging catheter life. Only one controlled laboratory study has explored the question (401), indicating that time to blockage with valves was extended by over 50% compared to controls. There is an opportunity for clinical research in this area.

Catheter-change frequency

There is no research evidence to support specific change intervals for IUC or SPC (391). Thus protocols vary widely between facilities from monthly to several months if the catheter is trouble-free.

Lubrication

Guidelines and clinical reports suggest that injury or discomfort may be minimised by using a sterile lubricant or anaesthetic gel (392) (393) for male catheterisation; few have considered the procedure for women or for supra-pubic catheterisation (394). Results are mixed on the benefit of lignocaine versus water-based lubricant for female catheterisation: one trial demonstrated lignocaine gel group had a significantly lower median procedural pain score compared to the group receiving a water-based lubricating gel (395), whilst another trial found no difference between lubricants (396). In a small trial with infants, intraurethral lidocaine resulted in less catheterisation distress than topical or topical and intraurethral water based lubricants (397).

The United Kingdom National Institute for Health and Care Excellence (NICE) guidelines on infection control (398) recommend: 'an appropriate lubricant from a single-use container should be used during catheterisation to minimise trauma and infection'. Anaesthetic gels may be contraindicated in patients with damaged or bleeding urethral membranes and should be used with caution in those with cardiac conditions, hepatic insufficiency and epilepsy (399). Lubricants that contain chlorhexidine have been reported to trigger anaphylaxis in a small number of patients during catheter insertion, and consequently, a careful history is required to screen for sensitivities (400).

Fluid intake

Apart from catheter maintenance solutions, laboratory studies suggest that dilute urine or increased urinary citrate concentration from orange juice or other fruit juices could be beneficial (324), but randomised clinical studies are needed to assess the benefit of fluid adjustments.

Catheter Securement

Catheter securement may prevent movement of - and tension on - the catheter and potentially reduce the incidence of urethral erosion, trauma and pain, prevent accidental dislodgement from traction (401), and possibly reduce the incidence of bacteriuria (402). Of note is that whilst securement is intuitively better care, it is not necessarily put into practice. Two studies highlight this: of 82 nurses (8 continence specialists), 98% recommended securement, but only 4% were documented using it (403); in a one-day point prevalence study in acute care, only 18% (8 of 44) of the catheters were secured (157).

Several securement devices are available, ranging from:

- Adhesive devices (potential for skin irritation).
- Non-adhesive straps covered in fabric (can slip down with full urine bag).
- Holster styles (404).
- Adhesive tape such as silicone tape can be gentler than paper tape, based on a single trial with children (405). One case report in paediatrics demonstrated efficacy in using an adult leg bag to hold the catheter in place (406).

The choice will depend on the individual's usual activity, clothing, size of the thighs and the weight of the bag it would support. All need to be comfortable, easy to use, and gentle to the skin (407).

Self-management

Self-monitoring, a component of self-management, involves awareness of what to notice and related measurements or observations (408). Self-monitoring urine flow was found to be helpful in preventing or minimising catheter-related problems in a pilot study with 11 community-based individuals over a six months' time period (224). In the follow up randomised trial (N=202), a self-management programme for long-term indwelling urinary catheter users was tested in an experimental design. The intervention consisted of a 3-day intake and urinary output diary, educational booklet, and three home visits by a study nurse (404). The outcomes of CAUTI, blockage and accidental dislodgement were evaluated over the 12 months' participation, measured in bi-monthly phone call interviews, using a general estimating equation and rates calculations. In the first six months of the study, blockage reports of occurrence (yes / no), but not frequencies of the event, were significantly lower in the experimental group than in the control group. No group differences were found for the full 12 months of the study or for other outcomes;

however, examination of rates indicated that both groups improved over the 12 months' study for all outcomes. Researchers believe that the self-monitoring through the use of repeated interviews and of a catheter calendar for data collection in both groups contributed to overall self-care management improvements (292).

Education of healthcare providers

Despite the development of quality guidelines and the attention on CAUTI, knowledge and understanding of appropriate catheter care and risks of prolonged use remains suboptimal in many centres (409) (410) (411) (412) (413) (414). Educational approaches to research-based recommendations for catheter selection and minimising problems are welcomed by healthcare professionals and need to be made available in a variety of ways as part of ongoing staff updates (415) (416) and as part of quality improvement/patient safety strategies. It is widely accepted that catheters should be avoided where possible, and dwell time should be minimised where a catheter is required. Numerous quality improvement and pre-post design studies report on interventions to reduce the use of catheters, often hospital-based with a focus on multifaceted catheter care bundles (417) (418) (419) (420) (421) (422).

Quality of life and catheterisation

Indwelling catheters can have both positive and negative effects on life quality. Users report reduced activities (423), embarrassment (333) (336), shame or stigma (223). Other concerns are loss of privacy (223) (335) (424) (425), end to sexual activity (426) (425) (427) (428), loss of manhood (429) and fear of odour and leakage (223) (428) (430) (431). Some indicate that care providers often dismiss their anxiety and concerns or do not provide enough information about sexuality or catheter care (425) (432) (Level of Evidence 3).

Positive benefits of catheterisation are also noted. In one qualitative study with 27 community-dwelling adults, perspectives differed (433). Some who were no longer wet regarded the catheter positively, and several developed more self-reliance as they dealt with catheter problems. Others described the challenge of finding bathrooms and adjusted or limited their outings accordingly **(Level of Evidence 2).** Similar results were found in another qualitative study of 36 persons; changes in sexuality, behaviour, and self-esteem varied among individuals. Some said the catheter had no impact and others indicated it had profound effects on body image and sexuality. A suprapubic catheter was of benefit to some, and the catheter position was importantly related to comfort, aesthetics, and body image (432).

The Consortium of Multiple Sclerosis Centres (434) oversaw a postal survey asking general questions about bladder and bowel management. Of the 9397 respondents, 12.8% used either intermittent or indwelling catheterisation. Fifty-three percent reported catheterisation having a positive impact. While the majority used intermittent catheterisation (64.7%), neither indwelling nor intermittent catheterisation appeared to affect QOL (435).

It is known that adherence to recommended bladder management post-SCI is not always optimum for a variety of reasons (436). People sometimes switch from IC to an indwelling catheter -- despite the inherent problems with an indwelling catheter -- because of QOL issues (436). Many use different bladder drainage methods over time (224) (437). In one chart review of people with SCI, 52% who were discharged using IC chose urethral catheterisation by 6 months, citing discontinuation because of: the need to depend on caregivers, poor hand functioning, spasticity, incontinence (despite anticholinergic drugs) and toileting inconvenience **(Level of Evidence 3).** Problem-solving by users for best catheter care is an area open for research. As part of a randomised clinical trial teaching self-management in 202 long-term indwelling catheter users, there were no group differences for QOL, though QOL improved somewhat during the 12 months of participation in each group (292).

Practical aspects of living with the catheter, such as managing the drainage bag, can be significant (see Section H). In a small pilot study based on a postal questionnaire to LTC catheter users (n=59) (525) almost 25% of respondents stated that wearing a bag had a major negative effect on everyday living. Concealment was a key concern (89%), and visibility of the bag can be considered demeaning and declares a loss of bladder control (223) (335), and the fear of the bag leaking contributes to vulnerability. Even a short-term catheter can assault one's dignity. In a study on post-operative short-term catheter use, people complained about feeling "on display" and objectified (424) **(Level of Evidence 3).**

Until recently, formal measurement of QOL has been limited because no validated instruments have been available. There are now two instruments measuring the quality of life in people with indwelling urinary catheters, an earlier version (438) validated in two small samples and a robust measure recently available (31). The latter measure is recommended for use**(Level of Evidence 3)**.

Cost-benefit of different catheters

Few studies have been published on the cost benefits of different catheters. The focus of economic studies has been in acute care using models to predict a proportion of patients with bacteriuria who will develop symptomatic UTI or bacteraemia. One UK based decision- analytic cost-effectiveness study was found in relation to a randomised trial over six weeks for short term catheterisation. The conclusion was that nitrofurazone coated catheters but not silver coated ones were more cost-effective (439). In a companion study of costs associated with long-term catheters in Swedish nursing homes, catheter care costs were associated more with basic care than acute interventions; 90% of the cost was for personnel (291).

Urinary catheters versus other care strategies

Few studies have compared indwelling catheterisation with other strategies to manage urinary incontinence, not least because of the difficulties in recruiting to and conducting robust trials. Sheath systems are associated with fewer incidences of bacteriuria, symptomatic UTI or death than indwelling catheters (123). Participants reported that sheaths were more comfortable and less painful than indwelling catheters.

Preferences for different urinary incontinence treatments have been studied in long-term care (440). Most respondents preferred non-invasive strategies (containment products and prompted voiding) to invasive strategies such as indwelling catheterisation (441). Older adults stated they would choose a treatment based, in part, on feeling dry, being natural, not causing embarrassment, being easy, and not resulting in dependence.

2. SUMMARY

- Asymptomatic bacteriuria should NOT be treated with antibiotics; routine urine culture is unnecessary (unless urological instrumentation is planned) **(Level of Evidence 1)**.
- Meatal cleansing of a catheterised individual by simple washing with soap and water (i.e., not with antimicrobial agents) during routine bathing or showering is recommended (Level of Evidence 1). The use of chlorhexidine for meatal cleansing before

catheterization rduced UTI for short term users in one study **(Level of Evidence 2)**.
- A closed drainage system reduces the risk of catheter-associated infection **(Level of Evidence 2)**.
- Midnight versus morning removal of catheters (see table) results in longer time to first void and larger first void and no difference in recatheterisation rate **(Level of Evidence 2)**.
- Use of alpha-blockers pre catheter removal after AUR results in fewer re-catheterisations and improved voiding **(Level of Evidence 2)**.
- Silver alloy coated catheters do not reduce the onset of CAUTI **(Level of Evidence 1)**. Antimicrobial catheters can prevent bacteriuria during short-term catheterisation (<14days) **(Level of Evidence 1)**.
- Nitrofurazone coated catheters reduce CAUTI risk but are associated with discomfort. Potential toxicity and / or antimicrobial resistance is unknown **(Level of Evidence 2)**.
- All currently available catheter materials are subject to bacterial biofilm formation **(Level of Evidence 1).**
- Recurrent urinary catheter blockage occurs in as many as 50% (range 24-50%) of all long-term catheterised patients **(Level of Evidence 2)**.
- Recurrent urinary catheter blockage caused by encrustation occurs in 40-50% of all long-term catheterised patients **(Level of Evidence 2)**.
- In most individuals with a long-term indwelling catheter, a characteristic pattern of 'catheter life' can be identified **(Level of Evidence 3)**.
- Evidence from *in vitro* models of the catheterised bladder indicates that: i) dilute urine; ii) high urine citrate content (> 1.5mg/mL) reduces the risk of blockage **(Level of Evidence 2)**.
- There is insufficient evidence from RCTs to assign an in vivo level of evidence for catheter washouts.
- Suprapubic catheterisation (SPC) is an appropriate alternative to urethral catheterisation **(Level of Evidence 1)**.
- There is some evidence for a reduction in catheter-associated infection in SPC use during short-term catheterisation **(Level of Evidence 2)** compared to urethral catheter insertion. However, there is no corresponding evidence for long-term suprapubic catheterisation **(Level of Evidence 2)**.
- Patient comfort, quality of life and satisfaction with SPC is generally good compared to urethral catheters **(Level of Evidence 1)**.
- Catheter valves provide a well-accepted system of bladder emptying for suitable patients who can manipulate the valve mechanism and empty the bladder regularly to avoid overfilling **(Level of Evidence 2)**.
- There is no evidence of increased risk of urinary tract infection with valves compared to conventional drainage systems **(Level of Evidence 2)**.

3. RECOMMENDATIONS

Recommendations relating to indwelling catheters are summarised in Table L-9

Table L-9: Recommendations relating to indwelling catheters.

- Indwelling catheters should only be used after alternative management strategies have been considered and rejected as unsatisfactory **(Grade of Recommendation A).**
- Duration of catheterisation should be minimal **(Grade of Recommendation A).**
- A closed drainage system should be maintained to reduce the risk of catheter-associated infection (Grade of Recommendation A). Meatal cleansing with plain soap and water (not with antimicrobial agents) is recommended for everyday washing **(Grade of Recommendation A).**
- Addition of disinfectants to drainage bags, bladder irrigation and antibiotic prophylaxis is NOT recommended as a routine infection-control measure **(Grade of Recommendation A).**
- Silver-alloy catheters are not recommended for use in acute or long-term care as they do not significantly reduce the incidence of CAUTI **(Grade of Recommendation A).**
- Routine urine culture in an asymptomatic patient is not recommended **(Grade of Recommendation B).**
- Catheter materials designed for long-term use (all-silicone, silicone or hydrogel-coating) should be used where a catheter is expected to be used long-term (i.e. >14days) **(Grade of Recommendation B).**
- If a long-term use is being considered, both SPC and UC should be offered, following appropriate risk assessment **(Grade of Recommendation B).**
- Routine washout solutions to reduce encrustation or debris are NOT recommended **(Grade of Recommendation B).**
- Preconnected urine drainage bags and catheters as a means to prevent CAUTI are NOT recommended **(Grade of Recommendation C).**
- UC and SPC catheters and drainage bags should be adequately supported to maintain patient comfort and prevent meatal or cystostomy tract damage from traction or abrasion **(Grade of Recommendation C).**
- UC and SPC insertion should be carried out only by appropriately trained and skilled practitioners, using an aseptic technique **(Grade of Recommendation C).**
- Effective handwashing before and after handling catheters and drainage equipment should be performed to reduce the incidence of CAUTI **(Grade of Recommendation C).**
- In patients with recurrent catheter encrustation and blockage, systematic monitoring should be undertaken to identify a characteristic pattern of 'catheter life' and instigate pre-emptive catheter changes prior to likely blockage **(Grade of Recommendation C).**

4. PRIORITIES FOR RESEARCH

1) General

- Agreement on key outcome measures to permit comparisons between studies:
  - Standardised definition of UTI for catheterised individuals.
  - Asymptomatic bacteriuria in a catheterised patient and its clinical / research implications.
  - Standardised time frames for following patients.
  - Documentation of the use of antibiotics prior to and during a study, e.g., preoperatively in surgery or commencement of antibiotics for other conditions during the study,
- Mixing study outcomes of asymptomatic bacteriuria and symptomatic urinary tract infection (CAUTI) limits meaningful comparisons and contributes to a lack of knowledge of effective ways to treat symptomatic CAUTI (442).
- Comparative studies of different patient groups, e.g., males and females, different age groups, patients at home and those in institutional care, including patients' comfort, satisfaction, and quality of life measures.

Indwelling catheters

- Address the barriers healthcare professionals face regarding optimum catheter management.
- Compare catheterisation techniques, e.g., CIC, suprapubic and urethral catheters, on CAUTI and other risks or potential benefits.
- Review any detrimental effects on bladder tissue from persistent asymptomatic bacteriuria in long-term catheterised patients.
- Studies demonstrating the efficacy of new designs of the catheter on reducing CAUTI, blockage and other catheter-associated harms and improving cost-effectiveness or quality of life for users.
- Conduct laboratory and clinically based research of strategies to reduce recurrent catheter encrustation and blockage, including maintaining dilute urine, increased level and acceptance of urinary citrate, the role of acidic 'catheter maintenance' solutions.
- Further development of catheter materials resistant to microbial biofilm formation, new approaches to disruption of the biofilm, or alternatives to catheterisation.
- Development of further self-management research focusing on decreasing blockage and CAUTI.
- Explore the role of caregivers in providing care to people with long-term catheters.

a) Catheter valves

- Clinical investigation of the effect of catheter valves on incidence and frequency of catheter encrustation and blockage.
- Cost-effectiveness studies of disposable versus re-useable valves.
- Studies designed to demonstrate if catheter valves promote maintenance of bladder tone and capacity.
- Further examination of combination management strategies such as valve during the day and free drainage overnight.
- Studies demonstrating the value of new designs in catheter valves, e.g., those operated by magnets for people lacking in hand dexterity.

M. INTERMITTENT CATHETERS

Intermittent catheterisation (IC) is the act of passing a catheter into the bladder to drain urine or maintain stricture patency via the urethra or a catheterisable channel such as a Mitrofanoff diversion. Urine is drained and the catheter removed until the next indicated time. IC avoids many problems associated with indwelling catheters, but urinary tract infections (UTI) remain an issue for many IC users and most research until recently has focused on UTI as an outcome. Intermittent catheterisation is a sterile technique in care settings and a clean procedure for community-based individuals who self-catheterise or have a single caregiver providing bladder care. Policy on sterile single-use catheters varies by country or re-use of catheters for IC. To date, there is an absence of evidence to support sterile single-use catheters for community-dwelling individuals with respect to prevention of UTI, although users may report improved quality of life with a single use catheter. In this section, we provide an overview of the current literature on IC related UTI, quality of life and cost-effectiveness.

The main factors that make intermittent catheterisation (un)suitable for people are listed in Table M-1.

Table M-1: The main factors that make intermittent catheterisation (un)suitable for people.

Intermittent catheterisation may be suitable for those with:
• Neurological disorders resulting in urinary retention or incomplete emptying.
• Detrusor sphincter dyssynergia.
• Incomplete emptying post-operatively, e.g. following Botox incontinence surgery.
• Acute urinary retention (most commonly in men).
• Urethral stricture requiring ongoing management.
• Continent urinary diversions such as a Mitrofanoff diversion.
Intermittent catheterisation is not suitable for those with:
• Poor hand dexterity or visual problems or no caregiver to assist.
• Insufficient cognition to understand the process.
• Reluctance or inability to perform the technique themselves, and unwillingness to accept the procedure from a caregiver.

1. EVIDENCE

At the time of the 6th International Consultation (36), there were 30 published randomised controlled trials on some aspect of IC and 7 Cochrane reviews including the topic. Findings from the last (6th) consultation are included in the summary below.

Since the last (6th) consultation (63), there have been three IC-related RCTs (443) (444, 445), one Cochrane review (446), five systematic reviews (447-450) (451, 452), five qualitative (or meta-synthesis) studies (453-457) and one laboratory-based study on catheter cleaning (458). Five cost analysis/effectiveness papers were found (459-463).

Most research on IC continues to relate to catheter-associated urinary tract infection (CAUTI), quality of life and cost-effectiveness.

1) Short-term bladder management

Under 14 days: Zhang *et al.* (464) conducted a systematic review and meta-analysis to compare the rates of UTI and postoperative urinary retention (POUR) in individuals who had undergone total joint arthroplasty, randomised to either an indwelling urethral catheter or IC. Nine RCTs involving 1771 patients were included. All indwelling catheters were removed within 24-48 hours postoperatively. Rates of UTI were similar between groups, and it was concluded that for patients at risk for POUR, indwelling catheterisation removed 24-48 hours postoperatively was the preferred option. For those low-risk patients, either indwelling catheterisation or IC could be appropriate or catheterisation following the surgery could be on a needed basis.

Choice of catheter
Comparison of short-term (<14 days) urethral indwelling or urethral intermittent or suprapubic catheterisation in adults hospitalised for a wide range of reasons, from urogynaecology surgery to medical management was presented in a Cochrane review (465). The authors concluded that suprapubic catheters reduced both asymptomatic bacteriuria, recatheterisation and pain compared with indwelling urethral catheters but that the evidence for symptomatic UTI and asymptomatic bacteriuria for indwelling urethral or IC was inconclusive. The evidence was also inconclusive for advantages of suprapubic versus IC.

In a cost comparison analysis (Markov Model) between three short-term catheter management pathways (indwelling catheter removed at a care facility, indwelling catheter removed by the patient at home or intermittent self-catheterisation), IC was found to be the most cost-saving option (472).

Long-term / continuing chronic bladder management

UTI prevention:
With respect to the incidence of UTI and long-term IC, a recent Cochrane review compared one type of catheter design versus another, aseptic versus clean technique, single-use versus multiple-use catheters, in both adults and children. Twenty-three trials met the inclusion criteria. The authors concluded that there is still no convincing evidence that the incidence of UTI is affected by any technique, coated or uncoated catheter or single or multiple-use 'clean' catheters. The authors noted that current evidence is weak, and trial design issues remain a significant issue (446). Four other reviews reported on either hydrophilic versus uncoated catheter or single-use versus reuse of catheter, and overall for both comparisons, it was found that evidence is generally weak, and further well-designed trials are needed to address whether there is any impact on the incidence of UTI (447-450).

Four papers reported on the use of Markov decision models to compare the cost-effectiveness of hydrophilic catheters with uncoated (459-462). All four reported that hydrophilic coated catheters were cost-effective but given the lack of clarity regarding the clinical effectiveness of hydrophilic coated catheters cost-effectiveness remains uncertain.

One review sought to establish whether the use of antiseptics for meatal cleansing was effective at reducing the incidence of UTI but found that the answer remains unclear (281).

A large scale RCT of 404 adults using IC compared the use of low dose antibiotic prophylaxis with no prophylaxis and found it to be effective in reducing UTI, but authors expressed concern about increased antimicrobial resistance with this strategy (443).

One RCT of 75 adults with neurogenic bladder compared single-use and reuse of PVC catheters and found no difference between the groups (444). One RCT 78 children with neurogenic bladder compared hydrophilic coated catheters with uncoated catheters and found that hydrophilic catheters might decrease the risk of UTI, but noted some participants had problems handling the coated catheters (445). One small scale study recruited people who reused catheters and provided single-use hydrophilic catheters and reported that the novel single-use hydrophilic catheters were preferred by most users (466).

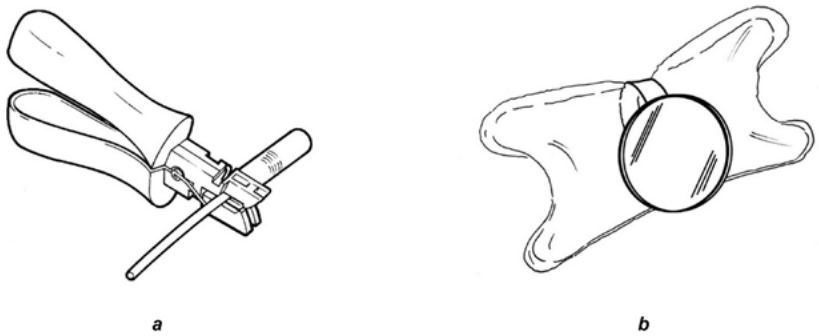
Quality of life / patient preferences
Moving away from UTI, recent research also focuses on IC users' quality of life and preferences. Research in this area predominately explores catheter designs (e.g. different lengths, 'ready to use' presentation) with different materials such as PVC-free and catheters with coatings, such as hydrophilic. Unsurprisingly, these studies are often industry-sponsored. Another trend in the literature is the focus on user groups with neurogenic bladder disorders and how IC can improve their quality of life. IC continues to be seen as the most commonly used procedure for those with incomplete bladder emptying and offers the ability to be self-caring, maintain independence and the opportunity to decide when and where to empty the bladder.

Other aspects that are evident in the literature are how long-term IC impacts an individual's daily life. Apart from obstacles such as insufficient hand movement or being unable to sit, which can restrict some patients access to IC, worries, embarrassment (467) and psychological coping mechanisms (468), studies also report that patients find intermittent catheters unwieldy, difficult to use or to carry discreetly (469). As one study reports moreover, the efficacy of CIC is often measured by the individual's quality of life. A randomised, crossover, multicentre study evaluated discreet design compact catheters compared to standard catheters, which were used by those with neurogenic bladder dysfunction. Results found that 63% preferred the discreet, compact hydrophilic coated intermittent catheter design as it contributed to a significant improvement in patient quality of life (469). Choice of product which offers discretion, ease of use and eliminates social anxiety is current user preference (468) (470).

IC users' views of UTIs have been explored, concluding that users are uncertain about signs and symptoms and when to seek help (453).

Perceptions of cleaning and re-using catheters have been reported from both the users and healthcare professionals' points of view, with a range of opinions found from both groups (454, 456).

Although there are several devices available to enable catheterisation by the individual - mirrors, catheter holders, and clothing retractors - it is of note that no published studies have explored IC users' impressions of these devices. Fig M-1 shows a catheterisation aid.



a *b*

Fig M-1: A catheter holder / insertion aid (a) and an inflatable cushion with mirror, to be held between the knees and provide a better view of the urethral meatus when self-catheterising (b).

Self-management research

a) One small trial has tested the feasibility and usability of a web-based intervention in a sample of people with spinal cord injury (N=34) using intermittent catheters (IC). Prior to the pilot with 30 individuals, the three-month intervention was pre-tested (N=4), and suggestions were given to refine the application, including modifying the web-based interactive urinary diary for mobile phone use. The single group pre-post study involved: a 23-page online educational booklet links to ICI's Catheter Products website and other related products, two phone calls with a study nurse in the first month and a follow-up phone call at three months to revise goals and approaches. In addition, discussion fora were provided, moderated by the study team and 2 peer advisors chosen from the pretesting group (471) (472). Measures about self-efficacy and self-management of IC were developed and tested. The web-based application was well received, with the forum being used the least often yet well liked. Catheter-related self-management was significantly improved with most comments about positive changes in fluid intake. Catheter self-efficacy and quality of life increased slightly, and UTI decreased from the three months prior to the study (42% to 30%), but these changes were not statistically significant.

2. SUMMARY

- There remains insufficient evidence to state that one catheter product or catheterisation technique is better than another in the prevention of UTI in IC users **(Level of Evidence 1)**.
- Soap and water combined with a 15-minute Milton soak (Milton method) renders catheters free of pathogenic organisms **(Level of Evidence 1)**.
- Quality of life might be improved with the use of compact portable IC catheters compared to standard length catheters or through single-use catheters (particularly hydrophilic coated catheters. **(Level of Evidence 2)**.
- Antibiotic prophylaxis may be beneficial for select individuals but must be weighed against the potential of antibiotic resistance **(Level of Evidence 2)**.
- There are several catheter products on the market: uncoated PVC requiring added lubricant; gel-coated; hydrophilic gel coated. Personal preference may determine use **(Level of Evidence 4).**
- Aids such as clothing holders, mirrors or catheter holders may facilitate catheterisation **(Level of Evidence 4).**

3. RECOMMENDATIONS

Recommendations relating to intermittent catheters are summarised in Table M-2.

Table M-2: Recommendations relating to intermittent catheters.

- Intermittent catheterisation (IC) should be routinely offered for those with ongoing bladder emptying problems and re-sidual urine > 100ml who are able to manage the technique **(Grade of Recommendation A).**
- IC technique can be taught to all ages of people with appropriate motivation and manual dexterity (or to a carer where this is acceptable to both parties). Appropriate education and ongoing support should be offered for optimum IC use and maintenance **(Grade of Recommendation C/D).**
- Offer advice on frequency of catheterisation. Ths should be based on individual needs to prevent over-filling of the bladder **(Grade of Recommendation C).**
- An external lubricant or lubricant-coated catheter should be offered to minimise urethral trauma **(Grade of Recommendation C).**
- IC users should be offered access to different catheters or catheter-packs for different purposes (e.g. ease of use may be particularly important when at work or in public) **(Grade of Recommendation C).**

4. PRIORITIES FOR RESEARCH

- Testing of catheter cleaning methods by large groups to assess safe multi-use of catheters.
- Ensure trials adhere to a consistent definition of symptomatic urinary tract infection.
- Cost-effectiveness studies should include patient acceptability/ satisfaction with the procedure and or product.
- Health utility in various situations needs to be considered, e.g., at home vs away.
- Further development of self-management research in IC users in various populations in multiple sites.
- Large, well-designed trials are needed to determine whether re-use of catheters is equivalent to single-use.

N. PRODUCTS AND DEVICES FOR PREVENTING OR MANAGING FAECAL INCONTINENCE AND ITS SEQUELAE

1. INTRODUCTION

Various products and devices may be used to manage faecal incontinence (FI) and its complications of skin damage and odour. Anal plugs, anal inserts, and vaginal inserts aim to prevent faecal leakage and are suitable for use by community-living, physically mobile individuals. Rectal catheters, long and short rectal tubes, and a non-balloon-based intra-rectal sheath redirect faeces from the rectum, collecting it in an external drainage bag in patients confined to bed in hospital or long-term care settings due to illness or functional disability (480-483). Peri-anal pouches and various types of absorbent pads collect or absorb faecal leakage for containment. Absorbent pads for managing faecal incontinence are covered in Section F . Incontinence-related skin and odour problems are addressed in Sections O and P, respectively. Other devices and products are reviewed for their ability to manage faecal incontinence here. Approaches to conservative management of faecal incontinence that are often concurrent with the use of products or devices are addressed comprehensively in chapters 16, 17 and 11.

1.1. Anal Plugs

Anal plugs were among the earliest product designs for preventing faecal leakage. An anal plug (Fig N-1) consists of a removable, small cup-shaped piece of foam that is held in a collapsed position by a film for insertion. When the film comes in contact with the moist rectal mucosa, the plug opens to block the passage of faeces (473) (474). An anal plug is inserted like a suppository using a lubricant gel and can be removed by pulling on an attached string or expelled by raising intra-abdominal pressure and pushing as during normal defaecation.

Fig N-1: An anal plug (from www.continenceproductadvisor.org)

Table N-1: Main factors that make anal plugs suitable or unsuitable for people with faecal incontinence

Anal plugs are suitable for individuals who:
• Wish to prevent leakage for a specific period (during exercise or after an enema or rectal irrigation).
• Who have leakage associated with spina bifida, anorectal malformation, rectal sphincter injury.
Anal plugs are not suitable for individuals:
• With active disease of the bowel or rectum.
• Who have a SCI and are at risk of autonomic dysreflexia.
• For whom a device might disrupt an established bowel routine.

An anal plug can successfully prevent FI in individuals with a variety of aetiologies, more so in adults than children (475) (476). The most recent Cochrane review of the effectiveness of anal plugs in preventing faecal incontinence published in 2015 (477) reached conclusions similar to those for the last International Continence Consultation, that anal plugs are useful as a treatment or adjuvant treatment of faecal incontinence in select individuals but that tolerance is limited (36). Individual studies have shown that the self-reported effectiveness of the plug in adults ranged from 83% (564) to 38% (478). In one study of children, 32% were completely continent using an anal plug, and 13% reported “total failure” (476).

The most common concerns and problems associated with wearing an anal plug include discomfort and failure to retain the plug (478). Children seemed to experience less discomfort than adults (476). The studies evaluating anal plugs had relatively small sample sizes unsupported by power analysis, and most had non-experimental designs. Table N-1 lists the main factors that make anal plugs suitable or suitable.

Another type of anal plug consists of an inflatable cuff or balloon at the end of a short pliable silicone catheter inserted into the rectum and connected to an external notification device (479). The cuff is inflated by the patient with approximately 30 cm^3 air using a syringe. When faeces enter the rectum, a signal from a photosensor on the catheter is sent to a pager which then notifies the person to inflate the balloon by pressing a button on the pager. Before a voluntary bowel movement, the balloon is deflated using a syringe and the catheter is withdrawn and can be reinserted. The catheter can be cleaned and reused for up to 28 days of actual time in the body. Replacing the fastener cap each day is recommended.

The latest design of this anal plug resulted in a significant decrease in FI after 14 days compared to baseline in 11 of 17 patients (64.7%) in a multi-centre trial according to two FI severity scores device (479). The Cleveland Clinic incontinence score decreased with the use of the device from a mean of 15.3 (range, 13–20) to 7.2 (range, 2–12) ($p<0.001$), and the American Medical Systems incontinence score decreased from a mean of 107 (range, 100–119) to 60 (range, 7–102) ($p<0.001$). There was a significant improvement in quality of life for all four domains of the FIQOL scale. Limitations of this plug are that some patients think it is too complicated to use, lack the dexterity to operate it and may be alerted when there were only small amounts of faeces in the rectum.

1.2. Anal Insert

An anal insert (Fig N-2) is made from supple silicone with two discs. The top or proximal disc sits inside the rectum beyond the anal sphincters and is available in two diameters and is intended to form a seal at the top of the anal canal. The bottom or distal disk remains outside the anus to avoid displacement into the rectum and ease manual removal (490). A removable applicator with

Fig N-2: An anal insert.
(from www.continenceproductadvisor.org)

a finger covering like a thimble and a spindle within the insert is used to introduce the device into the rectum and is then withdrawn after the device is in its final position. The anal insert is single-use and expelled during defaecation or can be removed manually by pulling on the bottom outer disc.

Use of an anal plug (Fig N-1) reduced the median daily frequency of faecal incontinence from 0.9 (mean 1.1 ± 0.9) episodes/d at baseline to 0.2 (mean 0.3 ± 0.4) episodes/d at 12 weeks ($p < 0.001$) in 73 adults who completed a non-randomised, single-group study (480). After the 4 weeks when the insert was no longer used, the median faecal incontinence frequency increased to 0.5 episodes/d (mean 0.7 ± 0.7), but this frequency was also significantly lower than baseline ($p < 0.0001$). Use of the anal insert resulted in a ≤50% reduction in FI frequency in 77% of the completers.

No serious adverse events and three moderate adverse events (faecal urgency, soreness, and bleeding haemorrhoids) in two subjects were reported using an intent to treat (ITT) analysis. Unpleasant symptoms were a sense of faecal urgency (26% of 91 subjects), irritation (13%), pain (7%), and soreness in the anal area (6%). Displacement of the insert into the anal canal occurred in 24% of subjects, which resolved with the expulsion of the device during bowel movements.

1.3. Vaginal Insert for Faecal Incontinence

A vaginal insert offers an alternative approach to preventing FI in women (481). The vaginal insert consists of an inflatable balloon on a silicone-coated stainless-steel base that is situated posteriorly in the vagina and ventrally to the rectum and a pressure-regulated pump. The wearer inflates the balloon insert to one of five preset pressures with the pump, which then occludes the distal rectum preventing leakage of faeces.

In a month-long study of 61 women who had FI at least four times in two weeks using a treatment group only design, the intent-to-treat analysis showed that 78.7% of the women could be fitted with the device and had their FI reduced by at least 50%. Using the device significantly improved QOL associated with FI. Nearly all users (96%) reported the device was comfortable or unnoticeable. Seventy-two percent of the original subjects used the vaginal bowel-control system for an additional two months with continued benefit.

There were 18 device-related adverse events (e.g., vaginal abrasions, erythema, irritation, ecchymosis, bruising) experienced by 23% of subjects. Adverse symptoms included discomfort of having the device in the vagina, cramping, pelvic pain, and UI, frequency, and urgency occurred in 3-10% of women, which were all more common during the fitting period. Limitations of the vaginal insert are the inability to be fitted with the device or adverse effects.

1.4. Rectal catheters and long and short rectal tubes

Rectal catheters (sometimes referred to as bowel catheters or faecal or bowel management systems) and rectal tubes of different sizes drain liquid faeces through openings at their proximal end into an external collection bag (Fig N-3). Rectal catheters and their collection bags are a closed system designed for extended use (US FDA approved for 29 days). Typically a balloon near the proximal tip is inflated to prevent faecal leakage around the catheter and to retard inadvertent expulsion of the tube during defaecation (482). Bowel management programs using these catheters often include daily or more frequent saline irrigations through the rectal catheter to maintain liquid consistency of stool and catheter patency (483).

Few studies of rectal catheters measure their effectiveness in preventing faecal incontinence or seepage; most focus on preventing or healing skin/wound problems. However, seepage around the catheter does occur (476, 484). In a study of 29 paediatric patients, the mean number of daily FI episodes decreased approximately 30-50% (486). In a study of 29 adult patients, varying degrees of leakage around the rectal catheter were reported in 71% of 198 assessments; 35% of these leakages extended to pads on the bed or beyond (484).

Non-blinded and non-independent endoscopic observations suggest the rectal catheter does not cause rectal mucosal damage during the recommended length of use (29 d in the US) (484) (475) (485). However, as the rectal catheter is used more in practice, there are reports of serious adverse events, including gastrointestinal haemorrhage and rectal bleeding requiring blood replacement, recto-urethral fistula, and mucosal pressure necrosis or ulceration, and unwanted expulsion (486) (487), (488), (489).

Use of a long rectal tube with or without inflating its balloon or off-label use of a short nasal-pharyngeal airway in the rectum (referred to as a rectal trumpet) can also redirect faeces to an external collection bag (490). A possible advantage of the rectal trumpet over longer rectal tubes is that it is easier for nurses to manage, and its shorter length has less contact with the rectal mucosa, reducing

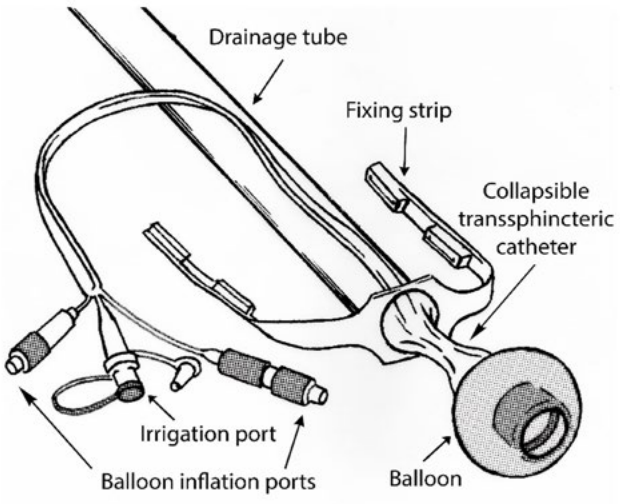


Fig N-3: A rectal catheter and drainage bag.

the area of possible damage. Limitations of the smaller rectal tube are similar to those for the rectal catheter including possible damage to the lower rectal mucosa and risk of expulsion from forceful Valsalva movements and dislodgement during repositioning of the patient and linen changes or from tugging on the collection bag (490). The use of these tubes is controversial because their safety has not been established and concerns of rectal bleeding, ulcerating or perforating the rectum, damaging the anal sphincter, or stimulating intestinal secretion worsening incontinence (482) (491-493)

Table N-2 lists the main factors that make rectal catheters / trumpets unsuitable for people with FI.

Table N-2: The main factors that make rectal cath-eters / tubes unsuitable for people with FI.

Rectal catheters / trumpets are not suitable for those with:
• Intestinal mucosal disease.
• Immunosuppression.
• Gastrointestinal bleeding or bleeding tendencies.
• Recent myocardial infarction or prostate surgery (492) (501).

Use of a rectal catheter with or without inflating the balloon is controversial because of concerns of ulcerating or perforating the rectum, damaging the anal sphincter, stimulating intestinal secretion worsening incontinence (482, 492, 493).

1.5. Perianal Pouch

An external perianal pouch consists of an external collection bag connected to a pliable wafer, which has an opening at its centre and an adhesive on the body side. The wafer adheres to the perianal skin (Fig N-4). The bag has a resealable port at its distal end through which faeces can be drained or connected to a larger, gravity drainage bag without the need to remove the wafer from the skin. Some pouches have a small, folded flap that allows flatus to escape so that it doesn't inflate and rupture the bag.

An external perianal pouch (491, 494) can collect leaked stool. The pouch avoids the risks of rectal mucosal or sphincter damage associated with rectal catheters or small tubes. Disadvantages of the anal pouch are difficulty in applying it and maintaining its seal and potential skin damage from removing the wafer or from the contact of faeces in the pouch with skin (490, 495).

There are few studies of rectal catheters, small rectal tubes, and anal pouches, and they often do not compare these products/devices or directly evaluate the ability to divert FI as an outcome. One study compared the effectiveness of a bowel catheter, rectal trumpet, or usual care in preventing or healing skin damage associated with FI , can be considered an indirect measure of FI management (496). Usual care included a perianal pouch. Critically ill patients (n=59) who were incontinent of liquid faeces were randomly assigned to one of the treatments. Results showed that the usual care group had significantly lower (better) scores for dermatitis-like skin after treatment compared to baseline, and there were no significant differences in the incidence or healing of pressure ulcers among groups. A validated and reliable instrument for assessing incontinence associated skin damage (IASD), (the IASD instrument (497) was used.

Fig N-4: An anal pouch.
(from www.continenceproductadvisor.org)

The pouch avoids the risks of rectal mucosal or sphincter damage associated with rectal catheters or small tubes. Disadvantages of the anal pouch are difficulty in applying it and maintaining its seal and potential skin damage from removing the wafer or from the contact of faeces in the pouch with skin (495) (490).

2. NEW EVIDENCE FOR THE CURRENT CONSULTATION

No recent studies of the effectiveness or tolerance of anal plugs were identified for this review. Regarding anal and vaginal inserts for FI six new studies and one systematic review (498) informed the current consultation. There are two studies about the anal insert (499) (500) and four about the vaginal insert. One of the four studies about the vaginal insert reports its effectiveness in preventing FI (501). Two studies, which are secondary analyses of the primary study reported by Richter *et al.*, examined other factors such as patient characteristics influencing fitting of the device and effects of the device on defecation and stool characteristics and (502, 503). In the fourth study, comfort, acceptability, and extent of rectal occlusion by the device were investigated (504). Regarding rectal catheters and peri-anal pouches, there are two new studies investigating a novel non-balloon, non-tube based intra-rectal device (505, 506) and one case report each of complications of a rectal catheter (507) and short rectal tube (508). One study evaluated the ability of a one-piece drainable pouch for preventing the development of incontinence associated skin damage in bedbound patients with FI (509), and a case report described the use of an ostomy pouch adapted to be a peri-anal pouch for a patient with FI to promote healing of gluteal abscess wound complicated by necrotising fasciitis (510).

Anal Insert

In a prospective pilot study investigating the effectiveness of the anal insert in decreasing FI , 15 patients (10 men, 5 women, median age 57 years (range (24-74)) who underwent restorative proctocolectomy for ulcerative colitis were asked to use the vaginal insert for 14 days, at least once during the day and once at night and to increase as tolerated (499). Six patients continued to take the same baseline dose of loperamide while using the insert and one continued cholestyramine. Patients completed the ICIQ-B instrument as a measure of anal incontinence at baseline and after 14 d. In an intent to treat analysis, ICIQ-B scores for night-time faecal leakage were significantly less at 14 days (0.93 (0-3)) (median (range)) compared

to baseline (1.8 (1-5)) (p=.03). Scores for faecal leakage during the day and other measures of the ICIQ-B were not significantly different. Regarding adverse effects, one patient reported bleeding and another pain when the device was inserted.

Regarding patient satisfaction, the same number of patients, six of 14 (43%), were satisfied or dissatisfied with the effectiveness of the device and 2 (14%) were neither satisfied nor dissatisfied (499). Eight of 14 patients (57%) were satisfied with the acceptability of the device, four (29%) were dissatisfied, and two (14%) were neither satisfied nor dissatisfied. Limitations of the study include the absence of a randomly assigned control group, lack of reporting the frequency of using the vaginal insert, small sample size, and an outcome measure for anal incontinence, which includes flatus versus FI

A retrospective review of the health records of 30 patients who were prescribed use of an anal insert after restorative proctocolectomy showed that there was a significant decrease in anal incontinence at follow-up (500). St. Mark's Incontinence score was calculated by patient interview at the time the device was prescribed (5(7-18)) (median (range)) and at the first follow-up clinic visit (10(2-18) (p<.001). The median follow-up time to the first clinic visit was 11 weeks (range = 8-14 weeks). Anal incontinence symptoms improved in 20 (67%) of patients, worsened in three (10%) and showed no difference in seven patients (23%). Approximately one-third (11, 37%) of patients used the regular sized insert, while the remainder (19, 63%) used the larger insert.

Adverse effects of the anal insert were rectal bleeding in one patient and pain/discomfort in four patients who discontinued use before the follow-up clinic visit (500). Eleven patients (37%) reported the anal insert fell out easily, three (10%) patients had difficulty inserting the device, and four (13%) stated it did not work as expected. Regarding user satisfaction, 20% of users disliked the device, and 80% liked it; 56.6% of users said they would like to continue using it. Limitations of the study are the lack of a randomly assigned control group, variability in the time to prescribing the anal insert after restorative proctocolectomy (which was not reported) and of the follow-up period, an outcome measure for anal vs faecal incontinence, reliance on patient recall vs a daily bowel diary for obtaining anal incontinence data in an unspecified number of patients, and other potentially missing data in the health record.

Vaginal Insert

In a prospective, multi-site, open-label one-group study, the clinical effectiveness and safety of the vaginal insert in 73 women with FI mean (SD) age 61.3 (11.5), number of vaginal births 2.2 (1.1), who had shown a decrease of 50% in FI episodes during a two-week trial period was studied (501). The median number of FI episodes over the two-week trial period was 10 (range 4-83). The primary outcome of effectiveness was having a 50% or greater reduction in FI episodes at 3 months compared to baseline as reported on a bowel diary during the 12-week study. At 3 months, 53 patients (73% (95% CI, 61-82%)) in the intent to treat (ITT) analysis had a successful outcome. In the per-protocol analysis, the success rate was 84% (52/83, (95% CI, 73-92%)). In the ITT group, the effectiveness of the vaginal insert at 6 and 12 months was 71% of 73 patients (95% CI, 59-81) and 70% (58-80), respectively. In the per protocol group, 54 patients were followed for 12 mos., and 94% of 54 patients (95% CI, 85-93%) met the primary outcome. There were no serious adverse events reported. Overall, 62 (85%) of subjects had a moderate or mild adverse event, and 28 (38%) of subjects had one related to the device, such as vaginal or pelvic discomfort/irritation, vaginal wall injury, lower urinary tract symptoms, vaginal infections, and constipation. Other adverse events occurred during fitting the device and were similar in type.

Satisfaction (using the Patient Global Impression of Improvement (PGI-I) scale and quality of life (using the FIQL tool) were measured in the per protocol group (501). Satisfaction was high (>89%) at three, six, and 12 mos. and all FIQL subscales improved. The strengths of the study were its inclusion of patients from multiple sites and follow-up period. The main outcome was measured at 3 months, but preliminary information about longer-term effectiveness up to one year was reported. Limitations were the lack of a control group and the severity of FI, limiting generalizability.

Matthews *et al.* (2016) (502), in a secondary analysis of the baseline diary data from the above study (501) compared characteristics of women who were successfully fitted with the vaginal insert and those who were not. Of the 10 women in whom fitting of the device was attempted, 61 (55.5%) were successfully fitted within four visits. Unsuccessful fitting was associated with previous prolapse surgery (p=.007) and shorted vaginal length, which was subjectively estimated using two fingers (p=.041). Limitations of the study are subjective estimations of vaginal length and widths and potential variations and small sample size.

In another secondary analysis of the reported by Richter *et al.* (501) the impact of the vaginal insert on bowel function, including frequency of bowel movements, urgency associated with a bowel movement, stool consistency, and degree of stool evacuation was examined (503). Data were reported by 52 women with FI (19-75 years old) on a two-week bowel diary during the baseline period and again at one month after using the vaginal insert. The total number of bowel movements per patient over a two-week period decreased from 20.9 at baseline to 15.3 at the follow-up at one month (p=.0002). Urgency was associated with an average of 54% of bowel movements at baseline to 26% at the follow-up p<.0001). The percentage of liquid stools (6-7 on the Bristol stool form scale) decreased from 36% at baseline to 21% at follow-up (p<.0001). Incomplete evacuation decreased from 39% of bowel movements during the baseline period to 26% at follow-up (p<.0034). Limitations of the study are lack of a randomised control group, a sample with severe levels ofFI , longer-term results based on a *per protocol* analysis, and the inability of women who could not be fit with the device to participate.

A study of 13 women with FI (mean age 70.7 years (range 40-90 years)) who were fitted with the vaginal insert reported on its comfort, acceptability, and degree of occlusion of the rectum when inflated (510). Comfort was reported by 12 patients after device insertion, during inflation, post inflation, and while walking using a 10-point scale from 1=no discomfort to 10=extremely uncomfortable. There was more discomfort (higher scores (mean (sd)) during inflation (3.3 (2.6)) and post inflation (3.5 (2.9) than during insertion (2.1 (2.0) orwalking (2.6 (2.0)). Five patients (45%) reported no discomfort for deflated and inflated states of the device. As many as 82% of the women indicated a willingness to use the vaginal insert after the study. Occlusion of the rectum was estimated by a physician during a digital rectal exam. When inflated, the device occluded ≥75% of the rectum in 54% (7/13) of patients and ≥50% of the rectum in 77% (10/13) of patients. Limitations of the study are non-validated measures of outcome variables, short time of assessment and subjective estimation of rectal occlusion.

Buono and Dave-Heliker (498) conducted a systematic review of studies about mechanical inserts (anal plugs, anal inserts, and vaginal inserts) published through July 2018. The review includ-

ed eight studies, some of which were addressed in previous ICI reviews.. The authors concluded that limited evidence indicates that these devices are effective, safe and can be recommended as a therapy for patients with FI.

Rectal Catheters and Tubes

Conventional rectal catheters are tube-shaped with an inflatable balloon surrounding the proximal end of the tube to anchor it within the rectum and reduce seepage around the tube. A new indwelling stool diversion closed system has a pliable diverter with a lattice design (resembling the shape of a badminton shuttlecock) that sits above the anorectal junction and is connected to a thin plastic sheath which in turn is connected to an external collection bag (505). The non-balloon-based diverter is folded into a disposable applicator used to insert it into the rectum, and the diverter self-expands after the applicator is removed. There is a withdrawal mechanism that collapses the internal diverter for removal. The collection bag has a one-way valve at its connection with the sheath and ports to obtain samples. Like other rectal catheters, this stool collection kit is approved for use for 29 days by the US FDA.

In a pilot study of 20 patients in an intensive care unit in the US, the non-balloon-based diverter was used for a mean of 3.54 (2.90) days (mean (sd)) (505). Patients were 60% male, 40% female, and (mean (sd) age 74 (12.3) years. Minor leakage from the diverter occurred in 86% patients and major leakage in 86% of patients. Spontaneous expulsion occurred in 10% of patients and no adverse events were observed. Limitations of the study are lack of a randomized control group, unknown measure of major and minor stool leakage, and short duration of device use and evaluation.

In a second study, the non-balloon-based diverter was used in 20 bedbound adults (16 male, 4 female, age = 56.7 (13.6)) (mean (sd))) with FI within the past 24 hours in a neurological unit in India (506). Ten patients had the device *in situ* for up to 24 hours in Phase 1, and 10 patients had the device in situ for up to 120 hours (5 days) in Phase 2. Perianal anal skin was examined for leakage every 4-6 hours. Of the 186 assessments of 20 patients, 174 assessments (93.5%) showed no leakage and 12 (6.4%) showed minor leakage. The device was dislodged or removed in five patients (25%). Sigmoidoscopy was performed in 16 of the 20 patients and two had minor mucosal erythema. Study limitations are similar to those in the study by (505).

There was a published case report about the development of a rectovaginal fistula in a patient treated with a rectal catheter/faecal management system (507). The patient was an 18-year-old female with leukaemia who developed multisystem complications including liquid FI after a matched unrelated donor stem cell transplant and preconditioning with chemotherapy and radiation and eventually died. The rectovaginal fistula was discovered by examination after 31 days of having the rectal catheter (which was beyond the recommended 29 days due to the severity of her illness).

In a quality improvement project, a retrospective chart review of 400 patients in a transitional care unit who received two types of short rectal tubes (a Mallinckrodt 32 Fr catheter or Robertazzi style 36 Fr rubber nasopharyngeal airway) for stool diversion and containment showed 9 probable and 3 possible cases of tube-associated rectal haemorrhage (508). The short rectal tubes were in place for a mean of 8.7 days. Of the 12 patients with the haemorrhages, 67% had cirrhosis, 58% were coagulopathic, and 91% required a transfusion of packed red blood cells after the haemorrhage. The hospital subsequently discontinued the use of the short rectal tubes. Study limitations are potential bias and incompleteness due to the indirect methods used to identify patients who received a short rectal tube and who experienced a rectal haemorrhage.

3. SUMMARY

An anal plug, anal insert, and vaginal insert can be useful as a treatment or adjuvant treatment of FI **(Level of Evidence 2).** These devices have been evaluated primarily in ambulatory, community-living individuals who need little to no assistance in managing FI and toileting. Both adults and children have used anal plugs.

An anal insert has been used by some patients up to 14 weeks. Many users liked the device, and more than half of users were interested in continuing use longer term. Symptoms of defecation urgency, irritation, pain, and expulsion may reduce tolerability. **(Level of Evidence 2)**

A vaginal insert can prevent FI and improve quality of life. Many users were satisfied with the device and were willing to use it long term. Some users may experience vaginal irritation, urgency, bleeding, or abrasions. **(Level of evidence 2)**. Some women may have difficulty being fitted with a vaginal insert; a history of prolapse surgery and short vaginal length reduces the likelihood of being successfully fitted **(Level of evidence 2).**

Rectal catheters and shorter rectal tubes successfully divert faeces to an external collection bag. Rectal catheters are primarily used in acutely and critically ill patients. Rectal catheters and shorter rectal tubes are often used to facilitate the healing of perineal wounds, but leakage around the catheters may result in perianal skin damage. **(Level of Evidence 3).**

The use of rectal catheters and shorter rectal tubes are associated with adverse events such as haemorrhage and rectal bleeding, especially in patients with bleeding tendencies or fistulae **(Level of Evidence 3)**.

A non-balloon-based stool diverter with a pliable lattice can be a useful option for diverting and containingFI. It has been evaluated mainly in bedbound patients. Minor rectal leakage and expulsion are limitations of its use. **(Level of Evidence 3)**.

An external perianal pouch can collect stool that would leak from the rectum. Difficulty in the application and long-term adherence of the pouch are limitations. **(Level of Evidence 3)**.

4. RECOMMENDATIONS

Recommendations relating to products for FI prevention and management are listed in Table N-3.

5. PRIORITIES FOR RESEARCH

- Additional evaluation of the anal plug, anal insert, and vaginal insert using experimental, well-controlled controlled designs, larger and adequately powered samples, and valid and reliable objective measures over longer periods of use
- Development of alternative devices to prevent FI , perhaps utilising wireless technology, intra-rectal plugs, or pouches that inflate and deflate as needed, which have fewer safety risks, come in a variety of sizes for adults and children, and are comfortable, tolerable, and effective.

Table N-3: Recommendations relating to products for FI prevention and management.

- Anal plugs may offered to reduce FI, but some patients are likely to use them on a limited basis or reject them due to discomfort **(Grade of Recommendation B)**
- An anal insert should be considered for decreasing FI. Its tolerability to adults seems to be better than the anal plug, but it is also associated with unpleasant symptoms such as minor irritation, defecation urgency, and expulsion may occur. **(Grade of Recommendation B)**
- A vaginal insert that compresses/occludes the rectum should be considered be a treatment option for women to prevent faecal incontinence. Discomfort, minor vaginal bleeding, and urinary urgency may occur. **(Grade of Recommendation B)**
- A non-balloon based faecal diverter with a lattice design maybe considered as an alternative option to a rectal catheter or short or long rectal tube in bedbound patients when more widely available. This device has been tested in patients in ICUs and neurological units. Minor rectal irritation, faecal seepage and unwanted expulsion in some patients have been identified as side effects to date. **(Grade of Recommendation C)**
- A rectal catheter should be considered for diverting faeces in acutely and critically ill patients unable to control bowel movements and at risk for skin damage or needing to heal wounds. Close monitoring for faecal seepage and integrity of perianal skin is recommended. **(Grade of Recommendation C)**
- The use of a short rectal tube (e.g., a naso-pharyngeal tube inserted into the rectum) may be offered to preserve perianal skin integrity or facilitate wound healing in patients with loose/liquid faecal incontinence. The safety of these types of tubes has not been fully evaluated. **(Grade of Recommendation C)**
- Thesetubes are not recommended for critically ill patients with high bleeding tendencies due to the risk of haemorrhage requiring treatment. **(Grade of Recommen-dation C)**
- A standard rectal tube with and without an inflatable balloon for faecal diversion is recommended primarily for non-ambulatory patients with liquid stool. The safety of these types of tubes has not been fully evaluated. **(Grade of Recommendation C)**
- Caution and close monitoring for complications and for appropriate balloon inflation is recommended when bowel catheters with balloons are used . **(Grade of Recommendation C)**
- An anal pouch attached to a drainage catheter can be considered to contain/divert liquid stool. Because there is a risk of skin damage when removing the wafer adhering the pouch it is not recommended where the skin is already damaged, or where need for faecal diversion is less acute (e.g., where stool is more formed) **(Grade of Recommendation C).**

- Development and evaluation of an external anal pouch that is easy to apply and remove, better adheres to skin, and perhaps, even promotes healing of damaged skin to which it would be applied.
- More rigorous evaluation of the non-balloon-based, faecal diverter with lattice design as well as rectal catheters with balloons and small tubes using experimental designs, larger and adequately powered samples, and valid and reliable measures

O. SKIN HEALTH

Skin repeatedly exposed to urine and/or stool is at high risk to develop incontinence-associated dermatitis (IAD). This concept was first introduced in the late 1980s (511), was later propagated by an expert group in the US (512) and is widely used today (513). It is included in the latest WHO ICD-11 classification under the label 'Irritant contact dermatitis due to incontinence' (EK02.22) and described as 'irritant contact dermatitis from prolonged contact with urine or faeces as a result of incontinence.' (514). IAD is characterised by cutaneous inflammation, often accompanied by secondary infection (512, 515). Early clinical signs include erythema, oedema and pain. Later stages are associated with maceration, erosions and excoriations (516, 517).

Depending on the care setting and the ways of measurement and reporting, published IAD prevalence estimates vary between 3% up to 60% (518-523). The exposure of the skin to urine and/or stool is a prerequisite to making the diagnosis of IAD, but not every incontinent patient develops IAD. Available evidence suggests that the following factors seem to increase the risk for IAD development: stool incontinence compared to UI alone (519, 521), dual incontinence (519, 524), high frequency of bowel movements (525), diarrhoea (525, 526), overall high care dependency including limited mobility (519, 524, 525, 527), diabetes mellitus (521, 526), and overweight (521, 528, 529).

IAD prevention and treatment includes promotion of continence (see chapter 20), the use of absorbent, diversionary and containment products, and topical skin-care procedures and products (513).

1. EVIDENCE

Since the 1940s, the design of absorbent hygiene products has constantly been improving in terms of absorptive capacity and breathability of materials (530). Since the 6th consultation (36), three RCTs (531-533) and one non-randomized study (534) were published comparing different absorbent products regarding the effects on preventing and treating IAD. In addition, one systematic and meta-analysis was published investigating the effects of faecal collection devices on IAD in critically ill patients (535).

Trowbridge *et al.* (531) compared two absorbent underwear products in 122 females (mean age 56 years) with UI during a 14 day wear period in the USA. There was very mild erythema in skin areas exposed to both products with minor differences between groups that were not clinically relevant. Both products were well tolerated, and two product-related adverse events occurred (erythema) that resolved during the study **(Level of Evidence 2).**

Francis *et al.* reported a cluster RCT on four medical-surgical wards in a US hospital (532). They compared superabsorbent disposable absorbent underpads with a breathable backsheet (n = 210, intervention group) with moderately absorbent reusable incontinence pads with a polyvinyl chloride backing (n = 252, control group) in patients with urinary and/or faecal incontinence (mean age 79 years). Hospital-acquired IAD was 17% in the control and 13% in

the intervention group, which was not statistically significantly different **(Level of Evidence 2)**.

Clarke-O'Neill *et al.* performed a cluster RCT in UK nursing homes (533). Four different pad designs (insert pads, all-in-one-diaper, pull-up pants, belt-shape diapers) were worn for two weeks by each of n = 78 nursing home residents (mean age 83 years) in a cross-over design. Skin problems occurred in nearly every nursing home resident in each pad design group, and there was no statistically significant difference between groups **(Level of Evidence 2)**.

The non-randomized study by Motta *et al.* was conducted in US nursing homes (534). Single-use disposable briefs and nonvapour, permeable moderately absorptive underpads were replaced by disposable high-fluid capacity underpads in nursing home residents with IAD or at risk for IAD. Forty residents (mean age 83 years) were followed up for four weeks. At baseline, n = 25 residents had IAD, n = 15 residents had intact skin. There was a statistically significant decline in residents with IAD over the study period, and the skin of the n = 15 residents remained intact **(Level of Evidence 3).**

IAD was considered in 16 RCTs and three quasi-experimental studies. The results of 12 studies were used in a meta-analysis (535). Review results suggest that anal pouch and anal catheter/tube collection devices reduce the occurrence of IAD in critically ill patients with faecal incontinence (535) **(Level of Evidence 1).**

Overall study results indicate that absorbent, diversionary and containment products prevent IAD development and/or promote IAD healing. There seem to be minor differences in terms of skin health when comparing similar absorbent products categories and designs (531, 533). Results also indicate that products with a higher absorptive capacity seem to decrease IAD development (532) and promote IAD healing (534).

Clinical studies on the effectiveness of skincare procedures for preventing and treating incontinence-associated dermatitis in adults

Skincare procedures to prevent and treat IAD include skin protection, cleansing and restoration. However, there are overlaps because many skincare activities have several effects on the skin (513, 536).

Since the last consultation (36), two systematic reviews have been published summarizing the evidence about the effects and the effectiveness of skincare products and procedures to prevent and treat IAD in adults (18+ years) (536, 537). A Cochrane review by Beeckman *et al.* (536) included 13 RCTs and quasi-RCTs, and a Joanna Briggs Institute review by Pather *et al.* (537) included 10 RCTs and quasi-RCTs. Both systematic reviews covered a search period until 2016 (536, 537). In 2020, a systematic review examined evidence to prevent and/or to treat IAD in older (65+ years) adults. The search period was between 1990 and 2018, and 13 RCTs and/or quasi-RCTs were included (538). Overall, these three systematic reviews summarized the evidence of 23 studies addressing IAD prevention or treatment using topical applications (536-538). All review authors concluded that there was a lack of high-quality evidence. Disregarding methodological limitations and risk of bias of the individual studies, the review results suggest that using any skin protection strategy and product is beneficial in preventing and treating IAD compared to 'standard care' or 'doing nothing'. Cleansers and washcloths containing low-irritating surfactants, dimethicone and/or emollients are more effective in protecting the skin compared to using water and traditional soap **(Level of Evidence 2).** When comparing low-irritating cleansers and cleansing strategies directly with each other, no differences in product performance were observed **(Level of Evidence 2).** The use of topical skin protectants such as barrier films or lipophilic barrier products ('barrier creams') reduced the IAD incidence compared to using no product **(Level of Evidence 2).** The superiority of one skin-protecting product against another could not be shown **(Level of Evidence 3).**

In addition to the studies included in the three systematic reviews (536-538), results of two RCTs (539, 540) and four non-randomized studies (541-544) and one case-series (545) have been published. One RCT compared a cyanoacrylate film-forming skin protectant (intervention group, n = 24) with a zinc oxide containing lipophilic barrier product (control group, n = 21) in n = 6 children and n = 39 adults (mean age 65 years) with IAD in the US (539). In the intervention group, there was a reduction of 11% and in the control group of 34% of an IAD severity score. Complete reepithelialisation was achieved in n = 6 patients in the intervention and n = 5 patients in the control group **(Level of Evidence 2).** No product-related adverse events occurred (539).

The other RCT compared the effects of the same cyanoacrylate film-forming skin protectant (intervention group, n = 10) with a standard IAD care approach (control group, n = 10) in hospital patients with IAD in two European hospitals (540). IAD severity improved in two patients in both groups each and one IAD lesion healed completely in the control group **(Level of Evidence 2)**.

Coyer *et al.* implemented a 'bundle' of IAD prevention measures, including the use of washcloths with 1% dimethicone and a barrier film based on acrylate terpolymer formulation in a general ICU in an Australian hospital (542). After the implementation, the IAD incidence was lower (15%) compared to baseline (32%). The implementation also reduced the IAD severity (542) **(Level of Evidence 3).**

Brennan *et al.* conducted a non-randomized IAD treatment study in an ICU in the US (541). Patients with IAD (n = 16, mean age 71 years) received twice-weekly an acrylate-based skin protectant by painting a thin layer on the affected areas. There was an IAD severity improvement in 13 patients **(Level of evidence 3).**

Avşar et al. implemented a complex skin care regimen in an ICU in Turkey, including the use of soft disposable cleaning wipes and the application of a barrier cream on healthy skin but also on IAD lesions to promote healing (543). The proportion of patients with IAD was lower after the intervention (10%) compared to baseline (3%) **(Level of Evidence 3).**

Takahashi *et al.* (544) followed 21 older patients (mean age 84 years, 8 male, 13 female) for four weeks who were incontinent, had confirmed genital candidiasis and wore diapers. At every washing at the time of diaper change, a 0.75% miconazole nitrate-containing soap was used. Over the four weeks of treatment, the IAD severity and the number of candida infections reduced substantially **(Level of Evidence 3).**

Woodward described three cases of adult patients with severe IAD (545). After treatment with a Medihoney containing leave-on product, IAD healing occurred **(Level of Evidence 4)**.

Taken together, the results of these additional studies support the conclusions of the three systematic reviews: The implementation of a structured IAD prevention and treatment strategy including mild skin cleansing and skin and/or IAD lesion protection using films

or barrier products prevents IAD and promotes healing (541-543, 545). Direct head-to-head comparisons seem to indicate little differences in IAD prevention and treatment products (539, 540). The use of an antifungal soap for skin cleansing also seems to support IAD healing (544).

There is an ongoing discussion as to whether and how topical products affect the absorbency of absorbent products, but so far, there are only four studies using artificial testing scenarios on the volar forearm skin (79). There are no studies investigating possible 'clogging' of briefs or pads and possible effects on skin health in incontinent patients.

2. SUMMARY

Skin exposed to urine and/or stool is at high risk of developing IAD. The best strategy to prevent IAD is to limit and/or to prevent prolonged and repeated exposure. Absorbent hygiene products (e.g. pads, diapers, pants) absorb moisture from incontinence (urine or liquid stool) and lock the liquid inside the absorbent core material and therefore reduce the moisture load on the skin surface (79, 530). The evidence summaries of the previous consultation (36) and this update indicates that products with high absorptive capacity (superabsorbent polymer core) and breathable material promote skin health compared to less absorptive and more occlusive products. This finding also corresponds to a Canadian guideline, recommending high absorbency pads in patients who are unable to toilet, and the use of external collection devices is not possible (546). The use of faecal collection devices also helps to prevent and/or to promote IAD healing. The skin should be cleaned with mild non-irritating cleansers using soft material (e.g. wipes). Evidence indicates that topical leave-on products (such as lipophilic or film-forming products) creating a barrier on the skin surface decrease IAD incidence and promote healing. A clear superiority of one skin protecting product against another could not be shown.

3. RECOMMENDATIONS

- Use absorbent products with high absorptive capacity and breathable material in subjects at risk for IAD or with IAD **(Grade of Recommendation B)**
- Use faecal containment devices in critically ill patients with faecal incontinence **(Grade of Recommendation B)**
- Use non-irritating skin cleansing products/procedures to remove stool and/or urine after incontinence episodes **(Grade of Recommendation B)**
- Use skin-protecting topical products at skin areas exposed to stool and/or urine (**Grade of Recommendation B)**
- Use topical products (e.g., barrier products, film-forming products) to protect IAD lesions and promote healing **(Grade of Recommendation B)**

4. PRIORITIES FOR RESEARCH

A major challenge in the field of IAD research is the wide range of different devices and products used in clinical studies to prevent and/or treat IAD (536). Even if particular products have been investigated in a trial, there is no guarantee that these products are still available because manufacturers constantly modify existing and develop new products (533). A solution could be the development of a device and product classification system based on main ingredients and/or performance characteristics using standardized terminology. This may enhance scientific communication and comparisons in the future.

Another main limitation is the use of many non-comparable outcomes and outcome measurement instruments in existing clinical trials (536-538). This impedes the comparison of prevention and treatment effects between studies and possible meta-analyses. Five core outcomes have been recently identified for clinical IAD trials: erythema, erosion, maceration, IAD-related pain and patient satisfaction (547), and the first attempts of how to measure these outcomes have been made (548). Research must further investigate how to best measure these five core outcomes, and they need to be implemented in a standardized fashion in future clinical trials.

P. ODOUR CONTROL PRODUCTS

Fear of odour from leaked urine, stool or flatus is a major concern that preoccupies many people suffering from incontinence. Worry about odour and the stigma associated with "smelling bad" is an issue consistently raised in studies that have explored experiences and opinions of patients with incontinence over time (36). The fear of odour plays a role in people's affective and behavioural responses to incontinence. Concern about odour can interfere with social relationships, cause people to isolate themselves within their home, or serve as a trigger to seek clinical care (549) (550) (551).

Additionally, caregivers are bothered by odour. Nurses caring for patients with diarrhoea during tube feeding rated odour as one of the most unpleasant aspects of caregiving (539). Malodours, trigger negative emotional reactions and avoidance. (552).

The odour associated with urine leakage is mainly due to the production of ammonia from urea by bacterial ureases, whereas factors that contribute to the odour of faeces and flatus include differing states of health and gastrointestinal function, diet composition, the profile of colonic microbes, relative concentrations of volatile sulphur and hydrogen-containing gases, and, possibly, short-chain fatty acids or ammonia (553) (554) (555) (556) (557). For example, dietary protein that escapes small intestinal digestion and absorption and reaches the colon provides a substrate for bacterial fermentation resulting in increased malodorous flatus (557). Using the frequency of searches on Google for information about unpleasant body odours as a surrogate of the presence of these symptoms, Korownyk (2018) (558) concluded that there is a seasonal variation in odours. The greatest number of searches about flatulence occurred in January, and the lowest was in July, and seasonality explained 88% of the variability in search frequency. A limitation of this study is that unlike the other body odours studied, the search about flatulence did not specify its odour component, but rather flatulence in general.

Odours associated with human faeces and urine are distinctive and recognizable to humans and can be detected at very low concentrations (552). Individual sensitivity to odours is affected by a variety of factors including genetics, age (with perception declining after age 60 years), sex (with women having greater perception than men), psychological state (anxiety is associated with greater odour sensitivity), and previous experience and exposure to a smell (increasing sensitivity in some persons). Furthermore, belief or expectation about the presence of body odour can result in a person misinterpreting an environmental odour as their own or perceiving an odour when none is present; thus, some individuals with incontinence mistrust their ability to detect bodily malodours (552).

Understandably, there is a demand for products that will mask or contain odour or, preferably, prevent it.

Odour control products play a key role in helping people with incontinence retain their sense of adulthood, identity, independence, and engagement in social life and in supporting their caregivers. Some patients with incontinence place a high value on products that mask, control, reduce, or eliminate odour (559). According to evaluations of different types of absorbent products for urinary (25) or faecal incontinence (560), the ability of absorbent products to reduce or contain odour is one of the top factors related to the selection or positive evaluation of a product. Women with light urinary incontinence rated 'the ability of absorbent products to contain smell' as the second most important factor when choosing a product, after the 'ability to hold urine' (25). Odour control had the lowest percentage of "good" ratings across various types of bodyworn incontinence absorbent products evaluated by community-living adults with faecal incontinence (n=189) (560).

Environmental odour is another concern when portable toileting devices are used. Where commodes were used for defecation in a home setting, carers identified the problem of odour lingering even after a commode had been emptied (53). Most bedpans do not have lids, resulting in odour spread when transporting their contentsfor disposal. There remains little research about cleaning frequency or products for commodes, bedpans, or urinals and their effectiveness in reducing any residual odour. Toilet bowl cleaning products are suitable for cleaning a commode or bedpan; many contain bleach or antibacterial ingredients, but their effect on reducing odour has not been studied. Gel formulations are advertised by manufacturers as being better able to cling to hard-to-reach surfaces than liquid agents. Use of a deodorizer in a room or near a commode can be considered.

There have been several innovative approaches to products for reducing odour associated with incontinence with varying levels of evidence and effectiveness. Current odour control products for faecal incontinence can be categorised as orally ingestible products that aim to reduce the production of malodorous gas or those that aim to contain or absorb expelled flatus odour.

Oral ingestible products that aim to reduce the production of malodorous gas include probiotics, the enzyme α-galactosidase, and oral charcoal mixtures.

a) Probiotics

In a randomised controlled trial, administration of *Lactobacillus plantarum* (5 x 107 CFU/ml) to patients with irritable bowel disease (n=60) was associated with a significant reduction in flatulence and pain (561) **(Level of Evidence 1).**

b) Enzymes (α-galactosidase)

In a randomised crossover trial, administration of 240 GalU alpha-galactosidase to healthy adults (n=19) was associated with less frequent flatulence events five hours after the test meal, but there was no difference in bloating or pain (562) **(Level of Evidence 1).**

In a randomised controlled trial, there was a significant reduction in the production of intestinal gas and the severity of flatulence after administration of 1200 GalU of alpha-galactosidase but not after administration of 300 GalU to healthy adults (n=8) following a test meal of beans (563) **(Level of Evidence 1).**

c) Oral charcoal mixtures

A randomised double-blind study comparing 194 mg of activated charcoal or placebo administered in a double-blind manner to healthy adults (n=13) immediately after a 'bean meal' and at 30-minute intervals for two hours after the meal showed a significant reduction in the mean number of flatus events in those given the activated charcoal (564). **(Level of Evidence 2)**

In a randomised controlled trial using 8 adult dogs, the production of hydrogen sulphide was significantly reduced following the administration of activated charcoal, *Yucca schidigera*, and zinc by 71, 38, and 58% respectively, and by 86% by the combination of all three agents (565).

In an *in vitro* study, flatus was collected from healthy adults (n=15) who had been given 15 g lactulose and had eaten a meal supplemented with beans and treated with activated charcoal and then with zinc acetate (554). Treating the collected flatus with zinc acetate reduced sulphur gas content but did not totally eliminate odour, while activated charcoal removed virtually all odour. **Level of evidence 3**

Products for trapping expelled odour comprise clothing, pads, and cushions containing activated charcoal (555), bedding fabrics and absorbent pads treated with antimicrobials (566) (567), a re-usable garment (568), lavender scent applied on body worn absorbent pads (24), and penile sheaths.

a) Products containing activated charcoal

The extent to which the odour associated with flatus was reduced by the use of different types of continence products containing activated charcoal was evaluated (555). The devices included four different types of charcoal-activated pads worn inside conventional underwear, two types of charcoal-activated wearable briefs, and five types of charcoal-activated cushions upon which to sit (555). The products that were reported as being the most effective were the briefs (95-99% absorbency), followed by the pads (55-77%), usual clothing (22%), and cushions (20%) **(Level of Evidence 3).** The briefs seem to provide the greatest surface area for contact with malodorous rectal gas. The limited absorption of malodorous gas by clothing suggests that washing the outer clothing, as well as underwear, is important to reduce odour.

b) Microbial treated fabrics and pads

In vitro experiments showed that cloth treated with acrylonitrile copper sulphide inhibited the growth of most bacteria causing urinary tract infection and that cloth treated with iron-phthalocyanine effectively eliminated bad-smelling gases (566).

In another *in vitro* study, suspensions of a range of bacterial, viral, fungal and yeast micro-organisms were applied to the cloth. N-halamine siloxane coatings were found to inactivate most antimicrobials and prevent odour caused by the bacterial generation of ammonia on urine-soaked fabrics (567).

c) Re-Usable Garments

The ability of a reusable under-garment called 'HealthDri' to control odour associated with UI was rated as adequate or excellent by 80% of men (n=84) and women (n=42) who used the product for one month (568).

d) Scents on disposable pads

In a multicentre evaluation of different disposable bodyworn absorbent pads for light UI, pads on which lavender scent was applied did not control odour significantly better than other pads (24).

Penile Sheaths

Penile sheaths are reported to reduce the odour associated with UI. In one study of 61 men, Conveen Optima urosheaths had higher ratings for odour management, feelings of security and freedom, self-image, discretion and skin integrity, but not for ease of use, compared to absorbent pads (60). In another study, nursing home staff rated the odour in the room of residents with UI and FI as being lower after urosheaths were used for 1 week (550).

A broader review of findings on the use of penile sheaths is given in Section G.

1. NEW EVIDENCE FOR THE CURRENT CONSULTATION

14 new peer-reviewed papers were identified to inform the current consultation about odour associated with incontinence and continence products:

- A theoretical paper about the role odour plays in human affective and behavioural responses to incontinence (552)
- Four qualitative studies about the impact of odour (569-571) (572)
- A descriptive in vitro study about a new technique to identify bacterially formed odorants and reduce the odour of UI in absorbent incontinence products - reported in four papers (573) (574) (575) (576).
- Two further papers about odour neutralising technology (ONT), including a randomised single-bind parallel study (531) and a descriptive study about the effects of using ONT in disposable incontinence products on skin health (577)
- A feasibility study about an odour detecting device (578).
- A publication about the development and validation of an instrument that includes an item to measure product users' concerns about the smell (29)
- Two randomized trials investigating the effects of ingestion of probiotics versus digestive enzymes (579) or bismuth subgallate (580) on flatus odour.

Probiotics or Digestive Enzymes

In a double-blind, randomized study (579), adult patients who underwent gastric bypass surgery for severe obesity and had adverse postoperative symptoms were randomly assigned to 1 of 3 groups: Probiotics group A (1g *Clostridium butyricum MIYAIRI* (5 billion colony-forming units (CFUs))), Probiotics group B (300 mg *Bifidobacterium longum BB536* (8 billion CFUs)), or Digestive enzymes group (Aczym containing 100 mg takadiastase N, 20 mg cellulose AP, 50 mg lipase MY, and 100 mg pancreatin). Products were taken twice daily for 2 weeks. Outcomes were measured by self-report using the Gastrointestinal Quality of Life Index that was modified to include 2 new items for foul-smelling flatus and oil flatus; possible scores range from 0 to 4 (0= the worst and 4=the best option).

Of the 60 participants, 53 completed the study (19 in Probiotics group A, 18 in Probiotics group B and 16 in Digestive enzymes group). The score for the foul smell of flatulence of all groups together improved from 1.02 before the intervention to 2.4 after, $p<.05$. Scores for an excessive amount of flatus also improved from 1.3 before to 2.5 after the intervention ($p<.05$). Study limitations include the absence of a control group and intent to treat analysis, modification of a validated tool, and inclusion of subjects with an altered gastrointestinal tract.

Bismuth Subgallate

In a prospective, randomized, double-blinded, placebo-controlled, crossover study (580), adults who reported flatus and/or stool odour changes at least 6 months after loop duodenal switch surgery for morbid obesity participated in two treatment periods, each lasting for 1 week, separated by a 1-week washout. Patients received 200 mg bismuth subgallate, 2 capsules per meal, or a placebo. Outcomes were measured by self-report using the Gastrointestinal Quality of Life Index that was modified to include 4 new items, including those for smelly gas and stool; possible scores range from 0 to 4 (0= the worst and 4=the best option). Of the 36 participants, 29 completed the study. The mean (sd) score for smelly gas improved from 0.4 (0.5) before the intervention to 1.8 (1.3) afterwards, $p=.001$. The mean (sd) score for smelly stool improved from 0.5 ± 0.6 before the intervention to 1.9 ± 1.3 afterwards, $p=.001$. Study limitations include potential carryover effects between periods, absence of an intent to treat analysis, modification of a validated tool, and inclusion of subjects with an altered gastrointestinal tract.

Odour Sensor and Alarm

Ortiz Perez *et al.* (578) describe the design and development of a prototype of a portable "smart" device for detection, discrimination, and notification of odours associated with urine and faeces. The device is an accessory to a mobile phone and uses Bluetooth to transfer raw data from the odour sensing unit to the smart device, which performs the data analysis and notification tasks. The gas detection is based on semiconducting metal oxide technology and was capable of detecting relevant trace gases in urine or faeces such as ammonia, methyl mercaptan, and dimethyl sulphide. Further development and performance testing is needed before the device will be available.

The impact of odour

Fear of odour associated with incontinence continues to emerge as a salient finding. Animut *et al.* (569) used a phenomenological approach to explore the experience of living with obstetric fistula and the experience of becoming an obstetric fistula patient in a small sample of women (average age 33.8yrs) in Ethiopia. Concern about smelling bad caused the women to experience psychological health and social problems. Changole *et al.* (570) also conducted qualitative interviews with women with obstetric fistula and their family members in Malawi. They reported the women and their families had very little prior awareness and knowledge about the condition or its causes. A qualitative study involving interviews with women with obstetric fistula in Nigeria reinforces the impact of the stigma associated with the odour of uncontrollable leakage of urine and faeces in some communities. Mohamed *et al.* (571) reported the women described socially removing themselves from community gatherings and having to frequently wash their clothes and use perfumes to cover the offensive odour and always carry extra clothes and water in order to control the urine incontinence and bad odour. Finally, according to the findings of a qualitative study of 22 community-dwelling women (65 years and older) with UI from South Korea, deodorising the smell was one of several self-management strategies the women adopted in order to preserve their self-respect in the sociocultural environment (572).

Drawing on research about the physiology of the olfactory system, Dalton & Maute (552) published a theoretical paper about odour

and malodour perception as it relates to the odours of urine and faeces. The authors discussed the biological and psychological bases underlying odour perception and ‘‘odour worry’’ among people with incontinence. They claimed odours, and malodours in particular, can trigger immediate, reflexive emotional, and behavioural responses. This is because, whilst olfactory signals are transmitted to the thalamus and neocortex, where they are translated into conscious awareness, they are also transmitted to the non-cognitive limbic area and are translated into emotional information. Malodours, such as the odour of urine and faeces, are by their very nature, perceived as negative and are associated with decay or contamination and risks for health and wellbeing. Moreover, malodour induces feelings of discomfort that can impede cognitive performance and elicit negative emotional responses such as disgust and behavioural responses such as social distancing. ‘If an odour is produced, a host of concerns arise around the social meaning of being a malodour source with the corresponding emotional anticipations and responses’ (p 129).

The authors also discussed the concept of hypervigilance about the potential for malodour from urine or faeces. Hypervigilance can lead a person with incontinence to smell odours that are not physically present, i.e., ‘a phantom odour.’ These findings suggest clinicians could play a role in allaying peoples’ concerns about real or perceived odour associated with incontinence.

Despite emerging research about the central role odour plays in peoples’ affective and behavioural responses to incontinence, it is rarely evaluated. However, a new self-reported quality of life questionnaire developed by *Yearwood-Martin et al.,* (29) could be used for this purpose. The ICIQ-PadPROM was designed to assess the treatment effect of absorbent continence products. It contains one item about ‘odour-worry’.

Products that aim to prevent, absorb, or control odour associated with UI

A new development in the science associated with odour, continence products and incontinence is a technique to identify bacterially formed odorants and reduce the odour of UI in absorbent incontinence products. Sponsored by industry, Forsgren-Brusk *et al.*, (573), Hall *et al.*, (574), Ryttsen *et al.,* (575) and Widen *et al.*, (576) described an *in vitro* study in which adjusting the pH of the superabsorbent from 6.0 to pH 4.5 and pH 4.9 significantly ($P < 0.05$) inhibited the bacterial growth rates, in most cases, both at 6 and 12 hours. The effect was greatest at pH 4.5.

In addition, two new studies were found that described the effects of adding an odour neutralising agent to absorbent disposable incontinence products. Sponsored by industry, Gutshall *et al.*, (577) evaluated the effect of odour neutralising technology (ONT) on skin health in a series of tests including the cumulative irritation test, the behind-the-knee study for trans epidermal loss and the Human Repeat Insult Patch Test for contact sensitisation. The ONT was a proprietary mixture of functional fragrance components that aimed to neutralize amines. The researchers reported ‘the ONT products produced minimal skin reactions that were like the non-irritant controls or in-market control products without ONT’. Sponsored by the same company, Trowbridge et al., study (531)conducted a single-blind randomised parallel study to compare the effect of a disposable incontinence product with ONT with non ONT products in a sample of 122 people (60 ONT product/52 non-ONT product). The outcomes of interest were skin health and overall comfort. The researchers reported ‘In-use 14-day testing demonstrated few statistical differences between an experimental product with unique ONT and currently marketed product for skin assessments and comfort. Both products were comfortable and well tolerated.

Products that aim to prevent, absorb, or control odour associated with FI

No new studies were identified.

2. SUMMARY

- Odour control products have a key role in helping people with incontinence retain their sense of personhood, identity, independence, and engagement in social life and supporting their caregivers **(Level of Evidence 3)**.
- The clinical effectiveness of treating fabric-based continence products with antimicrobial agents to reduce the odour associated with urine is unclear (548) (549) **(Level of Evidence 4)**.
- Compared with continence pads, penile sheaths may have a greater ability to reduce the odour associated with urine leakage 60) (550) **(Level of Evidence 2).**
- Users of a particular type of reusable undergarment reported being satisfied with their ability to control the odour associated with UI (551) **(Level of Evidence 3).**
- Users of disposable absorbent products reported being dissatisfied with products’ ability to control the odour associated with FI (552**) (Level of Evidence 3).**
- Oral intake of certain probiotics *(Lactobacillus plantarum*, 1 g *Clostridium butyricum MIYAIRI*, or 300 mg *Bifidobacterium longum* BB536), enzymes (α-galactosidase or Aczym), oral charcoal mixtures, or bismuth subgallate may reduce production of malodorous gas (541) (543) (544) (545) (546) (579), (580) **(Level of Evidence 1).**
- Products or devices that are activated with charcoal can absorb odour associated with flatus; charcoal activated wearable briefs are more effective than charcoal activated cushions or pads (542) **(Level of Evidence 3).**
- Applying scent to disposable body worn pads does little to reduce the odour associated with urine (20) **(Level of Evidence 3).**
- A portable sensor connected to a mobile phone can detect odours of urine and faeces and may have potential to notify patients of their presence (578) **(Level of Evidence 3)**.
- Evidence for cleaning the collection container of commodes or shower chairs or bedpans to reduce odour is scarce and relies on expert advice; anti-microbial cleaning solutions destroy bacteria responsible for the breakdown of urea in urine or producing flatus in faeces and may be used to wash these products **(Level of Evidence 4)**.

3. RECOMMENDATIONS

Recommendations relating to products for odour associated with incontinence are listed in Table P-1.

4. PRIORITIES FOR RESEARCH

- Development of an absorbent product that can eliminate, reduce, or mask the odour of leaked urine, faeces, and flatus while protecting the skin.
- Development of bodyworn undergarments and textile products (soft furnishings and bedding) for eliminating, reducing, or masking odour associated with urine, faeces, and flatus.

Table P-1: Recommendations relating to incontinence and odour.

- Inform patients with FI about the limited ability of disposable bodyworn incontinence products to reduce the odour associated with FI **(Grade of Recommendation C).**
- Inform patients that odoriferous rectal gas may be better absorbed with bodyworn briefs containing activated charcoal rather than with separate pads or cushions **(Grade of Recommendation C).**
- Since some pads absorb up to 75% of gas, offer patients who have smaller amounts of gas the opportunity to compare pads and briefs for themselves. **(Grade of Recommendation C).**
- Patients with irritable bowel syndrome should consider a trial of the probiotic **Lactobacillus plantarum** to reduce flatulence **(Grade of Recommendation C)**
- For those persons experiencing stool leakage due to flatus, over-the-counter α-galactosidase containing products, which reduce the production of malodorous gas can be tried **(Grade of Recommendation B).**
- Patients with malodorous flatus after bariatric surgery may be offered a trial of probiotics (1 g **Clostridium butyricum MIYAIRI** or 300 mg **Bifidobacterium longum BB536**) or digestive enzymes (Aczym) **(Grade of Recommendation B).**
- Washing of outer as well as underclothing after flatus should be performed to reduce odour due to absorption of gas by clothing **(Grade of Recommendation C).**
- Equipment used for toileting should be cleaned after each use following local infection control policies in institutional environments to reduce odour and maintain hygiene and aesthetics. **(Grade of Recommendation D).**
- Use of a deodorizer in a room or near a commode should be considered **(Grade of Recommendation D).**
- Investigation of whether probiotics or changes in dietary intake can eliminate or reduce the odour of flatulence or leaked faeces.
- Evidence-based guidelines to inform the cleaning and maintenance of commodes, shower chairs and bedpans in home and institutional environments.

APPENDIX 1

The literature search to identify material for this chapter - additional to that reviewed for the last (6th) consultation (63) - was conducted as follows. MEDLINE and CINAHL databases were searched from 2016 – 2020 for English language publications. Detailed search strategies were developed for each electronic database searched. Consideration was given to variations in terms used and spellings of terms in different countries so that studies were not missed. Relevant abstracts were examined, and then pertinent articles were retrieved and reviewed, and the reference lists were searched for further studies. For product categories associated with little or no research literature, the analysis relied on expert opinion from clinical practice papers.

The following main search terms were used: incon-tinence AND device*, toilet* AND facilities, female, male, urinal*, commode*, bedpan*, urin* AND sheath, condom AND catheter*, *, intermittent catheterisation, indwelling catheterisation, catheterisation, catheters, incontinence OR absorbent pad*, urinary AND catheter* (in title), urinary AND leg bag* OR legbag* OR drainage bag, faecal OR faecal AND incontinence AND plug OR pouch OR bag OR device, OR manage* system, incontinence OR perineal AND dermatitis OR in-flammation OR skin damage, incontinence OR perineal OR diaper AND dermatitis OR inflammation OR skin damage OR skin lesion OR erythema OR rash OR erosion.

APPENDIX 2

Details of Cochrane reviews relating to long-term and short-term catheter use are described in Table Ap21.

Table Ap2-1: Cochrane reviews on long term and short term catheterisation.

Date	Authors	Research Q	Comparisons	No. of Trials	Conclusions
Cochrane Reviews on LONG TERM Catheterisation					
2010	Hagen et al (576)	Long term: Are bladder washouts effective in maintaining catheter patency.	No washout vs saline or acidic solution; saline vs acidic solution vs antibiotic solution.	5	Insufficient evidence to state whether blockage, UTI or time to first catheter change is affected by washout.
2012	Niël-Weise et al (577)	Long term: Urinary catheter policies for LT catheter drainage.	IUC vs SPC/IC; prophylaxis vs sx treatment; vs AB P vs microbiology.	1 on IUC.	A possible benefit of ABP in LT IDC but resistance is a serious concern.
2012	Jahn et al (578)	Long term: Types of catheters for long term use.	Antiseptic vs standard catheters; standard vs standard catheter.	3	Evidence insufficient to effect of silver alloy catheter on CAUTI; hydrogel catheter may be better tolerated than silicone catheter.
2013	Jamison et al (579)	Long term: Catheter policies for LT voiding problems in neurogenic bladder.	IC vs IUD. IUD vs SPC Sheaths vs IUC or SPC. IC vs timed voiding.	0	No trials were found.
2016	Cooper et al (402)	Policies for replacing long-term indwelling urinary catheters in adults	different policies for replacing long□term indwelling urinary catheters in adults	3	Insufficient evidence to assess the value of different policies for replacing long□term urinary catheters on patient outcomes
2017	Shepherd et al (293)	Washout policies in long-term indwelling urinary catheterization in adults	catheter washout policies (e.g., washout versus no washout, different washout solutions, frequency, duration, volume, concentration, method of administration)	7	Evidence was not adequate to conclude if washouts were beneficial or harmful
Cochrane Reviews on SHORT TERM Catheterisation					
2006	Phipps et al (580)	ST urinary catheter policies following urogenital surgery.	UC vs no catheter; UC vs SPC; duration. Clamping prior to removal.	36	Recatheterisation higher in non-UC group or UC vs SPC; early removal reduces the risk of UTI; clamping may increase the risk of UTI and delay normal voiding.
2005	Griffiths and Fernandez (581)	Short term: Policies for urethral catheter removal (midnight vs morning).	Midnight vs other times (morning).	18	Possible benefit from midnight removal -larger 1st void/longer time to 1st void, shorter stay; no difference in recatheterisation rate.
2013	Lusardi (582)	Short term: Antibiotic prophylaxis in short term catheterisation.	Prophylaxis (vs none).	6	Weak evidence that ASB, pyuria and fever are reduced.
2014	Fisher (583)	Short term: Alpha blocker pre catheter removal in AUR.	Alpha-blocker vs placebo or no treatment.	9	Improved voiding with AB vs placebo and reduced incidence of repeated AUR.
2014	Lam et al (584)	Short term: types of catheters.	Silver alloy/oxide; Nitrofurazone; Minocycline + rifampicin all vs standard catheter.	26	Reduction of CAUTI: no difference with silver alloy; weak evidence that nitrofurazone reduced risk of CAUTI/ bacteriuria; may cause more discomfort than standard catheters.
2015	Kidd et al (474)	Short term use of SPC vs IUC.	IUC vs SPC; IUC vs IC.	25	SPC vs IUC: ASB, recatheterisation and pain reduced in SPC group; IUC vs IC: inconclusive re: UTI, ASB, pain.

ASB = asymptomatic bacteriuria. SPC = suprapubic catheter. IUC = indwelling urethral catheter. IC = intermittent catheterisation. AUR = acute urinary retention. CAUTI = catheter associated urinary tract infection. sx = signs and symptoms

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COMMITTEE 20

PRIMARY PREVENTION, CONTINENCE PROMOTION, MODELS OF CARE AND EDUCATION

Chair
Rantell, Angie (United Kingdom)

Members
Dufour, Sinéad (Canada)
Eustice, Sharon (United Kingdom)
Griebling, Tomas (United States)
Hegde, Aparna (United States)
Neels, Hedwig (Belgium)
Newman, Diane (United States)
Palmer, Mary (United States)
Richardson, Davina (United Kingdom)

COMMITTEE 20

PRIMARY PREVENTION, CONTINENCE PROMOTION, MODELS OF CARE AND EDUCATION

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ABBREVIATIONS

AHCPR Agency for Healthcare Policy Research
Apps Internet and mobile applications
AUA American Urological Association
BICS-Q Barriers to Incontinence Care Seeking Questionnaire
BMI Body mass index
BT Bladder training
CNA Continence nurse advisor
CNP Continence nurse practitioner
CNS Continence nurse specialist
EAU European Association of Urology
EMAS European menopause adropause society
ERIC Enuresis resource and Information charity
ESPU European society of pediatric urology
FI Faecal incontinence
GME Graduate medical education
GP General practitioner
HCP Health care professional
HRQoL Health-related quality of life
HSB Help-seeking behaviour
IBD Inflammatory bowel disease
IBS Irritable bowel syndrome
ICCS International Children Continence Society
ICI International Consultation on Incontinence
ICIQ-SF International Consultation on Incontinence questionnaire UI– short form
ICIQ-LUTSQoL International Consultation on Incontinence questionnaire lower urinary tract symptoms quality of life
ICS International Continence Society
KAB Knowledge, attitudes and beliefs
KPI Key performance indicators
LUTS Lower urinary tract symptoms
MS Multiple sclerosis
MSA Multiple systems atrophy
NC Nurse consultants
NH Nursing home
NHSE National Health Service England
NS Nurse specialist
OAB Overactive bladder
OCSS Optimal Continence Service Specification
PCP Primary care physician
PFD Pelvic floor disorders / dysfunction
PFDI-20 Pelvic floor dysfunction Index
PFM Pelvic floor muscle
PFME Pelvic floor muscle exercises
PFMT Pelvic floor muscle training
PIKQ Prolapse and Incontinence Knowledge Questionnaire
POP Pelvic organ prolapse
QoL Quality of Life
RCT Randomized Controlled Trial
RN Registered nurses
SoMe Social media
SUFU Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction
SUI Stress urinary incontinence
UDI-6 Urogenital distress inventory
UI Urinary incontinence
UK United Kingdom
UKCS United Kingdom Continence Society
U.S. United States
UUI Urgency urinary incontinence
WFIPP World Federation for Incontinence and Pelvic Problems
WHO World Health Organisation
WOCN Wound Ostomy Continence Nurses

I. INTRODUCTION

This chapter reports advances in knowledge on primary prevention, continence promotion, models of care, and education. It continues to reflect the shift in paradigms from a singular focus on secondary and tertiary treatment, and management to the inclusion of primary prevention and health promotion, i.e., promotion of bladder and bowel continence. The interest in primary prevention has led to the development of new theories and conceptual models about bladder health, especially continence, across the life-course[1] and new definitions for bladder and pelvic health[2, 3].

Traditionally urinary incontinence (UI) and faecal incontinence (FI) were topics not freely discussed or shared by the public, public health providers, or healthcare professionals interested in the promotion and maintenance of health. Many people with these conditions feel shame and stigmatized and do not seek help[4]. Despite this barrier however, empirical and evidence-based resources are becoming available to promote continence and prevent incontinence.

Research and public health initiatives funded by national governments have increased and practice guidelines have been developed and put into use in recent years. Inclusion of the public in research through community engagement and community-based participatory research practices has also increased[5]. Innovative approaches to research and individual and population-level interventions are being used to advance knowledge, change behaviour, and ultimately improve health outcomes. Social media use has increased to conduct research, disseminate knowledge, as a research recruitment means, a venue to provide updates on research advances, and obtain timely feedback about policy and research recommendations[6]. Many countries carry out national or local public awareness campaigns, often spearheaded by a national continence organisation, and the internet is increasingly being viewed as a convenient source of health information for the public[7].

This chapter updates the 2017 International Consultation on Incontinence (ICI) chapter in these areas: primary prevention, continence promotion, models of care, and education and provides recommendations in each area. Most information contained in this chapter primarily relates to UI and FI. These conditions are prevalent but continue to be under-investigated in many populations. As the evidence mounts for non-biologic determinants of urinary and faecal incontinence and for the sheer numbers of people at risk for developing these conditions, the focus in the first chapter section is on population-based primary prevention research. Emerging evidence supports strategies to promote continence in specific populations, yet more research is needed to quantify the benefits of primary preventative strategies, especially across the life-course.

It will review recent continence promotion literature and includes health promotion and help-seeking (care-seeking) behaviours (HSB) for faecal and urinary incontinence. Progress for continence promotion activities globally has been made, yet rapid adoption of existing primary prevention practices appears limited on an individual or population-level.

Information is provided about continence promotion programmes and advocacy through worldwide organisations. There remains inadequate information about the impact of these efforts on changing public and healthcare policies, public and health professional attitudes, beliefs, and knowledge about bowel and bladder continence.

The chapter discusses models of continence care and service delivery. It will consider variations in service delivery worldwide and recommended proven models of care. The final chapter topic addresses education of healthcare professionals about bowel and bladder continence, including the development and use of public health and medical guidelines and care pathways. Although the committee found information about recent practice and research initiatives, little evidence-based research to support widespread dissemination and translation exists.

II. PRIMARY PREVENTION OF UI AND FI

Literature search is found in Appendix 1.

1. BACKGROUND

Primary prevention aims to, "prevent a disease from ever occurring", and "refers to actions aimed at avoiding the manifestation of a disease". [8] These actions include interventions to improve health by: 1) changing the impact of social and economic determinants of health, 2) providing information about how to reduce risks of disease and clinical preventive services to people, and 3) delivering community and individual-level interventions to reduce risks. Although UI is not considered a disease, primary prevention of UI in adults is important because of its prevalence across the life-course, financial and societal costs, and impact on the quality of life (QoL) of affected individuals and caregivers. A report from the Global Coalition on Aging published in 2018 noted the importance of bladder health and that overactive bladder affected employee productivity and healthy active aging[9]. This document supported conclusions from an earlier consensus statement that healthcare professionals and policymakers and funding bodies need to address UI primary prevention efforts[10].

One driving force for developing primary prevention interventions for UI is epidemiological evidence of population aging. The United Nations reported there were 703 million people aged 65 years and over in 2019 and projected that the number will double to 1.5 billion people aged 65 years and over by 2050, representing 16% of the world's population. Forty-seven countries considered least developed (for statistical purposes) by the United Nations are projected to have the fastest increase of the older population, i.e., 37 million in 2019 to 120 million in 2050[11] These global aging estimates have significant implications for the number of people expected to develop UI + FI and other chronic non-communicable diseases associated with UI + FI (i.e., diabetes, arthritis, and neurological disorders). In addition to population aging another factor that has implications to UI + FI prevalence and incidence is obstetric fistula. The World Health Organization estimates 50,000 to 100,000 women annually experience obstetric fistula during childbirth and 2 million women in Asia and sub-Saharan Africa are living with untreated fistulas[12]. These fistulas are considered preventable and, left untreated, lead to untold suffering as a result of UI and FI[13]. Population aging and obstetric fistulas serve as exemplars for prioritizing primary prevention. The science of primary prevention of UI + FI incorporates an urgent need to reduce and eliminate existing inequities in healthcare access and utilization, reduce healthcare and societal costs from UI + FI and its causes across the human lifespan, and increase the workforce of educated and clinically competent healthcare and public health providers.

Two additional driving forces to develop primary prevention interventions are the accumulation of evidence that multiple factors extrinsic to the individual person influence the health and function of the lower urinary tract and increased scientific and professional interest in developing a prevention science agenda[14]. Since the Sixth ICI, multiple advances in primary prevention of UI science in women have occurred. For example, a research definition of bladder health in women and girls was developed by a transdisciplinary group of researchers in the United States. Bladder health was defined as, "A complete state of physical, mental, and social well-being related to bladder function and not merely the absence of lower urinary tract symptoms (LUTS). Healthy bladder function permits daily activities, adapts to short-term physical or environmental stressors, and allows optimal well-being (e.g., travel, exercise, social, occupational, or other activities)"[15]. Knowledge about women's perceptions of bladder health and associated function has deepened through qualitative research[16].

Research terminology was also developed to assess bladder health across the life-course of women[17]. In addition to a bladder health definition, pelvic floor health was defined as, "the physical and functional integrity of the pelvic floor unit through the life stages of an individual (male or female), permitting an optimal quality of life through its multifunctional role, where the individual possesses or has access to knowledge, which empowers the ability to prevent or manage dysfunction"[18].

To facilitate the development and organization of research questions and priorities, a conceptual framework that, "encompasses all facets of social ecology, integrates biology with social ecology, and emphasizes a life course perspective described the multi-level domains across the human life-course" was published[19] . This framework was adapted from Glass-McAtee Society-Behavior-Biology[20] and the World Health Organization framework of social determinants of health[21]. The resultant framework creates a foundation for researchers to use in developing interventions to prevent UI in women across their life-course. To differentiate the individual from population level outcomes, a model was proposed to illustrate the multi-stage approach to education, detection, intervention, embedded change, and outcomes (see Figure 1). At the intersection of individual and environment, evidence has emerged that potentially modifiable toileting behaviors in women are associated with UI[22]. The physical environment has been implicated in influencing women's toileting behaviors[23]. There are no systematic reviews of population-based primary prevention interventions.

Professional organisations sponsor activities and events to heighten the public's awareness of the importance of bladder health and continence. These include but are not limited to: The World Federation for Incontinence and Pelvic Problems (WFIPP) sponsorship of World Continence Week since 2013 (www.wfipp.org); the United Nations observes May 23rd to heighten the awareness of urgency to end obstetric fistula (www.un.org/en/observances/end-fistula-day); the Continence Foundation of Australia (www.continence.org.au), and Canadian Continence Foundation disseminates information to healthcare provider and public. The Continence Foundation of the American Urological Association (AUA) has designated November bladder health awareness month (www.auanet.org) in the United States. A listing of continence societies is located at Worldwide In-

continence Organizations – Managing Life with Incontinence. In the UK, the Urology Foundation runs a urology awareness month in September. Evaluation of the effectiveness of these programmes are not available.

2. PREVENTION OF UI IN SPECIFIC POPULATIONS

2.1. Hospitalised adults

UI is prevalent (26%) in hospitalized adults 65 to 74 years old, and more so in those 85 years and over (35.2%)[24]. There is little evidence for effects of intervention designed to prevent UI in hospitalized adults. Hospital based programs to detect and manage UI have been reported, and nursing education and standardized assessment improves nursing compliance to the clinical protocols[25,26]. Authors of a Cochrane review however noted there is insufficient evidence to guide UI care after stroke[27], and qualitative research revealed that nurses working in orthopaedic units often do not view UI as a priority in care, have inadequate knowledge and do not attempt to prevent UI[28]. Measures to facilitate knowledge implementation have been recommended[29], as has screening women annually for urinary incontinence as a preventative measure[30].

2.2. Women during pregnancy and postpartum

Interventions to prevent UI in prenatal women from twenty-four studies including 15982 women were evaluated in a systematic review and meta-analysis with the authors concluding that low to moderate evidence existed that pelvic floor muscle exercises (PFME) reduced the odds of UI during pregnancy and postpartum. The authors further noted that these women had been continent prior to starting PFME, but PFME did not treat the UI for those who had UI prenatally[31]. Authors of another systematic review concluded that PFME performed by continent women in early pregnancy may reduce risk of UI in late pregnancy[32]. There was insufficient information about the effects of antenatal PFME in the late postpartum period, i.e., 6 to 12 months post childbirth. Further the authors stated, “A population-based approach for delivering postnatal PFME is not likely to reduce UI.”

Interventions to prevent UI in postpartum women were evaluated in a systematic review[33]. The common intervention in the six studies included in the systematic review was pelvic floor muscle training (PFMT) although other behavioural interventions were used in some of the included studies, i.e., lifestyle modification, bladder training, programmed urination. The authors concluded that training of the pelvic floor in the immediate and late postpartum stages is effective in preventing UI. They further noted that barriers to exercise protocol adherence can be overcome with specific interventions.

In a qualitative study women identified barriers to performing PFMT including not having adequate information and training to sustain practice. The participants suggested that using an app with information and reminders about PFMT would be beneficial[34]. A continence app for the purpose of enhancing PFME adherence has been validated for clinical practice use[35].

The results from an implementation project for promoting PFME in women who were in the antenatal and postnatal periods at one hospital were reported. The authors found that both nurses and women had inadequate information and education about PFME prior to the project and nursing skills improved after implementation of the project as did women’s knowledge[36]. A narrative review that provided a summary of quantitative and qualitative evidence for PFME during pregnancy and the postpartum period concluded that PFME is effective in preventing UI. The authors noted that provider behavioral support is as important as the prescription for PFME[37]. In addition, authors of a systematic review concluded that group-based PFME during pregnancy was found to be more cost-effective effective than providing individualized PFME to postnatal women who are incontinent[38].

Urinary and fecal incontinence can be a preventable complication of childbirth in young women, especially those living in developing countries. A population-based study in India aiming to identify risk factors for and prevalence of obstetric fistulas found that inadequate pre-natal services, childbirth at home, and poorly equipped emergency obstetric services in health centers increased risk of fistulas. Overall prevalence of obstetric fistulas was 0.3% [39]. The authors recommended a community-level plan to increase emergency obstetric resources, address socio-economic determinants associated with obstetric fistulas, and training for community workers and healthcare providers to recognize women at risk of obstetric fistula during childbirth.

2.3. Older people

An international (i.e., Canada, France and UK) pragmatic cluster randomized trial was conducted with community-living women aged 65 to 98 years old who reported they had at least two UI episodes weekly. These women had not sought professional help for UI in the past year nor were they currently taking medications to treat UI. They were recruited from community organizations who participated in continence promotion workshops. There was sustainable one-year improvement in incontinence in the group that received a continence promotion workshop, i.e., an interactive discussion on myths, self-management techniques, and lifestyle interventions, compared to the group that received a healthy aging workshop[40]. A continence questionnaire, the Continence Index, was developed to predict future UI in older women. Factors that emerged as the strongest predictors of UI included body mass index, sneezing, belief of developing future UI, difficulty in stopping the urine stream, and problems with memory specifically with regard to remembering names[41].

A multisite randomized controlled trial, Translating Unique Learning for Incontinence Prevention, (TULIP), was conducted in the United States with community-living women 55 years and over (N= 647) in which women were followed 3, 12, and 24 months after the intervention. The intervention consisted of bladder health information by either 2-hour face to face instruction or a 20-minute DVD with the same information. Investigators found both methods equally effective. There was no difference in UI (measured by the International Consultation on Incontinence Short Form) between the groups at 3, 12, and 24 months[42]. Wu et al., noted that although PFME was effective in mid-life women who have UI, its effect on preventing UI is not clear[43].

A multi-site randomized controlled trial to prevent UI was conducted with older adults who had hip fracture. Adults who had UI prior to the fracture or cognitive impairment that did not allow individuals to participate or understand the educational intervention were excluded. Researchers used the urinary habit training intervention within the Nursing Intervention Classification. The goal of this intervention was to establish a predictable pattern of bladder emptying to prevent UI. The intervention was provided by one of the researchers during hospitalization in 30 minute sessions the second to fourth

day post- operation[44]. Incidence of UI at 3- and 6- months post hospital discharge was significantly lower in the education group (25.5%) compared to the control group (49%) relative risk 0.52, 95% confidence interval [0.3, 0.9].

2.4. Men postprostatectomy

Since the Sixth ICI[45], a systematic review with meta-analysis was published on the efficacy of PFME for post-prostatectomy incontinence. Twenty-two studies were included in the review and 15 studies were used for meta-analysis. The authors were interested in determining if variation in the content and delivery of the PFME protocol explained differences in outcomes among clinical trials. Meta-analysis revealed the PFME group had better outcomes compared to the control group when specific conditions were met including but not limited to where pre-operative PFME were performed, where instructions to contract urethra were given, and when continence was defined as no leakage[46] Recommendations were made to target exercises to UI pathophysiology and principles of motor learning as well as principles of exercise physiology[47].

2.5. Healthy men

No evidence for primary prevention was located for men across their life-course.

3. PREVENTION OF FI IN SPECIFIC POPULATIONS

3.1. Women in pregnancy and postpartum

A systematic review of literature to investigate the effectiveness of physiotherapy to prevent and treat FI in women was conducted. Twenty-two studies were included and the authors concluded that physiotherapy improves muscle strength, endurance, anal sensation and that biofeedback was beneficial in preventing FI[48]. Little evidence exists for the effects of PFME on FI in the postnatal period[49].

A systematic review was performed to determine if cesarean delivery could prevent postpartum FI[50]. However, from the 24 studies included FI was not found to be reliably prevented by cesarean delivery.

3.2. Other adult populations, e.g. older people and men

There remains a lack of research and understanding of the role of primary prevention for FI in comparison to UI. Most of the available evidence focuses on the risk factors for development and management of FI but does not consider the role of primary prevention. Research is needed to assess the role and effectiveness of population-based interventions as seen in UI such as improving education and understanding of bowel health and teaching self-management / conservative management techniques for FI.

4. PREVENTION OF UI + FI IN CHILDHOOD

Although research on primary prevention of UI and FI in children is limited, there is some evidence to suggest that early toilet training may help to prevent day and nighttime wetting later in childhood[51], [52], [53], [54]. Furthermore, there is some evidence that leaving bladder and bowel issues untreated may result in them continuing into adolescence and adulthood, or precipitate issues earlier in adulthood than would otherwise have been expected[55],[56] , [57].

The limited evidence focuses on identifying potential risk factors from childhood that increase the risk of development of UI and FI in later life. However, many of the primary prevention models in adults focus on early intervention of education and conservative therapies to prevent UI and FI. The challenge in children is that the benefit of these interventions is undetermined. A recent Cochrane review assessing the effects of conservative interventions (e.g., lifestyle behavioural advice, PFMT, biofeedback, urotherapy, etc.) for treating daytime UI in children found little reliable evidence that can help affected children, their carers and the clinicians working with them to make evidence-based treatment decisions[58]. Well-designed research investigations, with defined interventions and consistent outcome measurement are needed.

Summary

Primary prevention of urinary and fecal incontinence remains in its nascent stage, but population aging, preventable obstetric incontinence outcomes, and significant advances in understanding bladder health and UI primary prevention are driving the need to develop effective primary prevention interventions across the human life-course. Foundational evidence has demonstrated that modifiable risk factors exist across multiple levels: intrapersonal, environmental, and societal. High quality RCTs are needed in men, women and children at different life stages and across the life-course to develop evidence for the effectiveness of population and individual-level primary prevention intervention for UI and FI.

Levels of Evidence/Recommendations

- Pelvic floor muscle exercises can prevent UI and FI in pregnant and postpartum women. (Level of Evidence: 1)
- Education designed for community-dwelling older women can prevent UI. (Level of Evidence: 1)
- Pelvic floor muscle exercises should be provided to pregnant women. (Grade of Recommendations: A)
- Education to prevent UI for older women should be provided. (Grade of Recommendations: A

RESEARCH PRIORITIES

- We are unable to make recommendations on the role of primary prevention for UI in men, for FI for all populations and in Childhood. Further research is urgently required in these groups.

III. CONTINENCE AWARENESS AND PROMOTION

Literature Search is found in Appendix 1.

1. BACKGROUND

According to the World Health Organisation (WHO), health promotion is, "the process of enabling people to increase control over, and to improve, their health. It moves beyond a focus on individual behaviour towards a wide range of social and environmental interventions"[59]

Efforts to promote awareness about incontinence and its treatment can be enhanced by adopting evidence-based theories and methods from the field of health promotion and by heightening awareness of the World Health Organisation social determinants of health[60]. Health promotion frameworks can be used to plan and evaluate the effectiveness of strategies and programmes used to promote continence.

2. RAISING AWARENESS AND UNDERSTANDING

Consumer education is a critical component of effective continence promotion. Education of individuals with, or at risk of, UI and/or FI, their family members or informal caregivers, and healthcare professionals increases awareness about incontinence and the benefits of prevention and management. The goals of consumer education are elimination of stigma, promotion of help-seeking, and reduction of suffering[61].

A meta-ethnographic study by Toye and Barker (2020), analysed 41 studies of the experience of living with UI, including 1046 people from 13 countries[62]. All the studies included women and eleven included men. The concepts that emerged centered on whether UI was normal or an illness; the impact on the individuals' perceptions of self; the stigma, shame and guilt; the difficulties and benefits of talking; maintaining control of the incontinence and reaching the point of requiring help.

Toye and Barker found that UI was described as 'part and parcel of my life' and physical history and therefore not an illness. It was considered normal for older women and mothers to have UI: 'Leaking is associated with being decrepit and incompetent, which makes its secrecy imperative if I am to be seen as normal'. It 'symbolises infancy and extreme old age'. Help seeking was restricted when individuals felt that UI was personal, minor or low priority. Asking for intervention occurred when the impact of the UI on life and work was greater than the embarrassment of disclosure, or when there was anxiety about a possible serious medical condition. A 'culture of secrecy' and incontinence as 'taboo' was described with UI experienced as 'anomalous… it defies social categorization: I am ill and also not ill; urination is normal and also not normal; I am an adult and also not like an adult.'

Using a quantitative descriptive design, Day et al [63] surveyed 50 community-dwelling women's knowledge about UI. Findings revealed that the women had poor knowledge, principally in relation to UI risk factors (38.8%), prevention (40.5%), treatment (39.4%) and management (49.4%), suggesting that women have unmet

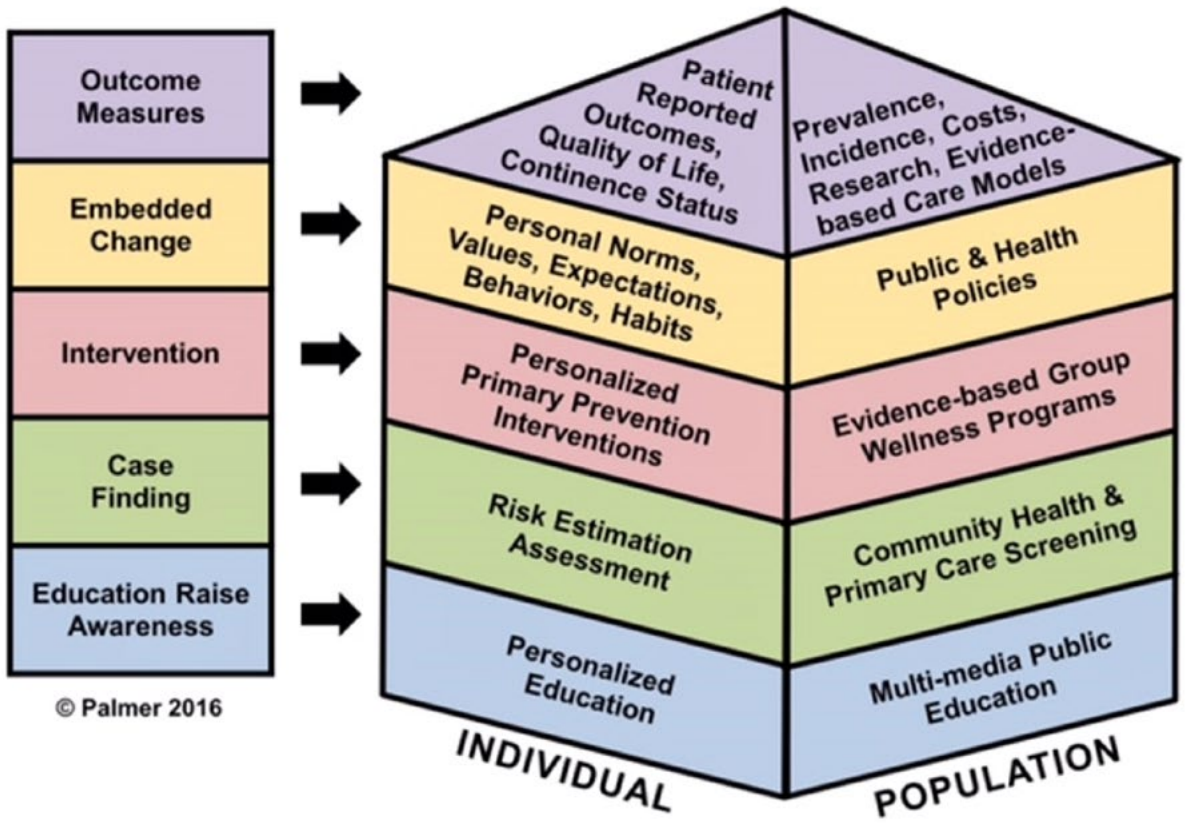

Figure 1: Primary prevention model

educational needs related to UI and indicating an area for improved consumer education. According to a qualitative analysis of open-ended questions from a survey of 1,458 women with UI in Washington State, women had a range of different interpretations and understanding about the causes of UI, with many believing it was a normal part of being female[64]. A systematic review of nineteen studies, including 11,512 women found that most women had poor knowledge of pelvic floor muscle dysfunction, (PFD) including risk factors and treatment options[65]. However, Siddiqqui et al (2016) in a study of 113 White, black and Latina women found that awareness of UI varied across ethnic groups, with Latina women least aware and awareness was influenced by how easily they could access information and through which media[66].

A cross-sectional study of 1092 college women aged 19 -24 and 25-30 years old found that the older age group had more awareness and understanding of UI and FI than the younger age group, with those who were majoring in science having the greatest awareness[67].

In a study of three hundred and forty-six women Chen et al (2019) found that the knowledge of women attending geriatric, community and primary care hospital clinics was similar[68]. However, knowledge of pelvic organ prolapse (POP) (78.2%) was higher than knowledge of UI (37.6%) in those with awareness of these conditions. They also found that lower educational attainment and being unaware that UI and POP are medical conditions was more strongly associated with low knowledge of PFD. Furthermore, the authors argue that promotion of awareness may increase presentation for early intervention and, therefore, for conservative treatment options.

There was a similar lack of awareness of FI with only 29.8% of 601 adults in Korea aware of the term. Knowing the term was 'significantly associated' with seeking help[69].

An important aspect of continence promotion involves dispelling the pervasive myth that incontinence is normal, temporary, not a medical issue or inevitable due to aging childbirth[70]. The lack of clear description of UI as a disease may also hinder continence promotion[71].

Spencer[72] described a pre and post evaluation of an education programme for women with UI and found education alone was insufficient to alter women's beliefs. The researcher emphasized the need for more engagement about the topic, and to consider individualized learning needs.

Mendes et al (2017) propose that knowledge is limited by lack of discussion about UI [71]. Clinicians play an important role in encouraging discussion and providing information about UI[73] and can empower an individual to make changes and set goals for UI self-management[74].

In a convenience sample survey of 360 women in Israel, researchers found that women who suffered from UI and those who were older generally had more knowledge about UI including causes and treatments[75]. Another small focus group study with African American and Latina women in the U.S. demonstrated general misconceptions about causes of pelvic floor disorders, symptoms, and treatments[76]. Participants were eager to gain more information, particularly to share with their daughters, and identified placing family demands before their own health needs as a barrier to seeking care. An online survey study of 1,092 adolescent and young women aged 19-30 years enrolled at a university in the U. S. revealed that those in the 25-30 years age cohort were more likely to have received information about UI, FI, and POP [67].

Some countries governments provide support for continence promotion but much of the health promotion effort related to continence issues is undertaken by professional bodies, non-governmental continence organisations, advocacy groups and industry. The ICS provides information about peak bodies and advocacy organisations that are active in the area of health promotion, advocacy and represent the interests of people with, or at risk of, incontinence (http://www.ics.org/SiteLinks.aspx). Through the activities of these organisations and with the engagement of external stakeholders such as educational, healthcare, and community service providers, these organisations aim to increase community awareness and understanding about incontinence, reduce social stigma, and raise public awareness about risk factors and options for managing incontinence.

Consumer knowledge about FI is also generally limited. Patel et al[77] conducted a content analysis of comments from 89 community-dwelling adults with FI to examine their continence literacy. The findings indicated that while many consumers had a significant emotional component to their experience of FI, their knowledge about terms to use to describe their condition was often limited[78], [79], [80].

As part of a larger study that used a postal and internet survey conducted with members of a National Crohn's and Colitis Support Group, Norton and Dibley[81] investigated factors that influenced help-seeking in people with inflammatory bowel disease (IBD) related FI, and their needs or desire for continence services. The most commonly cited reasons for not seeking help were: a lack of knowledge about from whom to seek help, how to seek help, and where to seek help.

3. USE OF THE INTERNET AND SOCIAL MEDIA

The internet is frequently searched for health information, and coverage of relevant health topics is growing. The benefits of acquiring health information via the internet include its wide accessibility, anonymity, and informality with eight in ten internet users in the U.S. looking online for health information[82]. The use of Social Media (SoMe) is popular internationally (4.14bn people worldwide); although the use of SoMe platforms varies with age, gender and educational attainment. Statistically, older adults still use significantly fewer digital applications and spend less time online, probably because it seems time consuming, or they might fear that they will get things wrong[83].

Amante et al[84] (63) investigated access to care and use of the internet to search for health information using data from the 2011 National Health Interview Study (NHIS). Of 32,139 adult respondents, 43.55% (13,997) reported searching the internet for health information. These authors suggested that a main reason for the widespread use of the internet to obtain health information was users did not consider their questions severe enough to warrant the effort or time to obtain routine, urgent, or emergent clinical attention.

Evaluations of internet-based information about incontinence suggest the internet may prove to be a useful tool for consumer education and public health outreach particularly in light of the reluctance of those affected by stigmatized illnesses such as incontinence to

seek treatment or to ask health care professionals for information[85]. For example, in a study of 208 people attending GP appointments in the UK conducted by Al-Shammary et al [86],the majority of people who used the internet felt able to discuss UI with their GPs or with the practice nurse, suggesting that information gleaned from the internet helped consumers make decisions about seeking help. Forty-five percent of respondents used the internet before consultation for the purpose of self-diagnosis. Mazloomdoost et al [87] evaluated the use of social networking and internet use as a source of information about pelvic floor disorders among women who presented to a clinical practice for female pelvic medicine and reconstructive surgery. The majority (75%) reported high internet use, with 53% using the internet or social networking to learn more about their pelvic floor condition, although only 4.9% primarily searched for information prior to seeking face to face help of their gynaecologists. Gonzales et al conducted a large-scale analysis of online social media posts to capture the experience, knowledge and perceptions among women with stress urinary incontinence (SUI). Extraction of 985 online posts by 762 unique users from 98 websites, demonstrated that SoME posts influence decision making when seeking care for stress urinary incontinence and choosing a treatment. Analysis of SoMe interactions can accordingly provide insight into patient behaviours, improve patient centred care and decision making in the future.

Several researchers have questioned the quality of continence information on the internet and social media, and all agree that there is a growing need for validation. Diering et al[88] evaluated the content, credibility, and function of 15 websites with UI content that had been developed by professional health care organisations for use by healthcare providers. The researchers concluded the internet served as a useful resource for 'state-of-the-art' knowledge about UI that health professionals can use to update their knowledge but also cautioned users to critically evaluate content. Using the World Health Organisation 'Health on the Net' (HON) principles, Saraswat et al[89] evaluated 150 websites using 17 commonly used terms for 'female UI' in English, French, German and Spanish, and compared website sponsors. The total number of websites for each term was variable, however 'female sling surgery', had the most websites (18 million), followed by 'incontinence surgery' (9.8 million). The most commonly encountered sponsors were physicians/surgeons (37%), followed by commercial sites (30%), government organisations or educational institutions (20%), and non-profit organisations (5%). The findings highlight the importance of assessing the quality and validity of internet health information, particularly as many websites also act as a platform for advertising. An evaluation by Dueñas-Garcia et al[90] of 13 patient-focused websites addressing treatment options for POP and stress UI also raised concern about the quality of information available to consumers. Using the DISCERN instrument, a validated instrument to assess the quality of written consumers health information relating to treatment options, the researchers reported available English-language professional websites written to inform patients about management choices for SUI and POP omit key components of quality patient information.

Clancy et al[91] reviewed 35 websites: their study aimed to evaluate the quality and readability of highly visible websites on overactive bladder (OAB). They concluded that popular websites on OAB are of low quality, written for a high school to college-level readership, and often lack adequate information to assess the potential for commercial bias. Patients should be cautioned that incomplete and potentially biased information on OAB is prevalent online. Leo et al,[92] aimed to investigate the utility of social media and search engines to disseminate FI information. They looked at Facebook, Twitter and search engines such as Google/Yahoo/Bing and agree that the internet appears to have potential to be a useful platform for patients to learn about FI and share information; however, given the lack of focus of available data, patients may struggle to identify valid and useful information.

Burton et al[93] agreed with the precautionary advice. They found that prevention and treatment strategies are common in online discussions of PFD, but at least one third of these recommendations have no evidential support. They suggest that there is a role for further online education and social media engagement by health care specialists to promote evidence-based practices, especially in the prevention of PFD. In addition, Alsyouf et al[94] looked further than primary prevention and focused on 'Fake News' on social media in genitourinary malignancies. They evaluated the accuracy of the articles shared most on popular social media platforms (Facebook, Twitter, Pinterest, and Reddit) and concluded that misleading or inaccurate information on genitourinary malignancies is commonly shared and they highlight the importance of directing patients to appropriate resources.

Qin et al[95] aimed to identify the prevalence, authorship, and type of information pertaining to topics in urogynecology on social media (Instagram) via hashtag and content analysis. More than 500,000 posts related to urogynecology were identified. The five most popular hashtags were pelvic floor, interstitial cystitis, pelvic pain, incontinence, and prolapse. Most were authored by patients (34.6%), allied health professionals (29.2%) and physicians (13.4%). Further authorship and content analysis revealed that allied health professionals authored the most informational posts, while patients authored more unrelated, patient experience, community building, and humorous posts. Qin et al hypothesized that greater physician participation may increase the quantity of educational posts and offer a low-cost platform for networking and connecting with patients and other providers.

Borgmann et al[96], published recommendations on the appropriate use of social media to improve online professionalism, as an initiative of the European Association of Urology.

Sajadi and Goldman's[97] study to assess the quality of incontinence resources available among social networks, also showed that most websites providing UI information were not certified by an accrediting body. Using the term 'incontinence', the researchers searched for information on Facebook, Twitter, and YouTube, to evaluate its usefulness. Their conclusion was that while social networks have great potential for consumers with incontinence to connect with each other and find medically informative resources, there was insufficient useful UI content, especially from healthcare professionals and incontinence organisations. Social network sites are a key future source of information for consumers about incontinence, and medical professionals and societies should target these avenues to reach and educate consumers. Healthcare professionals, continence organisations, and recognised advocacy organisations have a key role to play in assisting consumers to find reliable information about UI / FI by providing details of reputable web sites and by playing a role in interpreting findings from high quality research and reframing them for consumption by the general public.

Saiki and Cloyes [98]conducted a content analysis of publicly archived blog texts from 19 women living with UI. The findings revealed a focus on securing social connection and a place in the human community. Thus, blogging may offer women with UI a means by which they can safely disclose their condition and socially connect. Another recent evolution in digital communication is the growth of online communities and discussion groups. Frederiksen et al[99],

recognized the popularity of web-based discussion forums among pregnant women. Their findings suggested that online conversations and discussions significantly influence the health literacy in this population. Recognizing and supporting these new sources of information, may be useful for health professionals in consultations with pregnant women. Similar suggestions are confirmed by Grant et al[100]. They recruited postnatal women, using Facebook communities and explored women's barriers to access adequate information and education on how to do a PFMT contraction. Their respondents concluded that adding online education and apps about PFMT would be the most useful for their needs and circumstances.

Internet and mobile applications (apps) might target a specific barrier: several researchers tried to study the implementation of mobile resources to raise awareness. Sudol et al[101], reviewed patient-centered apps in female pelvic medicine and reconstructive surgery. They found that patients are likely to obtain information that is irrelevant or inaccurate, even if the appropriate search term is used. But after carefully excluding inaccurate apps, they were confident that 23 remaining apps scored well and could be shared with patients. Goode et al[102] performed a study providing physiotherapy education to postnatal women in an attempt to meet consumer needs in a changing hospital environment. Their quality assurance project demonstrated the advantage of digital health resources or apps but strategies to improve awareness of the resources should be investigated further.

Hofman et al[103], aimed to increase self-management of SUI via a mobile app and investigated the long-term effects of using a mobile app, in a RCT. Li et al[104], investigated a mobile application in postpartum pelvic floor dysfunction with a large cross-sectional study. Saboia et al[105], published their manuscript about the construction of an educational app for prevention of postnatal UI. Also, Asklund et al[106] performed a RCT using a mobile app for treatment of stress urinary incontinence. All these well-designed studies, found promising results on increasing compliance and adherence to treatment strategies, by using apps. Self-management might really be boosted by these digital strategies. Although it needs to be emphasized that there seems to be a striking lack of evidence about the added value of mobile applications to raise awareness. Applications rather tend to assist in treatment strategies. Once persons are offered them, they seem beneficial, but currently they are not the most common way to raise awareness, increase continence promotion or help seeking behaviour.

Meppelink et al[107], aimed to study the added value of social media for people with low health literacy in the Netherlands. Their conclusions are that for communication, professionals should make better use of digital messaging features. Videos, narration, and interactivity are scarcely used but can be valuable for people with low health literacy.

Although the internet has changed how many people access health information, internet access is far from universal, especially in developing nations, among older and poorer sections of society in developed nations, and among people with low levels of education and lower socioeconomic status[108].

In both developing nations and in countries with limited health systems and dispersed populations, innovative methods are needed to disseminate information about incontinence, such as through community nursing infrastructures and lay health workers.

4. RAISING AWARENESS IN CHILDHOOD

4.1. Children

Clinical experience often demonstrates a lack of awareness of the prevalence and impact of continence problems on children and their families. Healthcare professionals often have little or no education about bladder and bowel issues and may erroneously believe that in childhood they are self-limiting or the result of psychological issues[109], despite evidence that lower urinary tract symptoms in childhood increase the likelihood of adult nocturia and symptoms of overactive bladder.

Awareness raising among parents, childcare, education and healthcare professionals about the impact of delayed toilet learning beyond a child's second birthday, or suboptimal enactment of toilet learning on urinary continence is required[110].

4.2. Adolescents

Hebert-Beirne et al[111] identified that girls need appropriate education about pelvic health. 103 girls aged 13-17 participated in an educational intervention and 65 were the control group. Knowledge of anatomy, function and healthy hygiene practice was low prior to the intervention. They also found a high prevalence of at least occasional UI (46.7%) and that six one-hour sessions of education improved knowledge and awareness of pelvic health.

A cross-sectional study of 740 fourteen- to eighteen-year-old girls found that 37% had SUI, with 6% having symptoms more than once weekly; 54% had urgency UI (11% more than once weekly); 5% had enuresis, with 1.6% wet every night. While 56% found symptoms bothersome and it affected daily activities in 39% only 7% had visited a healthcare professional (HCP). Embarrassment and not knowing who to see were listed as reasons for this. The study suggests that UI is prevalent in adolescents and suggests that clinicians should be proactive in raising this when assessing and treating them[112].

Dix[113] reports that HCPs lack of awareness of continence conditions in young people, while Whale[114] advises that clinicians have a responsibility for ensuring that young people understand their bladder or bowel condition to be able to build trust, ensure appropriate psychological support and self-management. In a separate study Whale [115] also found that young people felt that school staff were unaware that continence problems could affect their age group but were motivated to address their lack of knowledge. Guidance is now available for them in the UK[116].

5. ENVIRONMENTAL FACTORS

Zhang[117] (2018) argues that UI is 'an environmental, social and cultural construct', in that society decides acceptable venues for urination and that perceptions of UI affects its culture and hence management. As an example, if UI is considered part of aging, then this belief will affect desire to treat. However, Zhang recognises that the immediate environment, such as access to the toilet is also influential.

Environmental barriers to seeking treatment for incontinence include the reactions of partners, families and colleagues[118]. Environmental factors that inhibit maintenance of continence include

availability of public toilets[119] , [120]. Poor quality, limited availability or employers restricting use of toilets in the workplace[121] and issues with cleanliness, availability, and privacy in public toilets[122] were all associated with increased likelihood of lower urinary tract conditions in women. Lack of aids and adaptations were also found to be barriers to continence in the home[119].

Inhibitory factors for continence within the hospital setting include the overuse of containment products and urinary catheters, delay in care, unfamiliar environments, lack of continence promotion, and deficits in HCP knowledge[123]. Within the community, the perception that incontinence is inevitable in patients with dementia and containment is the only response alongside family carers desire to protect privacy or avoid institutionalisation may present barriers to optimal continence[119]. A meta-ethnographic study found that the secrecy and shame associated with urinary incontinence had a significant impact on ability to seek help and that HCPs recognition of patient desire for concealment, but proactivity in questioning about UI would reduce taboos and promote continence[62].

For children and young people, barriers to continence include prolonged use of continence products[104, 110], restricted access to and poor condition of school toilets[115].

6. CONTINENCE ADVOCACY

Advocacy is defined as the act or process of defending or maintaining a cause or proposal. Advocacy, as it pertains to incontinence, involves assisting individuals to find necessary health care and treatment. Organisations composed of professional and public members promote continence advocacy as a core mission.

A central goal of most continence advocacy organisations is raising public awareness and understanding about the types of incontinence, risk factors for incontinence, and available treatments, services, and management products. These organisations provide a public voice for an unheard consumer population in political and health-care governance, development, and planning processes. In recent years, consumers and clinicians have been involved in identifying and prioritizing important areas of research relating to incontinence in order to inform research development and funding decisions[124], [125]. In addition, through advocacy organisations, consumers of health care have become more closely involved and influential in the activities of clinical professional organisations.

Another major role adopted by many continence organisations is the direct provision of information support to those affected by incontinence and their caregivers. The types of information provided include information and support about symptoms, risk factors and associated conditions, treatments and management strategies, and availability of, and access to, health and social services. Such information is provided through a variety of sources, including consumer-oriented magazines and electronic newsletters, internet-based information resources, telephone support lines (often staffed by qualified nursing or counseling staff), and printed media such as leaflets and booklets on a wide variety of topics. Other innovative strategies have included outreach work through travelling information roadshows and events[126]. Organisations also provided emotional supports to people with incontinence by putting them in touch with others similarly affected either through direct contact at meetings or through internet discussion forums, as well as providing specialist training and education to healthcare professionals.

Continence organisations reviewed varied in scale and in nature, from small consumer or clinician groups that focus on quite specific bladder symptoms or conditions, to large and well-funded national organisations that address bladder problems as a peak body. Often the founding and development of such organisations resulted from the dedication of a small group of consumers, clinicians, or both, that worked to promote awareness and understanding of incontinence among the public and healthcare providers and to provide optimal services and support to those affected. These organisations represented a wide diversity of models, including consumer-led, company-sponsored, consumer-only, professionals-only, and organisations which have deliberately set about trying to bring together all relevant stakeholders in a relatively democratic model. Globally, these organisations played a dynamic role in building both public and professional awareness and reducing the taboos associated with this under-served and under-reported condition.

6.1. Funding

The degree of funding available inevitably affects the level and scope of work. In some countries, such as Australia and to a lesser degree New Zealand, continence promotion organisations have government support for their work. In other countries such as the U.S. and UK, financial support generally came from charitable donations from individuals and foundations, or through the support of the pharmaceutical industry and continence products manufacturers. Most continence organisations believe that more funding from any source will improve advocacy work but there is no evidence to support this.

6.2. Research priorities

The James Lind Alliance, is a non-profit making initiative that allows clinicians, patients and carers to form Priority Setting Partnerships to agree on the ten most important evidence uncertainties, so that health researchers are aware of the issues that are most important for those affected by specific conditions.

6.3. Effectiveness

While the work of the voluntary and continence advocacy sector is extensive and appears appreciated by professionals and consumers, no quantitative or qualitative evidence of their effectiveness could be found, with this remaining an area for future research.

Summary

Based on survey and qualitative data regarding consumers' understandings and knowledge of incontinence, the general public has limited knowledge about incontinence. The effectiveness of strategies to promote awareness about incontinence and its treatment can be enhanced by adopting evidence-based theories and methods from the field of health promotion and should be underpinned by awareness of the social determinants of health. Consumers increasingly access the internet for health information but the quality of information about incontinence is variable.

Clinicians and continence promotional bodies play an important role in helping consumers find high quality reliable information. The majority of publications on Continence Promotion and Programmes are qualitative or mixed methods designs which the Oxford Level of Evidence does not recognize.

Advocacy is necessary for people who have continence issues and many organisations have advocacy as their mission. A wide

range of models of continence advocacy, including collaborative models that bring consumers and different groups of health professionals together, do exist. Recent research regarding formalized evaluation on the effectiveness of these organizations was not located.

Levels of Evidence/Recommendations

- Continence promotion is required to address broad gaps in knowledge about incontinence. This includes effective communication to and education of both HCPs and the public, through a variety of mediums, with regard to UI and FI potentially affecting all age groups (Level of Evidence 3).
- Strategies to promote awareness about incontinence and its treatment can be strengthened by the use of evidence-based theories and methods from the field of health promotion, including the social determinants of health (Level of Evidence 4)
- The internet represents an important source of information about incontinence, however the quality of information is variable (Level of Evidence 3)
- Evidence for the impact of continence advocacy worldwide was based on opinion (Level of Evidence: 4) (Grade of Recommendation: None)

Research priorities

How effective are Continence Advocacy Organisations? Does their effectiveness vary for different populations (eg the elderly, children and young people, males post prostatectomy, women post-partum etc.)?

How can awareness and accessibility to information for all ages and for different cultural groups be improved at a local / national / international level?

How effective are new methods of communication at raising awareness and is their impact different for varying client groups?

What can be done to improve awareness of new methods of communication to promote appropriate self-management and help seeking behaviours for UI and FI?

To improve the quality of the information on the internet / digital media

IV. HELP-SEEKING (CARE-SEEKING) BEHAVIOUR

Literature Search is found in Appendix 1.

1. BACKGROUND

UI, FI and other PFDs, such POP, are health issues not discussed as openly as other health issues. Help-seeking or care-seeking, for UI and in particular, FI remains poorly understood, likely due to the lack of rigorous exploration of this behaviour. Despite increased awareness among healthcare providers and consumers of healthcare over the last decade, health seeking behavior for these issues remains low, despite the high level of efficacy of conservative care strategies[127].

As described in the 6th ICI edition, a Model of Pathways to Treatment offers a framework to explore the existing literature on the barriers and facilitators to seeking care and sex-differences in help-seeking. This model proposes four sequential time intervals in the process of receiving treatment: 1) appraisal, 2) help-seeking, 3) diagnostic, and 4) pre-treatment, during the first time interval the person detects bodily changes. These changes may be appraised as a normal change or abnormal, such as a symptom of an underlying condition. If the person determines the bodily change is abnormal, s/he is motivated to seek help from a healthcare provider for one of two reasons: 1) concern that the change is from a serious underlying condition; or 2) due to the consequences of the change. During this time interval, the person considers seeking help from a healthcare provider based on the outcomes of their appraisal of the symptoms and their self-management. Situational, contextual, and social factors can play a role during this phase in creating facilitators and barriers to seeking help. Once the person makes the first consultation with a healthcare provider, the diagnostic process begins, and afterwards, treatment is initiated. In order for a consumer to be able to appraise their current health status with respect to continence, awareness and associated knowledge related to pelvic floor function and dysfunction is needed[128].

Four items related to help-seeking behavior are the focus of this section. 1) detection and appraisal of bodily changes related to PFDs; 2) self-reported reasons to discuss symptoms with a healthcare provider; 3) effective strategies to promote accurate appraisal of bodily changes as well as seeking guidance from a care provider and 4) how knowledge, attitudes and beliefs (KAB) impact help-seeking behavior. Using non-health professional and indirect resources (such as blogs, chat groups, and website) was considered to be self-management or self-care, not help-seeking behaviour.

The research questions are:

a) What factors act as barriers/facilitators to help-seeking for UI and FI?

b) How do knowledge, attitudes and beliefs impact help-seeking behaviour for UI, FI and PFDs?

c) Do sex differences exist for help-seeking for UI and FI?

d) What extrinsic factors influence help-seeking behaviour?

e) What strategies are effective to promote awareness and/or help-seeking for UI and FI?

2. FACTORS THAT ACT AS BARRIERS / FACILITATORS TO HELP-SEEKING

Since the publication of the 6th ICI edition[128], multiple descriptive studies, including quantitative and qualitative systematic reviews

were located noting that intrinsic and extrinsic factors can act as barriers/facilitators to help-seeking for PFDs. In addition, two RCTs were retrieved. The vast majority of this literature pertains to UI. Additionally, substantially more information about help-seeking behaviours in women across the adult lifespan than for men was retrieved.

It is well established that although prevalence estimates differ across studies, the available evidence indicates that UI and overactive bladder (OAB), in particular are highly prevalent conditions among women and that these conditions have a negative effect on quality of life[128]. A recent large population-based study (n=26,466 women) determined over 70% of women with UI and associated symptoms did not seek help [129].

2.1. Intrinsic factors associated with barriers/facilitators:

Studies capturing a global perspective, triangulate to affirm that help-seeking is facilitated by severity of symptoms, dealing with symptoms for a longer period of time and having a high degree of social support[130, 131]. In fact, discussing UI symptoms with a relative made the individual 3-5 times more likely to seek help in a large population- based study[129]. With respect to severity, a recent study determined that women with UI who sought care had higher median Pelvic Floor Dysfunction Index (PFDI-20) and Urogenital Distress Inventory (UDI-6) scores compared to non-care seekers (73.96 vs. 16.67, P < 0.0001, and 41.67 vs. 8.33, P < 0.0001). Specifically, a PFDI-20 score of 33.33 (83.33% sensitivity and 79.30% specificity) had very good discriminatory accuracy in distinguishing care and non-care seekers[132]. The same study determined a UDI-6 score of 25.00 (83.33% sensitivity and 83.59% specificity) had excellent discriminatory accuracy in distinguishing care and non-care seekers. In fact, the multivariable predictive model used in this study accurately identified 82.4% of care and non-care seekers[132]. Another psychometrically sound self-report questionnaire that has been found to best assess the knowledge, attitudes and associated practice regarding UI is the Barriers to Incontinence Care Seeking Questionnaire (BICS-Q)[133].

Reasons women who were postpartum gave for not seeking help were: low priority, belief it was normal part of childbirth, and feeling ashamed[134]. Among women with gynaecological cancers who experienced concomitant LUTS, the failure to seek help was attributed to a perception that the LUTS were not perceived by the women as serious enough symptoms to warrant attention and to their lack of awareness of treatment options[135].

Bothersomeness, the degree to which the symptoms interfere with an individuals' life, is another key factor that consistently correlates with help-seeking[128, 130, 136, 137]. Since the publication of the ICI 6, the degree of bother has been determined as the mediator between UI severity and help-seeking[138]. Furthermore the International Consultation on Incontinence Questionnaire-UI Short Form (ICIQ-SF) has been determined as a discriminative measure to delineate bothersome UI[138].

A recent large qualitative synthesis, conducted by Mendes and colleagues[71] extracted 189 findings from 28 studies, grouped them into 25 categories and synthesized them into eight themes shedding further light on the issue of help-seeking behaviour. The eight synthesized findings were: (i) cultural and religious backgrounds and personal reluctance contribute to delays in seeking UI treatment; (ii) the inevitable and regrettable problem of UI endured silently and alone affects women's daily activities and their social roles; (iii) poor knowledge and the vague nature of the symptoms mask the fact that UI is a disease; (iv) the experiences provoked by UI and the sense of shame regarding the condition have contributed to impair women's lives; (v) UI has provoked negative effects on women's intimacy and sexual satisfaction and provoked changes in the ways they experience their sexuality and sexual function; (vi) UI is considered a consequence of pregnancy and childbirth, inherent to aging or a religious punishment; (vii) the women affected by UI adopt several strategies to improve their health status; and (viii) women have personal preferences toward care providers and treatments; they confront difficulties through UI treatment and some care needs are not met[71]. Related, but different themes were determined by another research group who conducted a meta-ethnography to better understand the experience of living with UI[62]. Their analysis determined: i) not perceiving disease, ii) shame, iii) lack of support from important others, and iv) non-optimal health care system to be inhibitors of help-seeking behaviours. Facilitators were found to be reduced quality of life and positive support from important others. These finding corroborate the broad literature base and point to the facts that knowledge and beliefs regarding UI and associated care options and efficacy of treatment remain important gaps to be addressed.

Many women view UI as a societal taboo and fear stigmatization[139] and embarrassment in talking about PFDs[140], particularly UI and FI, as reasons identified as contributing to low rates of seeking care. A survey in Korea noted that women were embarrassed by being incontinent and did not seek help, but women who did not have UI said they would consult with a healthcare provider should they develop it[141]. In another study[142], women (61.9%) reported one reason for not seeking help for UI was that they hoped UI would spontaneously disappear (similar to findings by Buurman and Lagro-Janssen[135]) but interference with prayer, sexual, physical, and social activities were reasons to seek help. Using the Theory of Planned Change, researchers found that help-seeking intention can be predicted. They also found that high perceived self-efficacy in managing symptoms could act as a barrier to seeking help. They postulated that women viewed themselves as managing well and not needing help from others[143].

As far as FI is concerned, one study was located comparing help-seeking for UI to FI. While knowledge scores pertaining to participants understanding of UI and FI were low across the board, they were lower for FI[144].

3. KNOWLEDGE, ATTITUDES AND BELIEFS ABOUT UI & FI

Women's knowledge, attitudes, and beliefs (KAB) about PFD including UI, FI and POP have been long thought of as both barriers and facilitators to help-seeking behaviours. Research about KAB in women with PFDs is increasing, primarily in the U.S. A systematic review of 3,152 studies investigating whether women have adequate knowledge about PFDs found that knowledge was limited and was influenced by low socioeconomic status, African-American ethnicity, low educational level, and low access to information[65]. Many women believe PFDs, especially UI, are a normal part of aging[141, 145, 146] and thus do not seek help for what they perceive as a non-problem. A secondary analysis of the Canadian Institutes of Health Research-funded Continence Across Continents to Upend Stigma and Dependency (CACTUS-D) study of adult women (n=4446, mean age 78.2 years), found that of the 2022 with UI, 48.3% held the belief that UI is normal for ageing. This belief was held by women who had a more impaired quality of life but more

age, perception of overall health, severe incontinence and greater quantities of pad use did not make women less likely to hold this belief[147]. These women were also less likely to have performed previous PFME.

Lack of knowledge and attitude of neglect about UI combined with certain cultural and social systems can affect help-seeking behavior. This was demonstrated in a community-based qualitative study conducted in four villages in rural Western India to explore the attitude of women with UI[148]. Fourteen women (mean age 42.9 years) were interviewed and six themes emerged; i) attitude toward the problem and seeking help; ii) caste discrimination; iii) individual support system; iv) priorities and lack of time; v) lack of privacy; and vi) social taboo and personal belief. Women were unaware of this condition being abnormal and as they did not consider UI to be a health problem, they were ignorant about the remedy.

An Australian cross-sectional survey[149] was conducted to evaluate pregnant women's awareness, knowledge and beliefs about PFMs and the need to exercise these muscles. Seventy-six percent of respondents (n=633) knew that PFMs can prevent UI, but only 27% knew that they prevented FI, and 41% thought it was normal to leak urine when pregnant.

Women who believe that the cause of their UI is out of their control (e.g., part of being female, due to childbirth) believe that nothing can be done to treat it and so do not seek-treatment. Women report being too embarrassed to discuss their symptoms with anyone, including healthcare providers[150 151 152 153 154 155 156]. Several studies have shown a strong association between lack of UI knowledge proficiency and sociodemographic factors (e.g., lower levels of education and racial disparities)[157 158 159 160].

However, assessing someone's knowledge of a given subject is complex and requires the development of validated instruments[161]. Fante et al[65] conducted a systematic review of women's knowledge about the pelvic floor structures (muscles, ligaments, organs), its functions, dysfunctions, and possible conservative treatments for each disorder through surveys, questionnaires, or any other available instrument within the literature. Validated questionnaires and designed pilot-tested forms were the most frequently used ways of assessing knowledge with the prolapse incontinence knowledge 24-item questionnaire (12-item PIKQ-UI and 12-item PIKQ-POP) used most frequently. Using the PIKQ, Chen and colleagues[8] surveyed a population of adult women seeking primary care in the U.S. finding a considerable dearth of PFD knowledge; 72% of respondents were UI knowledge non-proficient and 54% were POP knowledge non-proficient. Several demographic factors (i.e. 40–49 and ≥ 80 years age groups, African-American race, income <$30,000/yr., lower educational attainment) were significantly associated with both UI and POP knowledge non-proficiency.

Overall, POP-related knowledge is low in women[159, 162] and understanding of the term, pelvic floor prolapse is low. Good and colleagues[163] conducted a cross-sectional study of English-speaking women (N=217) with POP symptoms who completed a self-administered questionnaire, that included 5 prolapse-related knowledge items modified from a previously PIKQ-POP validated questionnaire[161]. Only 44% of items were correctly answered. Although higher education increased knowledge, even college–educated women on average answered less than 50% of the questions correctly[164]

A study of women (age range 42-94 years) who had high literacy levels indicated significant knowledge deficits and a poor understanding of PFDs, including UI. Although this study had a small sample (N=36), the authors drew implications about women's ability to give informed consent because of the complexity of PFDs and the difficulty in understanding them[165]. In another study, knowledge deficits about UI were found to exist in women across all ages, income levels, and races[157]. A study of high-school and college age athletes in the U.S. found that more than 25% of the young women surveyed experienced UI during strenuous physical activity, but 90% had never reported their symptoms to anyone. Further, 91% had never heard of PFME, indicating a lack of knowledge about UI and pelvic floor functioning[166]. A study of adolescents (14-21 years) by Arbuckle and colleagues[167] found that only 19.5% had heard about POP and only 5.1% had heard about FI. However, this study and others[67] have shown that adolescent women have similar interest in learning more about PFD.

Beliefs play a role in help-seeking behavior. Telephone surveys of racially diverse women (i.e., African American and Caucasian) in the US reported that they did not seek help for UI because of their belief there were no available treatments[168]. Another study with an ethnically diverse group of women (median age 34 years) found that the women held similar attitudes about UI, although no differences were found among the women based on ethnicity in agreeing that good treatments for UI existed (OR, 0.91; 95% CI, 0.33–2.6)[169]. Authors of a systematic review on perceptions about female UI concluded that similarities existed among women from different racial and ethnic groups in terms of managing UI but their perceptions about UI differed[67].

From the literature reviewed, knowledge deficits along with varying attitudes and beliefs that normalize UI or created emotional responses of embarrassment about UI acted as barriers to help-seeking[66, 170 171 172]. Most of the research on KAB about PFD is on UI and in community-dwelling women, but the level of knowledge of UI has been studied in sub-populations such as minorities and in institutions[173].

Joh and colleagues (2018) conducted a cross-sectional survey to assess FI knowledge, attitudes and help-seeking behaviours among community-dwelling adults undergoing national health screening in Korea. Only 29.8% (n=601) were aware of the term FI and knowledge levels were low. As to attitudes, 24.6% considered FI to be very rare and 22.3% considered it to be moderately distressing. Knowing the term FI was significantly associated with overall help-seeking behaviour (OR:9.23;95%CI:2.09-40.77). Based on these studies, it would appear that a larger knowledge gap exists related to FI.

3.1. Level of severity and bothersomeness of UI symptoms and consequences of symptoms

UI severity in women between 58-70 years was the main reason for reporting UI to a healthcare provider[174]. Women had greater odds of getting treatment for UI when their symptoms had become more frequent (adjusted OR, 3.16, 95% CI, 1.15–8.67) and bothersome (adjusted OR, 1.09, 95% CI, 1.01–1.18) in the prior year[175]. Another study found however, that bother from UI mediated the relationship between UI severity and help seeking behaviour. Thus, women who perceived bother sought help for UI regardless of the level of severity[138]. Bother, as well as concern about a serious underlying condition, was also a reason to seek help for women between 45 -65 years living in Iran while neglect, embarrassment, an assumption that UI was caused by aging, and economic issues acted as barriers to seeking help[176] . The literature revealed that more severe UI and bother from UI can act as facilitators to help-seeking.

It is difficult however to generalize findings among studies because different definitions for help-seeking and various instruments were used, although it appears there are common findings including age, type and severity of UI, and feelings of embarrassment are significantly related to barriers to seeking care[177].

In a study conducted with men (N=1240), with a mean age 63.3+12.7 years, who sought help for LUTS at a urology clinic, subjects were asked by a physician before evaluation to select the most bothersome symptom. Nocturia accounted for 32.9% of initial complaints and it persisted in approximately 50% of men over time[178].

Men over 50 years old (n=18) who had visited their GPs were asked to participate in semi-structured interviews about reasons they sought help with LUTS. The researchers found that men could be grouped into 3 categories: those who were concerned about cancer, those who found the symptoms a nuisance, and those who were prompted to seek help after seeing public information about LUTS[179].

4. EXTRINSIC FACTORS THAT ACT AS BARRIERS/ FACILITATORS TO HELP-SEEKING FOR UI

Health care system factors constitute a number of issues cited across the international literature for help seeking. Women with low incomes (i.e., $30,000 USD annually) were less likely to discuss UI with a healthcare provider, even though they had health insurance, as compared to women at higher income levels[128]. Costs of care and inconvenience have been found to create barriers, highlighting the fact that social factors play a role in a woman's decision and ability to seek care as described in the ICI 6th edition[128].

Recent qualitative research has further developed the understanding of extrinsic influences. For example, of the eight themes established by Mendes and colleagues (2017), the majority incorporated social factors[71]. Moreover, a 'non-optimal healthcare system" was a found as a primary inhibitor of help seeking behavior in a recent meta-ethnography study[62]. The current health care system-related barriers that inhibit women from discussing their symptoms with healthcare professionals represent an important gap to address given that discovering treatment was available for UI was the trigger for 30% of women studied to seek help[180]. Additionally, Biyik and colleagues (2019) determined that an important trigger for seeking help for incontinence was healthcare providers' confirmation of continence problems. Thus, the role of healthcare professionals acting as facilitators to help-seeking care is effective and important[181].

A complex interaction between the use of adaptive or self-care behaviours, help-seeking and ultimately successful self-management of UI exists[182]. The literature clearly indicates a number of common adaptive behaviors in the process of coping with UI. These commonly include: convenience/defensive voiding (urinating often), restricting fluid intake, avoiding certain activities, using absorbent padding and wearing dark coloured clothing[183] [184]. An analysis of 1059 women with overactive bladder (OAB), determined the most common adaptive behavior to be convenience/defensive voiding[184]. Similarly, another recent study, which implemented a factor analysis that informed the validation of the Adaptive Behaviour Index, determined behaviours most often associated with both UI and FI, fall into the domains of hygiene and avoidance[185]. Bathroom mapping, and using absorbent pads were two key established adaptive behaviours under the hygiene domain. Urinating often (convenience/ defensive voiding) and wearing easy to remove clothing represent two key established factors in the avoidance domain. The analysis conducted by Wei and colleagues resulted in a 17-item index (Adaptive Behaviour Index) providing empiric evidence that women reporting greater pelvic floor symptom severity are more likely to use adaptive behaviors[185]. The Adaptive Behaviour Index quantifies adaptive behaviors and has potential to enhance understanding how individuals cope with UI and FI, what facilitates, or limits help seeking and associated successful self-management.

Appropriate self-management of UI and FI, demands active engagement and responsibility from the affected individuals . When people hide their PFDs and do not seek help, they are more likely to use poor coping strategies and adaptive behaviours. Understanding the distinction between self-management and similar concepts, such as coping, is necessary for conceptual clarity in the FI and UI literature. A recent concept analysis provides clarity on this issue, as specific to UI[182]. Through an analysis of 17 papers, Klein and colleagues determined that outcomes of UI self-management are directly influenced by an individuals ability to engage in self-management tasks and the provision of social support. Thus, sufficient knowledge seeking is essential for successful self-management of UI. It is certainly feasible for women to achieve acceptable self-management of UI without seeking health care, but people should feel empowered to broach the subject with a provider to avoid engaging in practices, such as restricting fluid intake or engaging in defensive voiding, that negatively impact health[182].

Social and cultural attitudes were previously cited[127] as barriers to help-seeking and this issue appeared to cross many cultures[128]. Likewise, additional research affirms "cultural and religious backgrounds and personal reluctance contribute to delays in seeking UI treatment" as represented as the first of one of 8 themes determined from a qualitative synthesis of 28 studies exploring health seeking for UI[71].

5. SEX DIFFERENCES FOR HELP-SEEKING BEHAVIOURS FOR UI

Very few studies have explored the differences in help-seeking behavior in women vs. men, and no studies that directly compared sex differences in help-seeking behaviours for UI were located. Nonetheless, women have been found to prefer not to seek medical advice for UI, while men tend to go to doctors more often than women[186]. Across multiple studies, women demonstrated a preference for discussing UI with other women, rather than an HCP[187]. Except for treatment seeking behaviours, both men and women are found to practice self-management coping methods for the management of UI such as going to the toilet more frequently[186].

Unique to women, the perinatal care period represents a time when several authors have noted the initiation of pelvic floor symptoms which is not surprising given the well-known relevant risk factors associated with PFD. This is also a time when women are interfacing more regularly with HCPs. A recent study conducted by Moossdorff-Steinhauser and colleagues (2021) is the first to report on women seeking help for UI when they are pregnant. Importantly, only 13% of the women in this study sought help for their symptoms. The majority of those who did seek help were already under the care of a specialized physiotherapist for other pregnancy-related complaints, typically pelvic girdle pain[188]. The authors discussed

reasons for pregnant women not seeking help including 40% believing symptoms would spontaneously recover in the post-partum period. This highlights women's lack of awareness of the UI during pregnancy being a risk factor (two- to six-fold risk) for the presence of UI postpartum[189]. Bothersomeness was also correlated with help seeking in this study and a high proportion of pregnant women reported low bother or few symptoms[188]. These findings indicate that non-help-seeking pregnant women experience little bother, just like women in the general population[190]. They also highlight an opportunity for improved care and knowledge translation for women through this time period to facilitate immediate and later help-seeking. However, current health care provider knowledge gaps need to be overcome[188].

These findings corroborate with those of a previous study that determined counselling about UI in pregnancy and during postpartum physical exercise, predicted 47.8% of the variance in treatment-seeking behaviour and that counselling during pregnancy can contribute substantially to increasing the number of women treated for postpartum UI[191].

Sex-differences in help-seeking behaviour can exist and research to determine the barriers and facilitators that are shared and that differ between the sexes are needed to develop effective strategies to encourage early help-seeking for UI.

Awareness and knowledge of UI and FI, satisfaction with the information strategy and self-efficacy appear to be important factors related to help-seeking behaviour. To date there is limited data related to the effectiveness of community-based population health approaches to promote knowledge of UI and FI and associated help seeking. It has been recommended that women interfacing with care in the perinatal care period be offered more tailored care regarding UI and FI [188 191]. Additionally, a small RCT examining help seeking among women concluded that all women in the general population over the age of 55 years should undergo screening and treatment if appropriate[192]. Public information campaigns have been suggested to enhance consultation rates providing that passively receiving and actively seeking information have the same effects on help-seeking behaviour[131]. However, only one small RCT (n = 168) determined clinically important improvement in pelvic health anatomy knowledge following a six-week educational intervention among girls 13-17 years of age when compared to a control group[111]. The quality of this RCT is too low to base any recommendation, although evidence is certainly indicating the benefits of structured education-based interventions before and throughout the perinatal care period for women. No studies have specifically explored effective strategies to improve help seeking for men.

Summary

The lack of an accurate denominator to determine the rate of adults who have UI undermines efforts to determine the proportion of adults with UI who seek help from healthcare providers for it. UI affects health-related quality of life (HRQoL) and is associated with activity impairments when compared to continent adults. Therefore, eliminating and minimizing barriers and reinforcing factors that facilitate help-seeking across the lifespan, across cultures and that are sex-specific should be a priority in research.

The literature reviewed supported the Model of Pathways to Treatment in that adults reported that bothersome or severe UI led them to seek help from a healthcare provider for UI symptoms and their consequences. Respondents to surveys also reported that extrinsic factors created significant barriers to seeking help.

Help-seeking is a complex behaviour influenced by multiple factors including social and cultural ones. Increased knowledge of PFDs can improve self-reporting of symptoms and reduce disease burden. Inclusion of qualitative methods to better understand how men and women think about and make meaning of bodily changes, symptoms and consequences of UI is needed to create foundational research that will lead to help-seeking interventional research. Common terminology and validated instruments are essential to advance knowledge. Analyses that examine sex-differences in factors that act as barriers and facilitators to help-seeking are also needed.

Levels of Evidence/Recommendations

- Only 2 small RCTs for help-seeking behaviour were located (Level of Evidence 1b)
- Knowledge, attitudes and beliefs about UI, FI and pelvic organ prolapse affect help-seeking behavior.
- Recommendation: No recommendation regarding help seeking behavior was possible based on the low quality of the RCTs focus and the low level of majority of the evidence provided by the available research.

V. MODELS OF CARE, DELIVERY AND ACCESSING CARE

Literature search in found in Appendix 1.

1. BACKGROUND

Global demographic trends suggest that with an aging population, the incidence of urinary incontinence will rise in the coming years, bringing significant health and economic implications for both patients and payers[193]. However, there is limited organizational evidence to guide payers and providers about appropriate service configurations which will deliver efficient guideline-compliant, high-quality patient care[174]. Internationally continence care is based on various care models that reflect the respective national health systems[194]. This global diversity of care challenges comparisons of different care models and hampers setting up of quality enhancement systems enabling iterative improvements in care provision, that are replicable worldwide. Also, even in the developed world, provision of appropriate patient-centric care is difficult due to the lack of appropriately skilled health care professionals, at all levels of care, embedded within an efficient and stratified care pathway. Low levels of integration of continence services result in duplication of provision, concentration of services in specialist centres and relatively low provision of community-based care[195], [196]. Additionally, provision of care may be dictated by imbalances in the level of reimbursement versus the true cost of providing treatment[193]. This has resulted in a bias towards surgical intervention over more conservative treatment strategies[197], [198]. In low- and middle-income countries, continence care is also hampered by the low cultural priority accorded to it and patriarchal morals that ensure women remain second class citizens[199].

Given the complexity of this landscape, this section attempts to evaluate different care models for provision of continence care and to understand the challenges and benefits of each model, especially when implemented in real world settings.

2. FACTORS UNDERLYING ACCESS TO SERVICES

2.1. Patient knowledge, attitudes, and preferences

A key factor underlying access to, and provision of services is how the patient navigates through the system. Therefore, discerning how the patient understands and seeks healthcare warrants attention. Knowledge and attitudes about UI and care may influence patient choice regarding services, suggesting that as QoL worsens, care-seeking increases[200]. UI may be perceived as a family issue rather than a disorder affecting only one family member in some cultures, particularly those where living with extended family is more typical[201]. Family support was often seen as an important component when dealing with UI[202]. This has been discussed in more depth earlier in the chapter.

Many women may prefer to take an active role in their own care. For example, in a survey of 265 Norwegian women with UI, O'Donnell and Hunskaar[203] found that 60% of women wanted to be actively involved in their care decisions about hormonal health, compared to only 38% for their general health care needs[204]. This finding may also have been influenced by the context of care and educational level of the woman[183] or associated with the desire for adequate clinical information rather than for active treatment decision-making[205]. Furthermore, a large cross-sectional community mail survey of women with UI in France, Germany, Spain, and the UK found that many women preferred to be treated for UI by their primary care providers, despite easy access to specialized services[206]. Appropriately trained continence nurses and physical therapists appeared able to provide quality UI care for women and patients women were satisfied with care provided by continence nurses[207 208 209].

More recently a systematic review that considered a worldwide perspective on how women experience UI portrayed significant difficulty for women to access healthcare influenced by reluctance, lack of knowledge and stigma[71] Lack of knowledge may be influenced by misinformation. Vasconcelos et al reviewed 19 papers focused on knowledge and attitude in women, which identified that misconceptions about UI continue to exist despite improved access to information[210]. Therefore, healthcare provider attention on how information is interpreted and understood is a fundamental first step.

2.2. Clinician's preferences

A UK cohort study investigating what determines clinicians' referring of women with UI onto secondary care identified that older women and those from ethnic backgrounds were less likely to be referred[211]. Therefore, a combination of patient and clinician beliefs possibly challenge care delivery. Incontinence and its consequences receive little respect[212]. Consequently the complexity of human nature and its fear of bodily functions have to be considered when striving for the best models of care.

3. MODELS OF CARE

A report on continence care services worldwide noted that services were scattered, inconsistent and that considerable discrepancies exist in their funding[213]. The report concluded that accessible (and affordable) continence care and multidisciplinary teamwork were necessary. Funding and reimbursement are key challenges regardless of the model of care employed in any country. Although vital, it is not a top priority for governments and payers around the world[214].

However, implementation of integrated services can be challenging due to infrastructure limitations and other barriers. Kirst et al (2017) identified measures of success for integrating care in their literature review of 65 international papers[215]. One of the key measures is the confidence with multidisciplinary working relationships. An example of integrating care is a study that aimed to provide an evidence-based specification for the procurement and organisation of continence care. Evidence was gathered through a systematic literature review and semi-structured interviews, resulting in the Optimal Continence Service Specification (OCSS) which provides useful guidance for service delivery[193]. Furthermore, a scoping review along with an international expert panel identified key performance indicators (KPIs) which offer measures for defining what continence care should look like[216].

A key challenge in the spread and adoption of the KPIs is the requirement of robust clinical leadership and convincing methods of implementation. Therefore, the development of improved strategic models, such as the OCSS[193] and KPIs [195] have the potential to support the development and strengthening of services.

The OCSS modules include: 1) case detection, 2) specialist assessment and treatment, 3) case coordination, 4) caregiver support, 5) community-based support, 6) use of containment products, and 7) use of technology (Figure-2). The key recommendations are detailed in Table-1.

There are many factors that can highlight the importance of adequate investment in community continence services to health care planners. For instance, a UK national policy document proposes a framework for commissioners and health care providers to develop continence services that reduce health related harm and costs[217]. The pursuit of dignity in care yet ensuring value for money may be challenging to reconcile in some cases, but outcome measures are critical for evidencing what works and informs further improvements. Despite the widespread launch of UK national policy, the potential of frontline continence services is yet to be fully realized.

The provision of continence care and services in each country depends on the organization and infrastructure of its health services. Because UI is prevalent and affects men and women of all ages who receive medical care from a variety of health care providers (e.g., PCP, family physician, geriatrician, gynaecologist, nurse practitioners), there will seldom be one point of entry to continence care.

A major barrier to facilitating continence services models is the lack of studies that compare effectiveness of specific continence care delivery systems. There is paucity of data on the effectiveness of services outlined by the OCSS. No published studies have directly compared the effectiveness of specific delivery systems for continence care. However, a cost-effectiveness study which implemented the OCSS strategy, identified that nurse-led specialist service improved care delivery for community-dwelling elderly[218]. Also, despite evidence for active intervention, emphasis often remains on urine containment and passive UI management rather than on

Table 1: Optimal Continence Services Specification Recommendations.

1. Ensure ease of access by the establishment of robust referral pathways from detection of incontinence through to appropriate assessment and treatment.
2. Shift the responsibility of basic continence care away from Primary Care Physicians (PCPs) to continence nurse specialists (CNSs) in primary care where available, where CNSs are unavailable, train existing healthcare professionals such as primary care-based nurse practitioners, community nurses, physician's assistants or, in developing countries, local community healthcare workers, to provide evidence-based continence care.
3. Where possible, use a case coordinator to ensure collaborative working, especially to help delay or prevent admission of patients to permanent care settings; given the general trend to more integrated clinical pathways, in particular concerning patients with multiple co-morbidities, it is necessary to strike a balance between specialization and holistic case management approaches.
4. Promote use of self-management tools and techniques, as well as the provision of information on the use of containment products.
5. Emphasize shared decision making between healthcare provider and patient/caregiver, and educational campaigns on the nature of the illness and treatment strategies.
6. Integrate specialists with other parts of the care pathway and ensure they play a key role in quality governance, training and the dissemination of best practice.
7. Use a comprehensive assessment of user, product, and usage related factors to assess the needs of patients and caregivers with regards to containment products. This process should be standardized, valid and easily reproducible. The final decision regarding choice of product should remain with the end-user: the patient and/or their informal or professional caregiver.
8. Use of technology should be integral to the delivery of continence care. Technology should enable self-care and connect patients, caregivers and enable providers to monitor progress and troubleshoot problems.
9. For payers: to provide the highest quality continence care, ensure care standards are incentivized. This can be achieved through stipulating the achievement of targets on certain outcome and operational measures, careful use of quality-related financial incentives, emphasis on clinical governance and optimal pricing that is most strongly correlated to the true cost of providing a service.
10. Establish accredited programmes of training for nurses who want to become CNSs and other health or social care professionals such as social workers wishing to improve their competence in delivering continence care.

active therapy. Evidence also points towards scarcity of product supplies. An audit of the continence services in the UK revealed that rationing of pads and absorbent products was widespread, with most patients limited to four pads per day[219]. In addition, 59% of the continence services surveyed provided pads for children under the age of four, which was outside of the published national guidelines. These findings indicated the need for improved implementation of continence services.

A range of existing service delivery models were found in the literature and described below.

3.1. Single Specialist

The single specialist model, offering both medical and surgical treatment, is most common in developed countries and is usually led by a specialist physician (i.e., urologist, gynaecologist or urogynaecologist). A nurse continence advisor or continence nurse specialist may be included as an integral part of the services.

According to international clinical guidelines, specialists in continence care should be part of the referral chain focused on those with severe symptoms or the patients who are unresponsive to conservative treatment strategies, complex patients and those with a clear indication for more invasive treatments[128]. Also, while providers of specialist assessment and treatment should probably be separate from those providing initial assessment and treatment, it is important that there is operational integration with other components of service[193]. In the real world however, single specialists, especially in private practice, often work in their own silos offering all services within their own practices. A greater focus on surgical management could be a concern.

Specialists have an important role in facilitating the sharing of best practice and training as well as in quality governance[193]. However, the integration of an academic centre with a community-based services has proven to be challenging in the past with barriers to overcome regarding funding sources and existing healthcare infrastructure[220]. Training of general gynaecologists in continence care is also a challenge. Amongst specialist physicians, such as gynaecologists and urologists, relatively few specialize in continence compared to the prevalence of the condition[193]. Also, in the era of the superspecialist (urogynecologist), gynaecologists may not be motivated to enquire about and manage UI: in a retrospective review, resident physicians documented any type of bladder symptom (incontinence, urgency, frequency, dysuria, nocturia) in only 16.3% of 196 charts[221]. The residents may think of prolapse and incontinence as the domain of the urogynaecologist and are still uncertain if they will perform these procedures in their future practice [221]. When the authors prospectively randomized patient charts (n = 88) to carry a chart-alert sticker (e.g., "Do you leak urine?") that reminded the residents to ask about UI in their general gynaecology clinics, the inquiry rate increased from 4% to 34%.

3.2. Nurse Specialist

Nurse-directed models of incontinence care have been popular and subject to several studies. Farrell and colleagues studied a stepwise care delivery model that included continence advisor and nurses[222]. The model concluded a positive effect compared with the traditional medical model. In Australia, New Zealand and the UK, a national network of Continence Nurse Advisors (CNAs) or Continence Nurses provides an example where they integrate services, and guide patients through the referral route most appropriate to meet their needs. The efficacy of Continence Nurse Practitioners (CNPs) in the UK was reported by Matharu et al who studied 450 women over 40 years of age who underwent urodynamic studies in the UK after seeing a trained CNP[223]. In women diagnosed with bladder overactivity, the CNP prescribed medications to 79% of patients and PFMT to 64.8% of the women. In those with urodynamic SUI, 88% had appropriately been prescribed PFMT. Nurses assessed and assigned women to appropriate conservative treatments, resulting in shortening waiting times for urodynamics and specialist assessment.

There is a long history of the efficacy of the nurse specialist in the delivery of community continence care [224] [225] [226] [227]. In the U.S.,

urology nurses have been trained as "teachers" to successfully implement behaviour modification programmes to groups[228]. Nurses played an important role in the evaluation and management of POP, a condition which is often associated with concomitant UI[229].

When compared to primary care providers, nurse specialists can offer effective care. For instance, Choi et al performed a case-controlled intervention study with primary care patients (male and female) who had LUTS in China[141]. The intervention group (N=360) received a nurse-led continence care programme and a control group (N=360) received usual care by their PCPs. Outcome measures included symptom severity, HRQOL, self-efficacy, global health, and self-reported health service utilization at 12-months. The intervention group had significant improvements in LUTS severity and HRQOL, although improvements in the amount of urine leakage were not significantly different between the two groups. A higher proportion of intervention group (as compared to control group) reported increased self-efficacy (43.48% vs. 66.83%), improved global health condition (17.74% vs. 41.5%), having doctor consultation (18.5% vs. 8.06%), having medication due to LUTS (26.50% vs.11.29%) and having non-drug therapy due to LUTS (59.5% vs.9.68%).

Holtzer-Goor conducted a study investigating cost-effectiveness of inclusion of a nurse specialist in the treatment of UI in primary care in the Netherlands[230]. A decision analytic model was developed comparing the current care pathway for UI in the Netherlands with the pathway as described in the OCSS[193]. The new care strategy was operationalised as the appointment of a continence nurse specialist (NS) located with the GP. With the new care strategy, a QALY gain of 0.005 per patient was achieved while saving €402 per patient over a 3-year period. Although no health gains were achieved in both groups, the authors concluded that a NS in the GP practice would likely reduce UI, improve QoL, and reduce costs.

The emergence of the nurse consultant role has also contributed to an alternative provision of care. Lee reported findings from a study investigating the introduction of nurse consultants (NC) in Hong Kong[231]. The study focused on a range of patient outcomes including UI. A total of 280 patients, 140 in each cohort under NC or non-NC care, participated in the study. The study showed that patients under NC care had favourable patient health and service outcomes compared with those under non-NC care. The NC cohort also reported a high level of patient satisfaction.

These studies offer confidence in the value of nurse specialists and nurse consultants for the delivery of continence care. However, consistency in role definitions isn't always clear. Despite this, the community nurse, NS and NCs all have a role to play in early identification, assessment and treatment of bladder and bowel dysfunction. A systematic review identified a dearth of available research to understand the community nurse role in continence care[232]. The review reveals the lack of educational preparation and recommends that UI is positioned as a priority area of care. Models of care should consider the role of the generalist and their place in first line interventions and robust signposting. Furthermore, optimum delivery can be influenced by organizational, contextual factors and educational preparation[233 234].

3.3. Multidisciplinary Resource and Referral Centre

As we develop an expanding knowledge base of effective investigation and management protocols for women with pelvic floor symptoms, there will be an increased emphasis on multi-agency management of PFD[235]. Urological, gynaecological and colorectal dysfunction do not exist in silos; a blinkered focus specified by the confines of a single specialty and perceived limited options for treatment is unlikely to address the multiple causations and consequences of PFD[235]. Hence a multidisciplinary team is imperative to provide comprehensive care, especially at the tertiary level.

The multidisciplinary approach is a means of synchronizing treatment between various specialties and streamlining the patient pathway[235]. A system of cross-referral of patients is enhanced by regular face-to-face meetings between specialists in the core areas of colorectal surgery, urogynaecology, urology, pain, psychology and functional gastroenterology[235]. It is vital to extend membership beyond doctors alone to include continence nurse specialists, pelvic floor physiotherapists, biofeedback nurses and physiologists, as they all have distinct skills central to the assessment and management of these patients with often multiple deficits.

The clinical experience and medical evidence of this diverse group inform the details of management of these patients. The multidisciplinary team approach should not be thought of as being restricted only to a tertiary setting. While some of the specialist expertise may not be widely available, it is still a valuable way of managing people with difficult symptom combinations / multiple comorbidities etc as well as streamlining management at the local community level, depending on the expertise available[235].

A multidisciplinary clinic dedicated to a specific cohort of patients (65 years or older) in Canada demonstrated its success in improving continence care, via a retrospective chart review, in older patients with complex medical issues, thereby promoting successful aging[236]. The collaboration of a nurse, physiotherapist and physician to assess and treat bladder and bowel symptoms, while tackling co-morbidities that underpinned many of the symptoms, illustrates an exciting yet uncommon approach. Condition-specific multidisciplinary clinics have the potential to significantly improve quality of life. A qualitative study highlighted the distress and psychological impact of living with UI for people with cognitive impairment leading to the incorporation of a urology service within a cognitive impairment clinic as a pilot[237]. Fundamental to the success of such a clinic will be the integration with nursing and therapy staff and effective clinical pathways.

3.4. Primary Care

Primary care providers hold a strategic position in the early detection and management of UI[238]. Most women, particularly those aged 60 or older, use a family practitioner or internist to provide ongoing medical care and persons aged 75 and older average 6.5 physician visits per year[239] Also, for those involved in some managed care plans, a primary care physician may be the only feasible pathway to specialized treatment, when this is deemed necessary[240]. Thus, involving primary care physicians in the care pathway for UI and setting up an efficient triage system whereby patients with the most complicated symptoms are referred to specialist providers would enable provision of cost-effective care to the largest number of patients[240]. In the UK[241] and Sweden[242 243], continence services usually fall under the remit of primary care providers through individual health improvement programmes[194].

However, in a 2002 survey amongst Canadian family physicians, almost two-thirds of the respondents reported that differentiating types of incontinence was difficult and over 60% of them considered managing UI to be a difficult task[244]. Only 37% indicated that they had an organized plan for continence issues. In the US, Cohen et. al. found that, among primary care providers, only 25% initiated

a discussion of incontinence with their patients[245]. In their cohort, older patients were less likely to be asked about incontinence compared with younger patients. To address these needs, the Agency for Health Care Policy and Research (AHCPR), now called Agency for Healthcare Research and Quality, put together structured recommendations for management of UI with a multifaceted approach for primary care providers including physician and office staff education, logistical support, frequent interaction and feedback, patient screening forms, and patient education materials[246]. However, a group randomized trial in the US in which 21 of the included 41 primary care practices were trained in the guidelines, showed that rates of assessment and management of existing UI were low in both the control and intervention groups[240].

Surveys of primary care providers regarding UI management have shown contrasting results. A descriptive survey of 158 family physicians in Alberta[246] revealed that while 53.8% reported that they proactively discussed UI with their patients and 70% felt fairly confident in managing UI, 24% of them had received no training in UI management since graduation. Most family physicians referred patients for specialist care, with few referrals to community services. Respondents thought that continence services were scarce, with long waiting times, and that such services were generally overstretched. Also, they believed that although high-quality continence care was a personal priority, it was not a priority focus for their practice partnerships or networks. On the other hand, a cross-sectional electronic survey of primary care providers in the US showed that they were twice as likely to screen for (75%) and felt better informed to manage UI versus FI (35%). High reported interest in educational materials, coupled with high reported rates of perceived importance of screening for UI and FI suggests that PCPs welcome informative interventions to streamline diagnosis and treatment[247].

While there is increasing demand for primary care services due to an ageing population and reforms that shift care from hospitals to the community, the supply of physicians is limited and there are cost constraints[207]. Shifting care from physicians to nurses in primary care can potentially reduce costs and physician workload and maintain quality of care[206]. Nurse-led continence services for patients with UI have been integrated into the health care system in many countries[144], such as the UK, the Netherlands, the US, Canada[248] and Sweden[242].

A multicentre RCT in the Netherlands (PromoCon Study) comparing a 1-year intervention by trained NS's with care-as-usual after initial diagnosis and assessment by general practitioners revealed better continence rates, after three months in the patients seen in nurse-led clinics after correction for known effect modifiers (UI type and BMI), however, no differences were found between the groups in the 1-year linear trend[249 250]. A focus group study of six nurse specialists involved in the RCT later revealed that they felt competent to offer the needed services and were appreciated by the patients[251]. They were confident that they added value to the practice, particularly since many of the GPs were seen as lacking interest in UI. However personal contact with the GPs, availability of enough time, adequate equipment and financial resources are important preconditions for effective nurse specialist care[251]. An RCT in the UK which evaluated the impact of an 8-week primary intervention package delivered by a continence nurse practitioner showed that the percentage of individuals who improved and were cured after 3 months was significantly higher in the study group, when compared with care provided by GPs and continence advisory services in the area[241]. The results were maintained at the 6 months point.

3.5. Group intervention models

Group intervention models for delivering first-line treatment for UI has long been found feasible[40 252 253 254] and these models may be an equally effective and potentially cost-saving approach[255]. Haque et al investigated group exercises classes for women aged 60-75 years across Bangladeshi villages delivered by a paramedic (who provide front-line health care in the area)[256]. The rate of UI reduced for those women who participated. As identified by the study, sustainability of health gain requires continuity of classes. However, implementation of group intervention models, such as the classes, draws on a variety of factors. For instance, Schmuhl et al highlights factors for effective implementation, such as adequate funding, staffing, good facilitation, and recruitment of participants whilst being sensitive to underpinning stigma that may inhibit attendance[257].

Using a group approach to improving awareness, empowerment, knowledge, and health seeking behaviours for those suffering with incontinence is gaining credibility. As identified by Cera in their single-group efficacy trial of a continence education programme delivered by a Nurse Practitioner, there is a strategic opportunity to embed such models into integrated models[258].

3.6. Models using lay instructors

A study has shown that non-medical lay instructors can be taught how to instruct patients in proper PFM exercises[259]. This train-the-trainer model may be useful to help disseminate behavioural therapy on a more widespread basis. Literature is scanty when searching for models using lay instructors specific to continence care. However, drawing on exercise for community dwelling elders, Kim et al provides a useful insight into using peer-community trained residents[260]. In their quasi-experimental study, the intervention and control groups (30 elders in each group) received either an experience programme over eight weeks, or two training sessions on aging and arthritis. Six lay people received 16 hours of training from a nurse educator. The findings didn't reveal any significant difference between the two groups for outcomes in pain, shoulder flexibility, depression, or life satisfaction. However, self-esteem increased for the intervention group. As the authors highlight, lack of experience may sit at the heart of the disappointing results.

3.7. Telemedicine

Telemedicine, which provides safe, equitable, patient-centred care, has gained significant momentum in recent years[261]. The use of telemedicine is at the heart of a virtual clinic, to support the assessment, monitoring and management of patients at a distance, away from traditional face to face clinic consultation[262]. Potential benefits include improved satisfaction, reduced carbon footprint and reduction in unnecessary appointments and journeys to a hospital[263]. It could also fill the gaps where resources and manpower are lacking[193]. The format and delivery of a virtual clinic varies widely depending on the technology deployed[264] including telephone[244], online web sessions[265] and Skype[266] .

There is a growing body of evidence in support of tech-based initiatives. Providers should use clinical judgement and existing data to guide them on which clinical conditions are appropriate for virtual care[261]. Telemedicine is unlikely to be appropriate in clinical situations where a physical examination or diagnostic test is required. However, an individualised approach encompassing a combination of virtual and face to face appointments may be an option[267].

A Swedish randomized controlled trial on pelvic floor muscle training for women with SUI had 3 months of either an internet-based treatment program (124 women), including email support and cognitive behavioural therapy assignments, or a treatment program sent by post, though the intention-to-treat analysis showed highly significant improvements ($p < 0.001$) with large effect sizes (>0.8) with both interventions, there were no significant differences between the two groups in the ICIQ-UI SF and ICIQ-LUTSQoL symptom scores[268]. However, more participants in the internet group perceived that they were much or very much improved, reported reduced usage of incontinence aids and were satisfied with the treatment program. Furthermore, health specific QoL improved in the internet group, but not in the postal group. A supportive patient-provider relationship was developed in the internet-based program, despite the lack of face-to-face contact. The researchers concluded that internet-based treatment programs can increase access to care and empower women.

However, in a randomized controlled trial in which 195 women with UI were randomized to either a standard clinic or a virtual clinic, the virtual arm had no impact on the short-term dimension of the Patient Experience Questionnaire and overall was not as cost-effective as standard care, due to greater clinic re-attendances[264]. The consultation times were, however, briefer, communication experience was enhanced, and personal costs were lower in the virtual clinic group. The authors conclude that for medical conditions of a sensitive or intimate nature, a virtual clinic has potential to support patients to communicate with health professionals about their condition.

Mobile health technologies including electronic application (app)-based treatment that delivers advice, training, and motivation for managing UI by oneself could offer advantages over usual care, removing the barriers to treatment access and improving adherence to training[269]. More than 100 apps for UI management are already available, yet evidence for their effectiveness is scarce. Furthermore, these apps tend to focus on SUI alone and to have diverse content[270]. In a Swedish study, app treatment improved UI symptoms and quality of life after 3 months compared with postponed treatment and was cost-effective at 12 months[271]. A recent small Brazilian study also showed increased adherence to pelvic floor muscle exercises and an improvement in UI symptoms after 3 months of app-based treatment compared with written instructions alone[267].

In the URinControl randomized controlled trial in Dutch primary care involved 262 women (randomized to UrinControl app or usual care). While both groups showed improvements, the change in symptom severity with app-based treatment was non-inferior to that with usual care[269]. App-based treatments, with their potential advantages of privacy, accessibility, and lower cost, may provide women with a good alternative to consultation[269].

3.8. Continence care during COVID 19 epidemic

Patients face unique challenges during the pandemic owing to inherent vulnerabilities of these populations[272]. A cross-sectional study in Austria found that women's QOL remained significantly impaired by their pelvic floor disorders, with associated symptoms maintained and psychological strain experienced during the lockdown imposed due to the pandemic[273]. All 99 interviewed women were strongly willing to continue their treatment.

Medical providers worldwide, especially those practicing continence care for elderly and vulnerable patients, have been required to adapt and streamline services to provide continued care while minimizing unwarranted, multiple healthcare facility attendances and patient contact where possible, by conducting remote consultations, delaying non-urgent visits, and optimizing provision of one-stop services[272]. To enable patients to retain access to healthcare, many countries have revised regulations to allow health care providers to use telemedicine and receive appropriate reimbursement[274]. For example, the Centers for Medicare and Medicaid Services in the US have broadened access to, and reimbursement for, telemedicine services[275].

Various international societies and organizations have published guidance for management mainly based on consensus and expert advice, given that the evidence base to support recommendations is still scarce[276] [277] [278] [279]. A rapid review that synthesized current recommendations on urogynaecological care during the pandemic revealed the following: Virtual clinics were recommended for new and follow-up patients, to assess and initiate treatment, as well as to triage patients who require face-to-face appointments[272]. Behavioural and medical therapies, initiated by virtual or remote clinics, were recommended as first line options. Deferment of outpatient investigations such as urodynamics and cystoscopy for benign indications and suspension of prolapse and continence surgery, was considered prudent, except in specific circumstances such as gross haematuria, procidentia with upper tract complications, failed pessaries, when stage I sacral neuromodulation was in place or in cases of neurogenic bladder with a high risk of upper tract complications.

Expanding the availability and accessibility of technology is increasingly required. However, the longer-term effects of deferment of majority of outpatient and inpatient procedures are as yet unclear. When seeing patients face-to-face, appropriate screening, use of adequate personal protective equipment (PPE), appropriate physical distancing and sanitation are needed.

Regional or local anaesthesia was recommended during surgery where possible, to reduce aerosol generation associated with general anaesthesia. Screening for COVID-19 symptoms and testing preoperatively is advised, as evidence has shown poorer surgical outcomes for asymptomatic COVID-19 patients, therefore surgery may worsen or accelerate progression.

The Brazilian Association of Physiotherapy in Women's Health put together a set of recommendations for physiotherapy management of urogynaecological disorders during the pandemic[280]. These included emphasis on telephysiotherapy care including the use of apps, phone calls, etc; physiotherapeutic assessment of PFD symptoms and PFM function using telehealth and provision of appropriate health education materials to patients, especially those who are able to contract their PFMs. Women who are not able to contract their PFMs need to be informed about the limitations of using all physiotherapeutic resources when receiving telephysiotherapy.

The pandemic has led to a new paradigm in patient care that may well sustain even after the pandemic has abated. While telemedicine has opened a new door for many medical specialties, allowing continued safe evidence-based care, the pandemic has tipped the balance away from surgery and towards nonsurgical treatments while attempting not to sacrifice outcomes or quality of care[271]. Research is needed to understand both the positive and negative impact these changes have had on patients and future service delivery models.

4. GLOBAL SERVICE DELIVERY MODELS (INCLUDING CARE IN THE DEVELOPING WORLD)

There are wide variations in continence care service delivery across the world. Factors that affect the delivery of a continence care service include population demographics and patient characteristics; cultural differences in healthcare seeking and disease recognition; geographical healthcare access; financial healthcare access; maturity and development of existing continence care provision; extent to which services are integrated; economic and regulatory levers available to influence healthcare provision and application of technology in the delivery of care[193].

In many countries, but particularly low-income ones, incontinence is not a priority with only basic levels of care provided by community health providers, if at all[281]. Continence services are a relative luxury, to which countries with a low per capita income are unlikely to devote scarce resources, especially while other population health issues have precedence. The potential demand for UI services in developing nations far outstrips the resources that are available. Many of the problems in continence care in these countries are related to the immaturity of the wider healthcare system[10]. Addressing continence care needs while these countries develop their healthcare infrastructure will likely require innovative solutions to make the most of limited resources[193].

Female continence care is an emerging field even in urban parts of developing countries such as India; a few specialists offer care in private practice with no integration into referral care pathways or linkages with the community leaving vast swathes of underserved populations in urban slums and rural parts of the country. The provision of services will depend on the commitment of dedicated HCPs who, with support of government, industry and local continence organizations, can educate a new generation of service providers who will carry the services to remote communities. Increased use of advanced communication technologies can help to disseminate continence promotion materials among nurses and other health professionals worldwide[261].

Where there is a paucity of continence nurse specialists and physicians, it will be necessary to train existing professionals, especially those who currently see people with incontinence, and those who are well placed to deliver continence care[193]. Healthcare professionals are capable of learning a variety of skills, often outside of their usual domain [193]. For example, in the Netherlands, primary care-based nurse practitioners (called Praktijk Ondersteuners, or POHs) have taken on an increasing role in the management of UI in some regions[282]. In the United States, advanced practice providers (nurse practitioners, physician assistants) have acquired additional education and training in providing continence services[283]. In rural Bangladesh, research is currently being undertaken to investigate the role of village “paramedics” or other trained healthcare workers to carry out basic continence care (unpublished data).

In communities largely outside the reach of pharmaceutical or surgical interventions, group exercise-based programs for UI, that include PFMT, mobility exercises, and bladder education, appear to be promising low-cost interventions[284]. Community-based education via a train-the trainer programme has shown promise, as described by Saiki and Morales[285]. Their qualitative investigation of 25 self-identified community workers in southern New Mexico identified a lack of knowledge on how best to help the women living with incontinence in rural communities. However, the enthusiasm for learning was apparent and findings revealed several themes for programme development, but education programmes such as this will require continuing cultural sensitivity to ensure effective initiation and sustainability. Additionally, in a cluster randomized trial in Bangladesh in which 625 women aged 60-75 years from 16 pairs of villages were randomized to receive either the group intervention or bladder health education alone[284], the change in the number of leakage episodes between baseline and 24 weeks was -6.64 in a random effects model accounting for cluster randomization. Post-trial, a further 6-month exercise intervention comprising of 48 exercise sessions led by village paramedics was initiated in 20 villages[256]. 130 women from nine villages in the exercise arm of the trial were followed up 12 months after the intervention concluded. Those exercising at follow-up had an odds ratio (OR) of 3.49 (95% confidence interval [CI], 1.86-6.58) of being continent at follow-up. At roll-out, 38.6% achieved continence, comparable to 43.0% in the trial using physiotherapy preceptors. Thus, group exercise classes led by paramedics resulted in a marked improvement in continence but maintenance requires exercise postintervention.

Global variation and diversity with continence care delivery will continue to be a challenge. That said, a fundamental shift to better care needs a powerful clinical voice that transcends politics and ego. The World Health Organisation (WHO) encourages integrated health care but advocates for political commitment[286]. Furthermore, WHO has included UI within one of their 10 proposed priorities ‘*aligning health systems to the needs of older people’* as part of their Decade of Healthy Ageing (2020–2030)[287].

5. CONTINENCE CARE IN OTHER CLINICAL SETTINGS

Continence promotion, education, and treatment can occur in a variety of clinical settings, particularly in relation to other associated clinical conditions. However, global diversity presents a real-world challenge on how best to do this. In higher income countries, opportunities present themselves and are ripe for improving continence care whatever the setting. For example, UI commonly occurs after acute stroke. Rehabilitation nurses who work with post-stroke patients could play an important role in continence care. Research shows this may not happen regularly[288]. Heart failure is another common clinical condition, particularly among older adults, associated with UI. A study of 182 heart failure patients with at least monthly UI revealed that 83% had not asked for help with their incontinence symptoms and 64% were interested in learning more[289]. Many patients, particularly those with concomitant diabetes, were contemplating changing their behaviours and seeking care for UI. These findings indicate that this group may be receptive to education and interventions that improve urinary symptoms.

A multinational qualitative study examined data from focus groups of rehabilitation nurses in the UK, Sweden, and China[290]. They found that only limited assessment of continence was routinely performed by most nurses in this setting with a particular focus on containment. Edwards concurs with these findings, having investigated patients aged 65 years and older with a fragility fracture because of a fall[291]. Of 3184 patients, 63% (2009) were assessed for urinary continence following a hip fracture and a problem was identified in 41% (817) of these. Twenty-one percent (1187) of 5642 patients with non-hip fragility fractures were assessed and a problem was found in 27% (316). Hip fracture patients were more likely ($p<0.0001$) to receive a continence assessment and have problems detected. Only about half of those with problems were offered inter-

vention or a referral to a continence service. Admission to hospital for non-hip fracture patients was a strong predictor of being assessed (p<0.0001). Edwards concluded rates of assessment and action for those who fall and have continence problems are low despite current national guidelines.

Older people can be the majority of those admitted to acute care[292]. This setting provides care to manage short-term, but urgent, health problems and UI was prevalent. For example, a prospective cohort study of 577 patients (mean age 82 +/- 6.9 years) admitted to general medical wards of three acute care hospitals in Brisbane, Australia, found UI rates of 43.8% (243/555) premorbid, 36.7% (176/479) during admission, and 35.3% (187/530) at discharge[293]. Moreover, of 438 patients at the time of discharge, 38 (12.8%) had new onset UI.

One group of patients with a high risk for developing UI in hospital are female hip fracture patients. In a previous study, secondary analyses of data from 6,516 hospitalised women with a fractured hip revealed 21% became incontinent during hospitalisation[294]. Similar findings were reported for elderly patients admitted to hospitals in Israel[295], Switzerland[296], and Italy[297]. Zisberg and colleagues conducted a prospective cohort study of 352 patients aged 70 and older who were continent prior to admission to an acute care hospital[295]. They found, 17.1% developed UI during their hospitalization, and in a multivariate analysis, the use of a urinary catheter or diaper were associated with the development of UI (4.26 95%CI 1.53-11.83 and 2.62 95%CI 1.17-5.87 respectively). Zurcher and colleagues surveyed 78 elderly inpatients in a Swiss hospital and found 41 (51%) screened positive for UI, yet only 10 (24%) of nursing records documented the presence of UI[296]. Moreover, the use of absorbent pads was the only intervention documented. The number of patients who declined to be asked about their continence status was minimal (n=5).

Other research on UI in acute care continues to draw attention to an over reliance on containment, and inadequate attention to identifying and addressing potentially contributing factors. For example, Ostaszkiewicz and colleagues conducted a point-prevalence survey of 447 hospitalised older adults in acute and subacute care settings in Australia and found 60% with a continence product or device, however, 50 (41%) patients with an absorbent pad denied having experienced UI or FI in the preceding 24 hours[298]. By contrast, 113 patients (16%) who reported UI or FI in the same period had no continence product or device.

The lack of awareness of UI and how it is interrelated with illness and disease continues to be a significant problem. Hälleberg Nyman highlighted the importance of leadership as a bedrock of improving evidence-based UI care[299]. For instance, their process evaluation involving two orthopaedic wards in Sweden identified that leadership quality influences facilitation and implementation of guidelines. Even though containment of UI appears to persist as the most common approach to continence care[300], efforts are being made to support decision making for non-specialised clinicians[301]. Facilitating good decisions at the right time and in the right context has the potential to improve continence care.

6. ELDER SERVICES (LONG TERM CARE OR NURSING HOMES)

Long term care for frail elderly persons is provided in a variety of types of institutional settings throughout the world. Continence care in these settings is dependent upon many factors (Box 1)

Despite UI being a quality indicator in U.S. nursing homes (NH), significant barriers exist with translating research on toileting assistance programmes, such as prompted voiding and other interventions into practice[302]. This issue is especially concerning given the current and future growth in the frail elderly population. Available evidence indicated that the focus was too often on containment and use of pads or absorbent products compared to active continence promotion or treatment. A Cochrane review supported this finding and noted that none of the studies reviewed focused on attempts to maintain continence in facility residents[303]. A systematic review of systematic reviews on the most frequently used behavioural interventions used in long-term care indicated limited evidence for short-term effectiveness[304].

Barriers for improving continence care were considered multi-level and included: lack of knowledge about UI, beliefs about UI, high workload, low commitment from co-workers, and lack of institutional support[305]. Multiple strategies were seen as necessary for quality improvement in continence care to occur. These included creating a sense of urgency about the problem and a sense of solidarity among co-workers and facility administration. Managerial oversight and communication about the evidence of performance before and after the quality improvement program and use of evidence to make decisions about how to modify the programme were considered essential to programmatic success[302]. Little evidence was available to determine how older adults who received the interventions perceive and respond to them[306]. Higher registered nurse to patient ratio was identified as a facilitator of better continence care[307].

Tools to assist care givers with treating and managing UI have been tried. For instance, the development of individualized continence profiles for use with NH residents that could identify residents who may benefit from various forms of assessment and interventions[308]. Likewise, another tool previously worked to involve NH residents more actively in their fluid intake and continence care. After a 12-week intervention, overall hydration status improved, and time spent in saturated incontinence absorbent products decreased significantly in a cohort of 153 NH residents who participated in the intervention[309]. Distance learning techniques have been successfully used to teach and implement programmes and strategies for management of UI in NH[310].

Ostaszkiewicz et al identified in a qualitative investigation of 19 nursing home staff that the underpinning ethos was one of low expectation for improvement[311]. Thus, their care centred on continence management only, as in cleaning and containing. As the authors encourage, educational preparation should challenge beliefs and increase understanding of bladder and bowel dysfunction. The use of technology within the nursing home setting has been gathering pace, such a smart incontinence wear. (Cho et al 2021) However, as Strauven et al informs us, embedding technology into this setting is complex and needs to address the human factors (for example, teamwork, tasks, equipment, workspace, culture, and organization)[312].

Box 1: Factors influencing continence care.

- Type of resident care need (those requiring long-term skilled and personal care, short-term rehabilitation, post-hospitalization care)
- Physical environment
- Organisational culture and leadership commitment to providing high quality care
- Number, education, and motivation of direct care staff
- Access to physicians with interest in and understanding of continence care
- Financial and regulatory incentives to provide appropriate continence care

7. CARE AT HOME

Optimum continence care at home can help prevent early admission to a long-term care setting. Drennan and colleagues[313] interviewed thirty-two caregivers about their strategies for managing older adults with UI and dementia at home. They recommended that professionals, especially those in primary care, should be more proactive in questioning patients about UI and toileting habits to identify counter-productive and harmful strategies. A more recent insight via a critical review of 57 papers into caregiving at home for those suffering with dementia identifies the under-development of evidence to inform best care[314]. There is a continued need for deliberation of specialist roles, responsibilities, and protocols to guide and encourage appropriate referrals and ensure good collaboration, such as the integrated service model.

Summary

This section has attempted to assess several continence care models and understand the problems and benefits of each, particularly when implemented in real-world settings. Complexity and diversity exist despite efforts to improve continence care.

A range of service delivery models have been considered; single specialist, nurse specialist, multidisciplinary resource and referral centre, primary care, and other models (group intervention, lay instructors, eldercare services, tech-based clinics and models in developing countries). Within this spectrum the evidence supports nurse-led community services leading to higher health-related QoL and in some instances higher cure rates. Multidisciplinary referral settings are also reporting favourable outcomes. There remains discrepancy between availability of guidelines for different healthcare delivery settings, leadership quality and educational preparation. The Optimum Continence Service Specification is an example of an integrated model, which has shown that within a 3-year period, cost-effectiveness can be achieved, especially when societal costs are considered. Further research on cost-effectiveness and patient-level effectiveness of continence care models in a variety of healthcare delivery settings is urgently needed.

Evidence Levels And Recommendations

- Service delivery models for Continence Care can be effective. (Level of Evidence: 4)
- A care delivery model should be based on the principles as described in the Optimum Continence Service Specification. (Grade of Recommendation: C)
- Increased emphasis is needed on non-physician models of care (nursing, nurse practitioner, continence advisor, physiotherapy, physician assistants, etc.). (Grade of Recommendation: C)
- Despite the proliferation of guidelines, there is increasing evidence that practicing clinicians and nurses (in the community, acute care, and in long term care) are not consistently following them. Implementation models should be developed on how to translate guidelines into practice. (Grade of Recommendation: C)

VI. EDUCATION AND CLINICAL GUIDELINES

Literature Search for Medical Literature is found in Appendix 1.

1. BACKGROUND

Professional education regarding continence occurs in a wide variety of settings ranging from undergraduate education in medicine, nursing, physiotherapy and other related disciplines, through the full continuum of graduate education, post-graduate training (e.g. Fellowship) and ongoing professional education. This includes both formal education incorporated into established curricula or clinical experiences, and informal types of education such as on-the-job training and point-of-care instruction. Education may be directed toward generalists or specialists and will differ based on the topic of interest and the target learners. The focus of educational topics can range from evaluation and care of individual patients or clinical conditions, to population health and health policy. Examples of clinical education could include surgical skills training for surgical residents and fellows, community and ambulatory care, bedside, or operating room care for nurses, or biofeedback training for physical therapists.

Education of the lay public and patients is a crucial part of overall efforts in education and continence promotion as discussed earlier in this chapter. In the creation and discussion about this section, the committee recognized that a number of different terms are often used interchangeably when referring to this population. These terms include public education, layperson education, patient education, client education, consumer education, etc. These terms can have important distinctions depending on the perspective of those involved. For example, ‘patients’ may indicate those receiving care or suffering from a particular condition such as UI. The term ‘clients’ implies that people are receiving some type of services from a professional provider. And the term ‘consumer’ implies that the person is using either goods or services related to their UI. For simplicity, the term patient education will be used when reviewing the evidence for those suffering from a particular condition and public education will be used to summarize the information generally available.

The term carer and care giver can represent many different populations. It can suggest qualified health care professionals, paid support workers who should have received some basic formal education (also termed professional care givers) or informal carers who may include spouses, family and friends of the dependent individual who have no training / education in continence care. Many individuals may be cared for by a combination of different care givers in a variety of settings including long term care facilities, the community, schools etc.

This section reviews professional education on continence from a broad perspective across disciplines and specialties alongside the available evidence regarding patient, public and caregiver education. It will also discuss the clinical guidelines that have been introduced or updated since the last ICI and the impact that these may have on patients and services.

2. PROFESSIONAL EDUCATION

Professional education forms a critical foundation for all aspects of continence care. This includes the full gamut of professions and disciplines involved in care in this field. While it is agreed that education across areas is vital, most of the published work in this field has been focused on nursing, physiotherapy, and medical education. This is not to diminish the importance of education in other areas including occupational therapy, pharmacy, social work, and others. The role of multi- and inter-disciplinary education is also important but has not been a strong focus in recent publications on continence education.

The COVID-19 pandemic has had an interesting effect on professional nursing and medical education, particularly in relation to live versus virtual educational delivery methods. It has also influenced clinical care delivery. A variety of platforms are available that can be used for both educational and clinical purposes[315]. There has been an increased emphasis on development and dissemination of virtual education platforms.

An intriguing aspect of virtual education is the opportunity to provide training in a more multidisciplinary setting, and across multiple sites. This has the potential to increase the reach of global and multinational educational efforts. It has several important implications including possible increased education in places where this has been limited or absent. Examples would include rural areas or developing countries where dedicated continence care is limited and where there are few trained professionals on this topic.

2.1. Nursing Education

Education related to continence is typically included as a part of overall nursing training. However, the amount and specifics of training can vary widely among programmes. Qualitative research with focus groups of nursing students and registered nurses in practice found that most received education on continence through self-learning, some classroom education, skills labs or on clinical wards[316]. However, although considered important, many respondents thought sessions were either too short or did not go into enough educational detail. E-learning has been successfully designed to teach nurses about the associations between continence and mobility[317]. Online educational courses on urinary incontinence have been successfully developed and disseminated to nurses practicing in isolated rural communities[318]. This type of educational programming could be expanded and used more widely to reach nurses living and training in a diverse variety of communities and areas.

Since the last ICI, the bulk of published work in the area of professional nursing education has focused on evaluation of baseline knowledge and attitudes of nurses, nursing assistants, and other related health care workers[319]. It was noted that some but not all research on the topic has examined subsequent clinical patient outcomes.

In a study in Korea, attitudes, facility bed capacity and continuing education on urinary incontinence were statistically associated with better practice scores for registered nurses[320]. However, improved scores for practice aides were only associated with knowledge and attitudes about urinary incontinence.

A recent study showed that targeted education on continence improved knowledge for licensed nurses following the intervention[321]. However, health care aides persisted with the incorrect belief that incontinence is a normal part of the aging process. This demonstrates that additional work is needed in this area to influence and shift knowledge for some providers. A meta-analysis has shown that in other published studies, many nurses incorrectly believe that incontinence is inevitable in elderly patients[222]. Particularly in studies examining attitudes and knowledge among community-based nurses. This is an important area for future exploration because underlying attitudes and knowledge play an essential role in translating information into actual clinical practice. These gaps in knowledge should be key targets for future educational efforts.

Detailed technical training related to catheter placement, maintenance and care still appears to be lacking in many programmes. Many nurses and physicians who do not routinely deal with urologic issues often defer or are unable to address clinical needs related to catheters. This frequently leads to urologic consultations for basic questions or concerns. Dedicated education on catheters could be useful to help minimize delays of care and allow for more rapid and direct patient management. This also applies to intermittent catheterization (IC). Gray et al surveyed 343 nurses and found wide variability in methods and use of resources used by nurses to teach IC[322]. Seventy percent of respondents were registered nurses (RNs), and 15.6% were advanced practice nurses. Surprisingly, when presented with four clinical scenarios, 9.0 – 20.9% of respondents selected the wrong type of urinary catheter for a given case. Less than half (48.1%) engaged lay caregivers or family members when trying to teach their patients IC. These results highlight the need for improved nursing education on this topic. Education on catheter use also influences attitudes and perceptions of technical issues such as single-use versus reusable catheters[323]. There has been technical information released that is designed to teach proper catheter care and removal methods[324]. Ongoing maintenance measures for patients living with chronic urinary catheters is also important, and nurses play a key role in this care[325 326].

Cobb et al conducted a needs assessment study of 985 nurses who specialized in wound, ostomy and continence care regarding colostomy irrigation practice[327]. Overall, 59% identified ostomy irrigation as an evidence-based practice, but half of nurses indicate they do not routinely teach this to patients. Dahlke et al recently examined educational needs for nursing staff taking care of geriatric patients in an acute care setting[328]. This identified a mismatch between self-reported knowledge gaps and higher actual quiz scores on knowledge assessment. Specific areas identified as needing additional education included managing behaviors in older adults with cognitive impairment, use of chemical and physical restraints, and the associations between mobility and continence. Additionally, a critical literature review has been published which summarizes recent work on nurse perception and management issues[329].

Several publications examined ostomy nursing training needs, and collated resources on nursing care for patients with ostomies to help improve self-care[330 331]. Simulation education tools using high-tech mannequins have been developed to improve nursing instruction for patients to irrigate continent catheterisable urinary reconstructions and orthotopic neobladders[332]. This teaching method improved knowledge and confidence for nurses instructing their patients about these procedures.

Implementation of technology is an important methodology in nursing education. For example, use of ultrasound scanners to measure bladder and post void residual volumes is common in acute care hospitals, but can also have important applications in long-term care facilities and other settings[333]. Nurse-led and evidence-based interventions often prove quite successful and are beneficial in a variety of areas. For example, rehabilitation nurses often function as team leaders in rehabilitation clinical settings, with a role that includes teaching of other team members[334]. Targeted continence education has also been shown to improve nurse compliance with formal assessment pathways and management methods for both urinary and fecal incontinence in the tertiary acute care setting[335].

Several current studies are investigating nursing attitudes and care related to specific conditions. A qualitative study examining neurogenic lower urinary tract dysfunction in people with multiple sclerosis (MS) that includes both patients and nursing professionals is being conducted in Ireland[336]. A prospective, multifaceted, randomized controlled educational trial addressing FI targeted to care givers in nursing homes is ongoing in Norway[337]. It is hypothesized that improved education will enhance attitudes and knowledge which in turn could translate into improved diagnosis and management. Another qualitative study examined an intervention for nursing staff caring for people with continence issues in clinical stroke care wards[338]. Communication was seen to be a challenge from the patient perspective. Nurses described improved knowledge and a shift from containment to rehabilitative approaches for continence care.

The concept of dignity has emerged as a core element of continence care, particularly within nursing[311]. This is a multidimensional concept that has important implications for patients and practitioners. It is inherently linked to both general and health-related quality of life. Additional research on this topic will help expand our understanding of how this critical issue influences not only nursing but other forms of care. It may also uncover other as yet unidentified aspects of the continence spectrum and lived experience that can enhance future understanding in this field.

Future educational research work should examine how to best sustain educational programs, and specific educational outcomes as even highly successful educational programmes have problems with funding and staffing. Many published studies only examine the effects of a specific educational effort in the short-term, with little research looking at continuing and ongoing educational efforts. Future research should include the long-term satisfaction of learners and educators, as recommendations for new and innovative training methods could not be made based on current evidence.

2.2. Physiotherapy Education

In terms of physiotherapy education, the majority of published work since the last ICI has focused on influences on patient outcomes. In contrast, there has been little published work on educational methods or results of educational programming for physical therapists.

Clinician beliefs are important in the perception of physiotherapists and can influence various aspects of education. A study using structured focus groups found three main themes associated with excellence in physiotherapy related to continence[339]. These included high levels of skill and experience; strong research capabilities and partnerships with other researchers; and the role of mentorship for new practitioners. Consumer-focused care was identified as a core skill for physiotherapists at all levels of practice.

The International Continence Society (ICS) has recently published a guideline on education for physiotherapists related to pelvic floor and continence care[340]. This outlines a progressive, three level set of knowledge, clinical skills and education fundamentals for physiotherapists working in the broad areas of continence.

As in all areas of health education, competency-based training has become an important aspect of development of educational curricula and educational evaluation for physiotherapists[341]. It is noted that pelvic floor physiotherapy is not included as part of the core curricula in many programs, but it should be a goal for future educational programming. This is substantiated by work that demonstrates that many trainees across disciplines lack baseline knowledge about the risk factors for urinary incontinence in women[342]. Among the groups studied, physiotherapy students had the lowest baseline knowledge about risk factors. All students were interested in receiving more education in this area.

Application of physiotherapy for continence in nursing homes is an intriguing and perhaps underutilized resource[343]. These clinicians provide a variety of care services targeted at improving mobility and functional status, which could include pelvic floor therapy and continence promotion. Additional work and development of a more uniform application, role specifics and dissemination are needed.

2.3. Medical Education

Medical education on continence and elimination typically forms a very small part of overall medical education. At the undergraduate level, there are so many aspects of basic and clinical science that need to be addressed that often just a cursory introduction to this field is provided. Most of the detailed professional education on continence within various fields of medicine tend to occur at the graduate medical education (GME) level. These include residency training programmes in urology, and obstetrics and gynecology. Some education on this topic may be included in other fields such as neurology, neurosurgery, physical medicine and rehabilitation, gastroenterology and colorectal surgery. Education in primary care fields such as internal medicine and family medicine is much more variable. Some programs may include specific training in this area while others may not include any training as part of their curriculum.

With training, it is noted that all levels of medical providers can effectively teach pelvic floor muscle strength assessment as part of the pelvic examination[344]. This is important for subsequent patient education in clinical practice.

Simulation education methods have continued to gain popularity, particularly in undergraduate and residency training[345]. This may become even more important as educational delivery has changed during the recent COVID-19 pandemic.

Most of the published work in professional medical education since the last ICI has focused on specific surgical techniques. These include methods to treat urinary incontinence such as various forms of slings for management of stress incontinence and pelvic organ

prolapse repair options. Resident training in graduate medical education has been shown to be safe and effective for this type of surgery[346].

There has been increased emphasis on laparoscopic and particularly robotic methods of surgery in the past five years. One study compared surgeon experience and bony anatomy of the pelvis to clinical outcomes for patients undergoing robot-assisted radical prostatectomy for prostate cancer[347]. This demonstrated that surgeon experience (considered a form of ongoing advanced education) and anatomy both influenced clinical outcomes.

Formal modular training has been successful in developing robotic skills to perform radical prostatectomy, a surgery that can be difficult to learn initially[348]. Training on the robot requires time and dedicated effort. Use of dual console technology, where both the trainee and the more experienced surgeon educator are operating together, can enhance education and improve clinical outcomes for patients[349].

Other published studies have looked at continence results of procedures where incontinence may be an adverse outcome. This includes radical prostatectomy in men, and other forms of prostate treatment for bladder outlet obstruction and benign prostatic hyperplasia. Prospective training has been shown to be effective for laser enucleation of the prostate, which is a newer technique that can be difficult to master[350]. The number of cases performed by each surgeon and case density over time were found to be important educational factors. This experiential learning is an important educational component for this type of surgery. Increased surgeon experience has been shown to reduce both surgical time and adverse events whilst improving outcomes for this type of procedure[351]. Dedicated resident education has also been shown to be effective[352].

Feedback to surgeons in the form of a 'report card' has also been studied. This provides direct information on clinical outcomes with the goal of improving outcomes and minimizing adverse events. A prospective study was designed and implemented for surgeons performing radical prostatectomy for prostate cancer[353]. Although this did provide immediate feedback which surgeons found useful, it ultimately did not appear to alter clinical outcomes for patients[354].

Further research is needed to understand the optimal methods of training for surgical procedures and to determine how competency is achieved and maintained.

3. PATIENT / PUBLIC EDUCATION

3.1. Patient Education

Patient education consists of healthcare professionals teaching patients about their disease and offering therapeutic instruction, particularly information about self-management strategies, drugs, adaptation of their dosage and side-effects[355]. Patient education regarding normal and abnormal bladder function has been found to be helpful in the establishment of healthy bladder habits[356].

However, there was very little evidence to highlight the benefit of patient education for people with bladder and bowel conditions and the difference it may make to their outcomes. Most patient education studies found did not meet the quality criteria for inclusion. There are also inherent issues with generalisability of data as there are no standardised methods, techniques, or delivery for patient education or even any agreement on the content required for education.

For example, Bladder training (BT) is a well established therapy for patients with OAB. However, there is no clarity about the techniques and methods used to deliver it. An international survey performed by Elnagger et al reported that there was no consistency from respondents in how BT programmes were implemented in different clinical settings and environments nor was there consistency on how and what the patients were educated to do[357]. As there are no clinical trials comparing different approaches, it makes it difficult to determine the most appropriate and effective BT protocol[358].

To try to overcome this, a consensus statement for adults has been developed by a virtual consultation subgroup of the ICS Nursing committee and an expert panel using a modified Delphi Approach[359]. No universal definition of bladder training or bowel training was found, therefore a consensus definition was developed and agreed for each. Limited high-quality studies of bladder training were identified but no studies investigating the use or effectiveness of bowel training for urgency faecal incontinence in adults were found. It is hoped that the consensus statements will support healthcare practitioners to design and develop consistent bladder and bowel training and enable future research. The International Children's Continence Society (ICCS) have also developed a standardization document for the definitions, indications and practice of urotherapy in children and adolescents[360].

Halpert et al performed a literature review on patient provider interactions and patient education in those with irritable bowel syndrome (IBS)[361]. Several IBS educational approaches have been studied ranging from self-help interventions such as guidebooks to cognitive behaviour-based self-management, and one versus multiple sessions of IBS education, alone or as part of a multicomponent intervention. They reported that even a brief one-time psycho-educational group intervention in the form of an IBS class, consisting of information on diet, a healthy lifestyle, and general information regarding pathophysiology and IBS symptoms, is efficacious in changing cognitions and fears about IBS and in improving disease-related quality of life. According to findings from a focus group study, obtaining information from people who have UI and their carers may be useful in helping these individuals to develop self management tools that women could use on their own in the future[67].

Not all studies had positive results from patient education. Landbrotndtner et al found that that in a real world clinical setting, the development of pathways which included a patient education programme for those with IBS was less effective than expected[362].

Another study showed that intensive education about UI related to radical prostatectomy for cancer did not lead to better continence outcomes following surgery[363]. Therefore, educational efforts alone may not be sufficient to yield successful outcomes. Further research to establish whether there are any measures alongside education for patients that will promote the best outcomes is required. Investigation into how, when and where education is being delivered to patients and the role of the family involvement in education may also be enlightening.

3.2. Public Education

Recently there has been a substantial increase in publications related to public education for incontinence. These have broadly focused on several areas including knowledge and perceptions about incontinence and associated conditions, development and dissemination of public education or programmes related to continence, and the availability and quality of social media and elec-

tronic applications for public education on continence and related topics. Many of these have already been discussed earlier in the chapter under continence promotion and help seeking behaviour, alongside a review of the challenges in the validity of the content of this information.

A challenge for all public education is in the terminology used in the content. In a review by Williams et al, 44 focus groups were conducted across seven US states with adolescent and adult women to explore lay language and discourse related to bladder health and function[364]. They reported a definitional discordance between medical and lay views of bladder problems, suggesting a need to clarify the meaning of medical terms for lay persons.

Du et al undertook a review of patient education materials on female pelvic floor disorders available online from a variety of National / International Organisations[365]. They found that most of the materials evaluated were written at a minimum of high school level and were above the target readability recommended by the National Institutes for Health and Joint Commission. Providing information in a format and at a level that enhances comprehension of the material is essential to promote continence and improve patient care.

Innovations in public education treatment programmes for UI and associated conditions incorporated technology applications[366]. Delivery of a PFM programme via the internet was found to be more effective at one year among those with initial short-term improvement in symptoms, increasing age, and among those who continued regular PFME[367]. Other researchers have shown a mobile app was effective in helping train women with SUI about PFME and could be useful to enhance education about the condition[368]. Another study of 41 women demonstrated that an avatar based online educational programme was effective in improving health related quality.

4. CARER / CAREGIVER EDUCATION

4.1. Professional caregiver education

Very little evidence is available regarding carer or caregiver education. In a recent ICS white paper on ethical considerations in older adults with UI, it is acknowledged that in intimate continence care for older adults with cognitive impairment, caregivers require advanced knowledge and skills to manage the care interaction in ways than minimize the risk of harm to both the carer and to the care recipient, while also protecting the person's dignity and providing good continence care[369].

The 'Dignity in Continence Care Framework' is a theoretical framework developed by Ostaszkiewicz, which suggests strategies for the future education of nurses and formal care workers supporting care dependent individuals about continence care[370]. It suggests an educational program based on seven learning outcomes:-

1. To develop an empathic understanding about the range of human emotional responses to incontinence and care-dependence, and to recognize the effect of these responses on behaviours
2. To discuss practices that dignify a care dependent person with continence care needs
3. To describe a person-centred approach to continence care for cognitively impaired care dependent individuals
4. To demonstrate therapeutic communication strategies that build a care dependent person's resilience, and promotes their physiological and psychological wellbeing
5. To describe strategies that promote a partnership-centred approach to continence care that affirms the relationship between a care dependent person and their family
6. To conduct a foundational continence assessment
7. To describe practices that represent targeted and individualized partnership-centred continence care.

This education program is currently being developed and trialled, but results were not available at the time of publication.

4.2. Informal caregiver education

These is a paucity of data in the understanding of the educational needs of informal care givers. It has been reported that informal caregivers under reported their care recipient's UI and needed substantially more support from HCPs to manage the condition[371]. Yet it has also been reported that a third of professional care givers do not know how to teach family members about incontinence and this may represent a significant barrier to the continence care that the family can provide[372].

For many family members continence education is provided by national charities / advocacy organisations. An example of this are the parent/carer workshops that are run by ERIC, The Children's Bowel and Bladder charity[373].

5. CLINICAL GUIDELINES

An extensive array of clinical guidelines related to the evaluation and management of urinary and fecal incontinence have been published. These have been developed and disseminated by a wide variety of professional and public health groups, with each guideline tending to focus on specifics unique to the given field connected with the development group. In many ways, guidelines serve as a form of enduring professional education. They are essentially a collection of mostly evidence-based information that is used to create standardized methods of assessment and treatment for a given condition or set of clinical problems.

Since the last ICI, none of the previously published clinical guidelines have been formally retired or discontinued. However, some guidelines have been updated or expanded, and several other new guidelines have been published.

Drake et al published an update summarizing the International Continence Society fundamentals of good urodynamic practice[374]. This is the standard to which urodynamic studies should be conducted and includes information on both study technique and reporting methods. Another guideline has made recommendations for urodynamics in patients with spinal cord injury[375]. The International Children's Continence Society also published a recommendation on standardization of urodynamic studies in pediatric patients[376].

The UK Continence Society (UKCS) published a guideline summarizing the minimum standards for continence care in the UK in adults[377] and in paediatrics[378]. This took a multidisciplinary and multiprofessional approach to continence care and management. The document includes recommendations for standardization of education and training, clinical care, and a framework for service delivery.

It is broad and extensive in scope and covers both urinary and fecal continence topics.

The prior AUA/SUFU guideline on non-neurogenic overactive bladder in adults was updated in 2019[379 380]. The main change was that pharmacological therapies were changed from second line to an optional part of first line therapy in combination with behavioral measures. This reflects modern practice as many practitioners and patients chose this option at the time of initial treatment. The AUA/SUFU guideline on surgical management of female stress urinary incontinence was also updated[381]. This evidence-based review incorporated new surgical techniques and methods and removed some that are now considered outdated. Finally, the AUA and SUFU jointly developed a new guideline related to incontinence after prostate treatment including the full spectrum of prostate care[382]. This includes information on risk factors, patient assessment prior to and after prostate interventions, and a stepwise approach to therapies. Several algorithms are included related to patient evaluation, surgical management and device failure for artificial urinary sphincters and other devices.

The Japanese clinical guideline regarding female lower urinary tract symptoms was also updated in the interim[383]. This incorporated new evidence-based data that was developed since the prior publication in 2013.

Although use of mesh and other implanted materials remains controversial in some aspects of surgical treatment for female incontinence and pelvic organ prolapse, there continues to be ongoing research. Two consensus statements have been published on the topic since the last ICI[384 385].

One of the new condition-specific guidelines examines management of bladder dysfunction in patients with Parkinson's disease and with other forms of gait pathology[386]. Voiding dysfunction and other continence issues are common in this condition, and this provides recommendations for management. It also includes information that helps differentiate Parkinson's disease from other conditions such as multisystem atrophy (MSA). Collaboration between neurologists and urologists is highlighted.

The Wound Ostomy Continence Nursing Society (WOCN) published a clinical guideline focused on the management of adults with fecal and/or urinary ostomies[387]. This comprehensive guideline includes recommendations on pre- and postoperative patient education, stoma site marking, selection and use of appliances and pouching systems and other aspects of stoma care and quality of life. A similar guideline was also published in Italy[388].

Several guidelines have examined issues related to fecal incontinence. This includes a European consensus statement on the use of sacral neuromodulation for this condition[389]. A two-part Japanese guideline examines definitions, risk factors, epidemiology, quality of life questionnaires, methods of evaluation and conservative measures for therapy[390 391]. Fecal incontinence in children was also addressed by the International Children's Continence Society[392].

A summary article examining published guidelines for urinary incontinence in women was recently published[393]. This was a structured literature review which identified guidelines on the topic and synthesized information in a single document. This provides a succinct resource for researchers and clinicians seeking more information on the diversity and range of published guidelines for female urinary incontinence.

Several guidelines on pediatric continence issues have been published or updated since the last ICI. This includes the guideline from the ICCS on nocturnal enuresis, one on treatment of daytime incontinence and one in neuropdevelopmental disorders and incontinence in children and adolescents[394 395 396]. NICE guidelines on urinary tract infection and constipation have also been published[397 398]. There is also a new two part guideline from the European Association of Urology (EAU) and the European Society of Pediatric Urology (ESPU) on both the conservative and surgical management of neurogenic bladder in children and adolescents[399 400] Overall, this advocates a proactive approach to care and supports surgical management in select patients but notes a relatively high revision rate of 50% overall.

The Canadian Agency for Drugs and Technologies in Health published a review of available guidelines on long-term indwelling urinary catheters[401]. This included several scenarios which highlighted both accurate indications for use, and examples of misuse.

Vaginal hormone replacement therapy and other non-hormonal treatments are frequently prescribed for treatment of atrophic vaginitis, vulvovaginal atrophy, and prevention of recurrent UTIs. A new clinical guide on this topic was recently published by the European Menopause Andropause Society (EMAS)[402]. They note that this can be useful in select patients with mild urinary incontinence symptoms. This group also recently published an evidence-based guideline that summarizes treatment options for urinary incontinence in postmenopausal women[403] which includes the full spectrum of options including behavioral measures, diet modification, pelvic floor exercise, pharmacologic treatments, neuromodulation and chemodenervation of the bladder, and various surgeries.

Unfortunately, there has been little substantive research in the interim since the last ICI examining how guidelines are used, and the degree to which clinicians tend to follow guidelines in actual care settings. This would be important and could provide valuable insight into how practical guidelines really are in daily practice, and if they ultimately make a demonstrable difference in patient care outcomes.

Summary

Professional continence education across disciplines and specialties remains variable. Many health care providers do not receive formal education on UI, FI, or other continence-related topics as part of their general education and for those who do, many feel that it is insufficient. There is an ongoing need to continue to expand and evaluate educational offerings on topics related to continence and bladder and bowel health across all levels of training and for both generalist and specialist professionals. Virtual platforms and simulation training may prove to be valuable tools in times where classroom-based learning is challenging, but also as a way to reach a wider audience and provide an 'on-demand' education that allows flexible learning around individual schedules.

Public education directed toward patients, clients and consumers is an important part of the overall spectrum of information and dissemination of continence promotion. This can take many forms ranging from the provision of health information between health care providers and individual patients to public service announcements and other mass media communications. Although there has been a recent increase in public education efforts, research in this area is still in its relative infancy.

Methods of guideline dissemination are variable, and clinician awareness of guidelines can be a challenge. It can also be difficult to make clinical choices in cases where different guidelines may provide conflicting recommendations. Future work is needed to continue to assess existing and new guidelines, methods of guideline dissemination, ways to improve awareness of guidelines, and techniques to continually improve practice, along with a need understand the impact of clinical guidelines on patient outcomes.

Levels of Evidence/Recommendations

- Professional and public education of UI, FI and POP is not evidence based on the materials reviewed (Levels of Evidence: 3-4)
- There is a need for research on both educational content and methodology across all disciplines, particularly as the emphasis on primary care education increases and the opportunities for exposure to targeted content decreases (Recommendation Grade C)
- There is a need for additional research on interdisciplinary and team education, virtual education methods, and hands-on and simulation training related broadly to continence care (Recommendation Grade C)
- There is a need for additional focused research on methods to enhance patient and public education about UI, FI and POP, both at an individual and broader public level (Recommendation Grade C)
- Research is needed to examine methods to improve efficiency of public education including group training, mass marketing, and other techniques (Recommendation Grade C)
- The role of technology in public education for continence promotion should be examined in more depth (Recommendation Grade C)
- Future research methodologies should incorporate the standardised methods and definitions as set out in new consensus and standardisation documents (Recommendation Grade C)
- Guidelines for various aspects of continence evaluation and management have been established (Levels of Evidence: 3 to 4)
- There is a need to continue to evaluate the quality and relevance of existing clinical guidelines, particularly in the context of updating these materials or creating new guidelines based on emerging evidence (Recommendation Grade B)
- There is a need to continue to evaluate the quality and relevance of existing clinical guidelines, particularly in the context of updating these materials or creating new guidelines based on emerging evidence (Recommendation Grade B)
- There is a need for additional research on guideline dissemination, awareness and adoption among clinicians, and the impact on a wide range of outcomes including incidence and prevalence of disease, treatment efficacy, prevention efforts, costs, and health care policies (Recommendation Grade C)

VII. CONCLUSIONS

Continence promotion involves many different components including primary prevention strategies, health care advocacy, and methods of encouraging help-seeking behaviours. It also includes development of models to enhance provision of and access to health care in a wide variety of settings ranging from community programmes, to facility-based and institutional programmes, to widespread governmental initiatives. Education, of both health care providers and the public remains a cornerstone of successful continence promotion. Although there has been an increase in attention to these topics in recent years, additional work will be needed to actively advance our knowledge and to foster future progress.

APPENDIX 1

Primary Prevention
Online databases Pub Med, Cinahl, Pychinfo, and Medline were searched, with focus on literature published in and after 2010. Search terms used (aware* OR educat* OR promot* OR instruct* OR interven* OR teach* OR learn* OR lifestyle OR behav* OR change*) AND prevent* AND (incontinen* OR continent* OR continence*) NOT continental Sort by: Relevance Filters: Publication date from 2011/01/01; Adult: 19+ years

Continence Awareness, Promotion and Advocacy:
Online databases Pub Med, Cinahl, Pychinfo, and Medline were searched, with focus on literature published in and after 2016. Search terms used: 'awareness', 'consumer', 'education', 'urinary incontinence', 'faecal incontinence', 'incontinence', 'continence', 'continence awareness', 'continence promotion', 'health education', 'public education', 'public awareness', 'pelvic organ prolapse', health literacy, health promotion', 'outcome measures'

Continence Promotion Programmes: Online databases Pub Med, Cinahl, Pychinfo, and Medline were searched, with focus on literature published in and after 2016. Search terms used: 'awareness', 'consumer', 'education', 'urinary incontinence', 'faecal incontinence', 'incontinence', 'continence', 'continence awareness', 'continence promotion', 'promotion programme', 'health education', 'public education', 'public awareness', 'health literacy', 'health promotion'

Continence Advocacy: Online databases Pub Med, Cinahl, Pychinfo, and Medline were searched, with focus on literature published in and after 2016. Search terms used: 'awareness', 'consumer', 'urinary incontinence', 'faecal incontinence', 'incontinence', 'continence', 'continence promotion', 'promotion programme', 'public awareness', 'advocacy', 'consumer awareness', 'continence advocacy'

Patient advisory groups: Online databases Pub Med, Cinahl, Pychinfo, and Medline were searched, with focus on literature published in and after 2016. Search terms used: 'patient advisory groups', 'patient advisory groups' AND 'bladder' OR 'bowel' OR 'continence' OR 'incontinence' OR public floor

Awareness in Children: Online databases Pub Med, Cinahl, Pychinfo, and Medline were searched, with focus on literature published in and after 2016. Search terms used: 'children' AND 'continence' AND 'awareness'

Help-seeking (care-seeking) behaviour:
Search of pubmed /embase /cinahl/psyc /psychlit/eric/biosis /Scopus/Cochrane /WOS/JBI was conducted for the years 2011 to 2016. The search terms for each search were: PUBMED: (((health*[tw] OR care[tw] OR help[tw]) AND (acceptance[tw] OR accepting[tw] OR accept[tw] OR seek[tw] OR seeks[tw] OR seeker[tw] OR seeking[tw])) OR "Patient Acceptance of Health Care" [Mesh] OR "help-seeking"[tw] OR "care-seeking"[tw]) AND ((incontinen*[tw] OR continen*[tw]) NOT continental) AND ((Adult[Mesh]) OR adult*) CINAHL/PSYC/ERIC: ((TX (health* OR care OR help) N5 (acceptance OR accepting OR accept OR seek OR seeks OR seeker OR seeking)) OR (MH "Help Seeking Behaviour") OR (TX "help-seeking" OR "care-seeking")) AND (TX (incontinen* OR continen*) NOT continental) AND (MH "Adult+" OR TX adult*) FROM 2011 EMBASE: health*:ab,ti OR care:ab,ti OR help:ab,ti AND (acceptance:ab,ti OR accepting:ab,ti OR accept:ab,ti OR seek:ab,ti OR seeks:ab,ti OR seeker:ab,ti OR seeking:ab,ti) OR 'help-seeking':ab,ti OR 'care-seeking':ab,ti OR 'help seeking behaviour'/exp OR 'patient acceptance of health care'/exp incontinent OR incontinence OR continence NOT continental 'adult'/exp OR adult*#9 AND #10 AND #12 AND [2011-2016]/py WOS: ((health* OR care OR help) AND (acceptance OR accepting OR accept OR seek OR seeks OR seeker OR seeking)) OR TOPIC: ("help-seeking" OR "care-seeking") Refined by: TOPIC: (incontinence OR incontinent OR continence OR continent) AND TOPIC: (adult* OR man OR woman OR men OR women) Timespan: 2011-2016. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC. SCOPUS: (TITLE-ABS-KEY((health* OR care OR help) AND (acceptance OR accepting OR accept OR seek OR seeks OR seeker OR seeking)) OR TITLE-ABS-KEY("help-seeking" OR "care-seeking")) AND (TITLE-ABS-KEY(incontinence OR incontinent OR continence)) AND (adult* OR man OR woman OR men OR women) AND (LIMIT-TO(PUBYEAR,2016) OR LIMIT-TO(PUBYEAR,2015) OR LIMIT-TO(PUBYEAR,2014) OR LIMIT-TO(PUBYEAR,2013) OR LIMIT-TO(PUBYEAR,2012) OR LIMIT-TO(PUBYEAR,2011))

BIOSIS: You searched for: TOPIC: (((health* OR care OR help) AND (acceptance OR accepting OR accept OR seek OR seeks OR seeker OR seeking)) OR TOPIC: ("help-seeking" OR "care-seeking")) Refined by: TOPIC: ((incontinence OR incontinent OR continence OR continent)) AND TOPIC: ((adult* OR man OR woman OR men OR women)) AND PUBLICATION YEARS: (2015 OR 2014 OR 2013 OR 2012 OR 2011 OR 2016) Timespan: All years. Indexes: BCI. COCHRANE: '((health* OR care OR help) AND (acceptance OR accepting OR accept OR seek OR seeks OR seeker OR seeking)) OR "help-seeking" OR "care-seeking" in Title, Abstract, Keywords and (incontinence OR incontinent OR continence OR continent) in Title, Abstract, Keywords and adult* OR man OR men OR woman OR women JBI: (((health* or care or help) and (acceptance or accepting or accept or seek or seeks or seeker or seeking)) or "help-seeking" or "care-seeking").tx. (incontinence or incontinent or continence or continent).tx. (adult* or man or men or woman or women).af. Abstracts for the retrieved citations were reviewed in Covidence and the full text of each included papers was reviewed. No interventional research studies or systematic literature reviews for help-seeking or care-seeking since 2013 were found.

Models of Care
Models of Care, Delivery and Accessing Care: Online databases Pub Med, Embase, Medline and Cochrane were searched, with focus on literature published in and after 2010. Search terms used: 'urinary incontinence', 'faecal incontinence', 'incontinence', 'continence', 'models', 'service', 'delivery', 'economics', 'strategy', 'video consultation', 'telemedicine', 'telecare', 'telehealth', strategy', 'transitional care' and 'virtual'

Online databases Pub Med, Embase, Medline and Cochrane were searched, with focus on literature published in and after 2010. Search terms used: 'urinary incontinence', 'faecal incontinence', 'incontinence', 'continence', 'models', 'service', 'delivery', 'economics', 'strategy'.

Education
Online databases Pub Med, Cinahl, Pychinfo, and Medline were searched, with focus on literature published in and after 2010. Search terms used: 'continence', 'continuing education', 'curriculum', 'education', 'faecal incontinence', 'graduate education', 'fellowship', 'health education', 'incontinence', 'pelvic organ prolapse', 'professional education', 'residency', 'resident', 'student', 'training', 'urinary incontinence'.

Nursing Education: Databases searched – Embase, Cinhal. Medline, Cochrane, ERIC, Web of Knowledge. Search terms (including variations and /or) – education, urinary incontinence, faecal incontinence, continence, health education, allied health professional, physiotherapist, bladder and bowel, nursing, care assistants.

Impact of Clinical Guidelines: Databases: PubMed, CINAHL, Embase. Terms: (Continence or Incontinence or Bladder or Bowel) AND (Clinical Guideline or Guidelines or Consensus or Best Practice or Audit). Language: English

Public Education: Databases: PubMed, Medline, Embase, Google scholar. Terms: patient education or patient knowledge public education, layperson education, client education, consumer education AND (Continence or Incontinence or Bladder or Bowel) Language: English

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COMMITTEE 21

ECONOMICS OF URINARY AND FAECAL INCONTINENCE, AND PELVIC ORGAN PROLAPSE

Co-Chairs
Kilonzo, Mary (United Kingdom)
Vale, Luke (United Kingdom)

Members
Gariss, Jeffrey (United States)
Horčička, Lukáš (Czechia)
Khalifa, Ahmad (United Kingdom)
Wagner, Todd (United States)

COMMITTEE 21

ECONOMICS OF URINARY AND FAECAL INCONTINENCE, AND PELVIC ORGAN PROLAPSE

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I. INTRODUCTION

Urinary and faecal incontinence and prolapse are problems that affect many people in society. Not only do they cause considerable distress to those affected and their families but there are significant impacts on both quality and quantity of life. In addition to the impacts on health and wellbeing, these conditions impose a considerable cost to individuals and families, health services and society in general. The magnitude of these costs is not precisely known but cost of illness studies (see section on types of economic studies below) have estimated that in 1995 the annual costs of urinary incontinence in both men and women was over USD 26.2 billion(1) Roughly, 50% of this cost was related to stress urinary incontinence and 35% fell directly on those with stress urinary incontinence (mainly from the purchase of containment products and cleaning)(1,2).

Since then, this cost would have increased substantially due to an ageing population and price inflation. These financial costs do not fully reflect the health impact. Villoro (2016)(3) estimated that in Spain alone over 350,000 quality-adjusted life-years (QALYs) were lost due to UI amongst women 60 years of age and older. Assuming that each QALY is valued at USD 50,000 then the cost to Spanish society would be USD17.5 billion (in 2019 USD). With respect to overactive bladder associated with urinary incontinence a recent cost analysis of estimated a total annual direct of health care cost in 2007 of $65.9 billion with projected cost of $76.2 billion in 2015 and $82.6 billion in 2020 for overactive bladder associated with urinary incontinence(4) .

For faecal incontinence the prevalence in the general population is 2-3% but for people aged over 65 years and living in a care home it is 40%. It has significant social, psychological, and economic ramifications(5-8). Incontinence can compromise quality of life for patients with concomitant significant impact on patient's families, caregivers, friends, and the healthcare team. As the general population grows, the prevalence of faecal incontinence is expected to grow(8,9) which will result in a substantial increase in economic burden both on patients and society. The full economic cost of faecal incontinence is not clear with few new data available in the last twenty years) (10). A 1995 estimate of community-based healthcare cost for faecal incontinence exceeded $11 billion annually in the United States(5). If adjusted for the rate of inflation, the comparative 2021 annual rate of healthcare cost for faecal incontinence would exceed $19.1 billion per year.

With respect to pelvic organ prolapse it has been estimated that in the US roughly 9.2 million women will be affected by pelvic organ prolapse by 2050(9), with approximately 300,000 undergoing surgery each year at a cost over US$1bn. Similar estimates for a European context were provided by Subramanian (2009)(11) who estimated that the annual cost of managing pelvic organ prolapse in 2005 Euros was €144m, €83m and €81m in Germany, France and England, respectively.

These costs illustrate that as societies we devote considerable resources to the management of these conditions. The question that arises is could we use these resources in a better way? We need to ask this question because regardless of which country we live in, the resources available to provide health care are not sufficient to meet all the many different needs that exist. This means that we need to make choices about what we do and what we do not do. One criterion which might be used to inform a judgement is the economic concept of efficiency. An efficient allocation of resources occurs when we allocate the resources we have available to maximise the benefits. This situation occurs when the benefits we obtain from using the resources one way are greater than those we would have obtained in the next best alternative use of these resources. This gets us to the economic definition of cost, where the cost of using resources in one way is that we give up the opportunity to use the resources in other desirable ways.

This chapter starts with a summary of the findings from the preceding consultation. It provides key background material to help the reader understand the methods used in economic evaluation (Section III) before summarising the finding of economic evaluations published since the preceding consultation (Section IV). Finally, it concludes with a summary and future research priorities (Section V).

II. SUMMARY OF THE MAJOR FINDINGS FROM THE PRECEDING CONSULTATION

The last edition of this chapter found that very few studies estimated lifetime costs and benefits. When comparing treatments that had very different initial treatment costs, this could create a bias towards treatments that have lower initial costs (behavioural or pharmacological treatment), as opposed to treatments that are initially expensive (surgical). When considering the results of all identified studies this needs to be borne in mind.

The following sub-sections summarise the evidence from the last edition.

1. STRESS INCONTINENCE AND OAB

1.1. Behavioural therapies

There were seven articles identified that evaluated economic aspects of behavioural techniques. The evidence suggested that behavioural programs were more costly than usual care. However, it remained unclear if they provided value in part because there was heterogeneous adherence to these treatments between studies. Some studies reported improved continence (measured using pad tests, pads used per week, post void residual, functional impairment measure, and the ICIQ(12) . However, these impacts were not reflected in measures of health-related quality of life measured using generic tools, such as the EQ-5D. This raised questions whether these generic instruments were sufficiently sensitive to small but important changes or whether these changes were actually important to patients. Consideration is also needed as to whether initial treatment with less costly (and less intensive) care followed by more intensive options for non-responders is worthwhile economically. The use of incentives to encourage adherence to, and maintenance of these behavioural therapies may also have value.

1.2. Surgery for stress incontinence

Thirty-five new papers were identified in the prior search related to the economics of surgery for stress incontinence. Most studies lacked end point data beyond 12 months on costs or effectiveness. Many studies also only compared different surgical treatments to each other. Thus, in general, given the follow-up time frame and the restricted set of treatment comparisons, it made it very difficult to make statements about the cost-effectiveness of surgical treatments compared to non-surgical treatments.

Studies were quite heterogeneous in terms of the type of comparison made. For example, one study(13) looked at the use of pre-operative urodynamic testing for sling surgery and concluded that there are times when it is overused and other times when it is underused both of which could affect the cost and effectiveness of care. Other studies considered issues of surgical timing and were not excluded from the last consultation.

Included studies were both trial and model based (see Section III.5) comparing surgical treatment such as mid-urethral sling (MUS), single incision mini slings to non-surgical interventions such as surgery to PFMT. The focus of many of the papers identified from the consultation was the comparison of similar surgical techniques utilizing a substitute material (e.g., a commercial sling versus a handmade sling).

Unfortunately, many of the identified studies presented weak evidence, made unwarranted conclusions, were unclear in presentation, or made errors in calculations. One notable error identified in more than one study was in the calculation of the incremental cost-effectiveness ratio; which is critical when assessing relative efficiency (see Section III).

1.3. Surgery for urge incontinence and refractory OAB

Two primary treatments for urge urinary incontinence and refractory OAB were identified: sacral nerve stimulation (SNS) and Botulinum Toxin A. The studies compared cost-effectiveness of SNS to Botulinum Toxin injection, and to oral medical treatment (14,15). In addition, two publications looked at economic aspects of different SNS test phases(16,17). The results of the different mid- to long-term cost-effectiveness analyses supported a therapeutic pathway starting with SNS compared to Botulinum Toxin injection(18,19). Reducing need for hospitalisation (e.g., local instead of general anaesthesia) and optimal lead placement (e.g., less need for revision, lower amplitude for stimulation) appeared to be important influencing factors. The Committee reiterated the need to collect primary data for quality adjusted life year (QALY) outcomes in future studies of SNS.

1.4. Pharmacotherapy of stress incontinence

No pharmacotherapy cost-effectiveness analyses for stress urinary incontinence (SUI) were identified as in the last report. This was consistent with the lack of available approved pharmacological therapies for stress incontinence.

1.5. Pharmacotherapy Urge Incontinence and OAB

A few cost-effectiveness (CEA) and cost-utility (CUA) analyses (see Section III for explanation of these types of analysis) on commonly used pharmacological treatments for overactive bladder and urgency urinary incontinence were identified. Treatments considered included oxybutynin (Ditropan®) as a tablet or as a patch (Oxytrol®); tolterodine (Detrol®), darifenacin (Enablex®), trospium (Sanctura®), solifenacin (Vesicare®), fesoterodine (Toviaz®), and mirabegron (Myrbetriq®). Most of the studies were funded or performed by individual pharmaceutical manufacturer creating a strong possibility of potential conflicts of interest. Other common limitations included the use of incontinence-specific utility measures, limited time frame and limited comparison to alternative treatments. The previous consultation highlighted the fact that while industry funded studies often include experts in performing CEA and can use, on first sight, sound methods, they must be interpreted carefully for the possibility of bias. For example, the selection of assumptions included in the models like the values used for the probability of events (e.g., drug response, likelihood of transitioning to a different treatment strategy, probability of side effects or adverse events), timeframe, costs and perspective can all be chosen to have subtle (or not so subtle) but cumulatively important impacts on estimates of cost, effects and cost-effectiveness.

2. PROLAPSE TREATMENTS, COST IMPLICATIONS

Newer surgical approaches for POP identified in the last report included laparoscopic sacrocolpopexy, robotic sacrocolpopexy, and vaginal mesh. It was assumed that these new modalities may include very costly capital investments in equipment (such as robotic systems), use expensive disposable instruments, use costly mesh kit products, take longer (or shorter) operative time, and/or be associated with (more or less) adverse events and future procedures. They might also be associated with shorter hospital stay and more rapid recovery. Therefore, cost-effectiveness was well suited for these modalities and several economic analysis studies were identified.

The identified studies included a retrospective cross sectional longitudinal study(20) whose findings could not be elucidated, two cost minimisation studies(21,22) that compared robot-assisted with open sacrocolpopexy and laparoscopic sacral colpopexy (LSC) with total vaginal mesh, a systematic review(23)that included only randomized controlled trials (2 trials, n = 156) comparing laparoscopic and robot-assisted sacrocolpopexy (heterogeneity between the two studies precluded a meta-analysis)(24) among other studies.

The meta-analysis studies showed that robot-assisted sacrocolpopexy was costlier than laparoscopic sacrocolpopexy with similar clinical outcomes. The results of the systematic review that had small, randomized studies, suggested that robotic surgery significantly increased cost compared to the conventional laparoscopic sacrocolpopexy with no improvement in outcome. A decision-analytic model was developed to assess the cost-effectiveness of abdominal sacral colpopexy (ASC) vs. sacrospinous ligament fixation (SSLF) to determine if the improved outcomes of ASC justify the increased expense(25). In this study, abdominal sacrocolpopexy was a cost-effective alternative compared with sacrospinous ligament fixation.

The committee concluded that by standard thresholds, abdominal sacrocolpopexy (ASC) may be cost-effective compared to sacrospinous ligament fixation (SSLF) and performing a mid-urethral sling with ASC may be cost-effective compared to ASC alone. Mesh-augmented anterior vaginal wall repair was not cost-effective compared with a non-mesh fascial plication repair and pre-operative screening for endometrial cancer before prolapse surgery is likely not cost effective in asymptomatic, postmenopausal women. They also highlighted the fact that in the field of prolapse, it was not yet known whether any currently available health status measures were sensitive to treatment benefit, so that CEA may still not be feasible in this area.

3. ECONOMIC CONSEQUENCES OF FAECAL INCONTINENCE

3.1. Prevention

Two costing studies(26,27) were identified but there was only one cost-effectiveness analysis(28) that compared cost-effectiveness of primary sphincter repair versus delayed sphincter repair for anal

Society. This is potentially the widest approach. It would include productivity effects and health effects as well as costs and effects that fall both in and outside the health care sector. It can be difficult to identify, measure and value all costs and benefits, so it is more common to see costs that fall on the health care sector, patients and productivity effects (this perspective is recommended by several health care regulatory organisations internationally)
Health and care systems (common in studies conducted in several European countries). Here the focus is on costs to the health care system and health outcomes measure in clinical units (e.g., numbers cured) or QALYs. This is the recommended perspective by the National institute of Health and Care Excellence in the UK
Patient. Here the focus might on costs and outcomes most relevant to the individual patient so it might include out of pocket expenses (directly purchased health care and co-payments), insurance premiums. It may also include costs to the individual of time away from work or reduced ability to carry out normal activities – so lost in wages and incomes and lost leisure time
Health service payer. This shares similarities with the health care system perspective but where in the health system perspective we consider all costs that fall on the health system here we would only include costs that fall on an individual payer. For example, if the payer is an insurance company, then this perspective would exclude costs falling on others (like patients). The costs considered would not be the cost of producing health care but the cost of purchasing it (i.e.), the charge that may be much higher. Outcomes may be measured in a variety of different ways (see types of economic study below)
Health Care provider. If it is only a single provider, the focus is on the production cost of care to that provider. It excludes costs falling on other groups (other care providers, patients, etc). Outcomes can be measured in a variety of different ways (see types of economic study below).

Box 1: Common perspectives taken in Economic Evaluation

sphincter injury in the prevention of faecal incontinence. The study concluded that primary sphincter repair was the most cost-effective strategy being associated with 5.72 QALYs for a cost of £2750 compared with delayed sphincter repair, which yielded 3.73 QALYs for a cost of £2667 over ten years.

3.2. Treatment

Cost-effectiveness analyses on the treatment of faecal incontinence primarily focused on sacral nerve stimulation (SNS) as a first-line surgical treatment for patients with faecal incontinence. The studies that were identified for SNS compared to conservative treatments had mixed reviews. Three studies assessed the cost-effectiveness of sacral nerve stimulation in comparison with other surgical treatments. The strength and weakness of these studies were noted, and the committee acknowledged that it was encouraging to see economic analyses of Sacral Nerve stimulation for faecal incontinence. However, more data about long-term cost-effectiveness in faecal incontinence were urgently needed.

4. SUMMARY AND FUTURE RESEARCH PRIORITIES

The committee noted that some high-quality economic analyses had been published. They attributed this to the requirement for cost-effectiveness data from NICE and other similar bodies. This along with standardization of methods in trial-based analyses had led to higher overall quality. As regards methodology, they noted that researchers needed to consider carefully how they construct the model-based analyses so that that “real life” assumptions are made. Finally, the committee encouraged researchers to provide information on the uncertainty around an incremental cost-effectiveness ratio (see Section III.6 on sensitivity analysis).

III. IMPORTANCE OF ECONOMIC EVALUATION

1. INTRODUCTION

As the previous section illustrates, economic evaluation has the capacity to inform judgements about the opportunity costs of using health care resources in a given way. Economic evaluation has been defined as the “comparative analysis of alternative courses of action in terms of their benefits (e.g., health effects) and costs (e.g., the resource use)(29).” The types of economic evaluation are described in more detail in the next section, but all involve the same three steps:

- Identify
- Measure
- Value

Critical to this process is once the interventions to be compared have been clearly defined, is to define which costs and benefits are important to the decision-maker. There is no single right answer about which costs and benefits are important rather this is dictated by who the decision-maker is. Therefore, in any economic evaluation it is important to define the perspective. Different studies may adopt different perspectives, and this can affect the conclusions that are drawn. Typical perspectives are set out in Box 1.

2. TYPES OF ECONOMIC ANALYSIS

There are several types of economic analyses that can be conducted for health and medicine. The analyses apart from cost of illness studies, aim to provide information about a choice (or set of choices). The methods to assess costs for the different types of economic analyses are the same but what differs is how outcomes are measured and valued.

2.1. Cost minimisation analysis

Cost minimisation analysis (CMA) compares the costs of alternative interventions which are known to have equivalent clinical outcomes. Outcome equivalence should be supported by clinical evidence. This analysis aims to establish which intervention has the lowest cost. A common problem with many published cost minimisation analyses is that outcome equivalence is assumed or based on the erroneous assumption that failure to detect a statistically significant difference is evidence that there is no difference between interventions compared.

2.2. Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) compares the costs and outcomes of alternative health interventions where outcomes are measured in terms of a single natural, or clinical measures. For example, one such outcome could be episodes of incontinence avoided. In a cost-effectiveness analysis, the effectiveness of treatments is reported relative to their costs. To do this the difference in (often called the incremental) cost and incremental effect are combined into a single metric known as the incremental cost-effectiveness ratio (ICER). The ICER is:

$$ICER = \frac{Average\ Cost_{\ 1} - Average\ Cost_{\ 2}}{Average\ Effect_1 - Average\ Effect_2}$$

Where, $_1$ and $_2$ refer to intervention 1 and Intervention 2 respectively. Whilst still being a very common form of economic analysis, over time the number of CEAs reported has decreased due to the previously published guidelines on the conduct of economic analyses produced by the Washington panel(30) or due to guidelines set by agencies that oversee reimbursement decisions.

2.3. Cost consequence analysis

A cost-consequence analysis (CCA) can be thought of lying in between a CEA and a cost utility analysis (CUA). In a CCA costs are equated against multiple consequences (for example episodes of incontinence, adverse events, need for further treatment, etc). There is no attempt to aggregate these effects into a single measure as there is in CUA and no ICER is calculated. Rather the goal is to present the trade-off between costs and the different outcomes.

2.4. Cost utility analysis

CUA compares the costs and outcomes of alternative interventions and measures health outcomes in terms of both quantity (life years) and quality of life. This analysis is a variation of cost-effectiveness analysis. Effects are commonly reported in terms of outcomes such as quality-adjusted life years (QALYs) or disability adjusted life years (DALYs)(31). The former is more commonly used in high income countries, with the latter more commonly used in low and middle income country settings. The advantage of the QALY is that it combines gains from reduced morbidity (quality gains) and reduced mortality (quantity gains) into a single measure. The value of a given health state is measured in utilities (see Section 5.2 below) which represent the preference for a given health state relative to other health states

CUA shows how an intervention extends people's lives (life year gains) and improves the quality of life compared to alternative options. The use of QALY as a measure of health outcome enables comparisons to be made across disease areas, and thus are particularly useful for broad-based resource allocation decision-making.

2.5. Cost benefit analysis

CBA measures both costs and effects of interventions in the same units, normally monetary. With this type of analysis, health (and potentially other benefits of health care) has a monetary value placed on them. This monetary value might be based upon someone's productive worth or by estimating willingness to pay for the specific health care or intervention. There are challenges in valuing benefits in this way. For example, great care would be needed when valuing benefits based on someone's productive worth as such an approach can systematically bias against those on lower wages and salaries. In general researchers and policy makers can be averse to placing a monetary value to life. Furthermore, many published studies that purport to be a cost benefit analysis do not attempt to measure the benefit of care but rather equate costs with monetary savings – this makes them cost analyses only.

3. MEASURING AND VALUING COST

3.1. Which costs to include?

Economic evaluations need to identify all the important and relevant costs of alternative interventions(29,32). A common pitfall in economic evaluation is losing sight on what costs should be measured. The key is understanding the opportunity costs. As described in Box 1, the perspective of a study should inform what specific costs are appropriate to include in the analysis. Which perspective should be adopted depends upon where differences are expected to be incurred and what costs are relevant to the decision-maker. In CMA, CEA, CUA and CBA identical costs can be excluded as they would not contribute to the difference in costs.

3.2. Correcting for the effects of inflation

When estimating costs, we often measure the direct costs that are closely related to healthcare and any type of care because of illness. The easiest way to present costs is relative to a specific year (e.g., 2020). However, as costs change over time, this needs to be accounted for in the analysis. Costs incurred in previous years should be inflated using published inflation indices such as the US Consumer Price Index (www.stats.bls.gov) or the UK Health services cost index or the Retail Price Index (www.statistics.uk.gov).

3.3. Discounting future costs

When costs occur is also important to consider in an economic analysis. People tend to prefer to receive income now but to defer costs until the future. What this means is that costs (and savings) that occur in the future are given less weight in an economic analysis as compared to costs that occur in the present.

People have time preference for money and futures costs should be discounted to represent present value. Investment in preventative healthcare reduces the possibility of costlier problems in the future. Economic analyses use discount rates to estimate the net present value of future costs. There is some debate about the appropriate discount rate(33-35) but many international studies use a discount rate of 3-5% per annum.

4. MEASURING AND VALUING HEALTH BENEFITS

As described in Section 3 above, the nature of assessing benefits between the different types of economic evaluation varies consid-

erably. This section focuses on how health benefits are measured. This is because there is an increasing interest in the use of patient reported outcome measures more generally in health research but also that these measures can be used in CUAs.

4.1. Health status and quality of life measures

There are several validated health status measures that are frequently used which describe an individual's current health state. These instruments are referred to as heath related quality of life (HRQoL) measures and they can be either condition specific or generic. Condition specific measures, as the name implies are designed to focus on a specific condition and as such have limited or no applicability to other conditions. Generic measures in contrast are designed to measure impact of health across many conditions and as such can be used draw comparisons between treatments for different conditions.

With respect to incontinence there are numerous clinical measures used e.g., 24-hour pad test, voiding diary or urodynamics. These clinical measures can be useful, but they may reflect the impact of the condition or changes in the severity of that condition on an individual. It is for this reason a variety of validated condition specific HRQoL instruments for OAB, prolapse or incontinence are used (e.g., Incontinence quality of life (I-QOL)(36). Generic measures, for example EQ-5D(37) and SF-12(38), often consider a broad range of dimensions of quality of life using phrasing that make them relevant to multiple conditions. Although generic quality of life measures have broader applications, comparisons of treatments will usually require an algorithm to generate a summary score and not all measures have an algorithm.

Both condition specific and generic measures of HRQoL can be used in CEA (with results presented as the incremental cost per unit change in HRQoL or incremental cost per additional person achieving a minimally important difference), however, they can be of limited value for economic evaluation if their scoring algorithm is not based upon the preferences of patients or the public for health.

4.2. Utility measurement

A feature of CUA is the health effect considered including change in quantity and quality of life, with valuation of quality of life based on formal consideration of preferences for the health states(29). The

Instrument	Description
ED-5D	The most commonly used MAU instrument is the EQ-5D(37). The EQ-5D is made up of 5 attributes mobility, self-care, anxiety/depression, usual activities and pain/discomfort. In the original instrument (the EQ-5D-3L) each attribute has 3 severity levels: no problem, some problems and major problems. More recently, a new version, EQ-5D-5L, which has increased the number of severity levels for each attribute to 5 has been developed. Value sets can be identified from the tool developers' website (www.healthfoundationb.org) as can country versions of the questionnaires. It is also possible to convert questionnaire responses from the EQ-5D-5L into the older 3L value set using the results of validated mapping studies(40).
Short Form 6D (SF-6D)	This instrument is based on the popular Short form 36 (SF-36) and it can also be derived from the SF-12. The SF-6D consists of a multi attribute clarification system with six attributes: physical functioning, role limitations, social functioning, pain a, mental health and vitality, developed from information collected from the SF-36(41) questionnaire and a scoring table. The initial scoring model was developed using standard gamble methods on a random sample of the general population in the UK(42).
Health Utilities Index (HUI)	The HUI(43) consists of HUI2 and HUI3. The HUI2 classification system includes 7 attributes: Sensation, Mobility, Emotion, Cognition, Self-Care, Pain and Fertility – each with 3 to 5 levels. The HUI3 classification system comprised of 8 attributes – Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain – each with 5 or 6 levels of ability/disability. Each has a health status classification system and a scoring formula based on standard gamble utilities measured from the general population. The scores are on the conventional dead (0) to health (1). HUI3 should be used as the primary analysis as it has the more detailed descriptive system, full structural independence and population norms. Whilst the HUI may be more sensitive for some conditions it is worth noting that the value set was derived from a Canadian population only.
15D	The 15D is a less commonly used generic, comprehensive, 15-dimensional, standardized, self-administered measure of health-related quality of life (HRQoL) that can be used both as a profile and single index score measure(44). The dimensions include breathing, mental function, speech (communication), vision, mobility, usual activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, sexual activity, and depression. Each dimension is divided into 5 levels. The single index score (15D score) on a 0-1 scale, representing the overall HRQoL, is calculated from the health state descriptive system by using a set of population-based preference or utility weights.
Assessment of Quality of Life (AQoL)	The AQoL(45) is a multi-attribute utility measure for use in economic evaluation, measuring health-related quality of life. The AQoL measures 5 dimensions: illness, independent living, social relationships, physical senses and psychological wellbeing. Each has three items. The lower bound of the utility score is -0.04 and the upper bound is 1.
King's health questionnaire (KHQ)	There is also a mapping of the King's Health Questionnaire to utility weights, and the OAB-q questionnaire (46,47) (Brazier J et 2008, Yang Y. et al 2009). These mapped algorithms have shown responsiveness but, as with all tools, a significant difference does not imply a meaningful difference. For example, a 10 point increase from base-line has been suggested to represent a minimally important difference on the OAB-q(48).

Box 2: Summary of the more common HRQoL tools used as the basis for estimating health state utilities

measures of these preferences are typically described as health state utilities. To understand utilities, consider the following: most people would prefer to be healthy over a given period of time rather than suffer constant urinary or faecal incontinence. Utility measurement refers to valuing these preferences on a scale where the best state of health (normally taken to be perfect health) is score 1 with death scored as 0. For example, if the measured utility for urinary incontinence is 0.60 and treatment improves this to 0.70, then the value of the treatment is 0.70 – 0.60 = 0.10. If this utility gain is maintained over time, say for 10 years, then the gain is 0.10 x 10 = 1.00 QALY.

Utilities can be based upon condition specific or generic measures of HRQoL. The use of a condition specific measure allows a single metric combining quantity and quality of life to be estimated but is not best suited to compare across conditions e.g., compare treatments for faecal incontinence to with those to prolapse, if they have impacts on different dimensions of health. Generic measures however are routinely used compare the effect of interventions in different health fields, or different interventions within the same field. For example, the QALYs gained from treatment for incontinence could be compared with those gained from treatment for depression.

Direct and indirect methods have been used to elicit utilities(39). The most common direct elicitation methods for valuation include time trade off (TTO), standard gamble (SG), the visual analogue scale (VAS). For a description of these methods, see the previous chapter in this ICI series.

Indirect utility elicitation is frequently used in clinical research because it is low cost and easier for participants than direct elicitation. Most indirect measures are based on multi-attribute utility (MAU) instruments, which split HRQoL into health domains (e.g., mobility and emotions). Respondents provide estimates for each attribute, which are then 'valued' based on pre-defined weights and summarized into a single utility score. Table 1 summarises key aspects of commonly used instruments in incontinence and prolapse research.

5. TRIAL AND MODEL BASED ECONOMIC EVALUATIONS

The assembly of the data that is required for an economic evaluation can take the one of two stylised forms(29). First it can be collected as part of a single empirical study like a randomised trial. This is often called a within trial economic evaluation(49). The alternative approach is to take data from multiple sources and to integrate them into a mathematical model(50). These two approaches are best thought as being complementary and indeed some economic evaluations will include an element of modelling.

5.1. Within trial analysis

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has issued guidance on within trial analysis(51). Trials themselves are designed to determine the relative effects (i.e., efficacy, effectiveness and safety) of interventions (i.e., new drugs, devices or ways) in delivering care. As estimates of costs, and cost-effectiveness can be thought of as just other measures of relative effect, it may be possible to integrate an economic evaluation into a study. This can have numerous benefits. First, a well-designed RCT can estimate marginal difference in costs and outcomes in an empirically unbiased manner. Second, the additional research cost and burden of collecting the economic data can be modest. Third, the data collected as part of a trial can be used to explore statistical imprecision surrounding costs, effects and cost-effectiveness. As cost-effectiveness is a ratio of two correlated measures, standard statistical tests like t-tests should not be used to do this. More frequently bootstrapping is used to estimate statistical imprecision.

However, not all RCTs are ideal candidates for incorporation of an economic evaluation. One reason for this is that the external validity of a trial (its generalisability) can be limited due to restrictive inclusion criteria. Exclusion criteria are often used to increase safety and improve statistical power; however, the results may not generalize to broader populations. There are pressures to balance a trial's internal validity and its external validity, and the Precis 2(52) provides tools for understanding factors that affect the internal and external validity (https://www.precis-2.org/). A second reason that may restrict a trial's usefulness is that the trial may not compare the most relevant alternatives, or the alternatives compared may not reflect current practice. A final issue is that the follow-up period of many trials is too short to capture all relevant costs and effects.

5.2. Model based economic evaluations

An economic evaluation model can be based upon a single empirical study, or a synthesis of multiple studies. Common arguments advanced for the adoption of model based economic evaluations include:

- Structure the economic question and compare all relevant alternatives
- Extrapolate beyond observed data
- Link intermediate and final endpoints (e.g., death)
- Non-availability of parameter estimates
- Generalise results to other settings/patient groups
- Use synthesised evidence and facilitate head-to-head comparisons where RCTs do not exist
- Enables all variability and uncertainty to be explored
- Indicate the need for further research

Reflecting on these bullet points are the 5 steps involved in building an economic evaluation model. The first step involves identifying the structure of the problem and this requires the listing of all decision alternatives, all clinical outcomes, the possible sequence of events, and the time over which the model will measure. Step two involves assigning probabilities to all chance events (e.g., death). Step three involves quantifying the benefits (e.g., QALYs) for all outcomes. The fourth step involves the mathematical calculation of expected value for each strategy in order to identify the preferred strategy. The final step involves conducting sensitivity analysis to check that the model is robust across a range of clinically meaningful possibilities. As an extension of this final step, it also identifies key areas for further research.

Every economic evaluation model involves some assumptions. Frequently, assumptions are needed to incorporate trial data in the model. For example, a common assumption is that the effect shown in a randomised trial is generalizable to the modelled population. Published economic evaluation models should include a table of assumptions along with other data inputs; frequently this is the first table in the study report.

The structure of the problem (step 1) often points to a specific type of economic evaluation model. A taxonomy of model types is provided by Brennan and colleagues(53) and has recently been updated(54). Common modelling approaches are: Decision trees; Markov models; Individual patient simulation models and discrete event simulations.

5.2.1. Decision tree analysis

Decision trees are so named because they look like a tree with a trunk, branches and leaves. They are best suited to addressing questions where there is no interaction between patients (e.g., the treatment of one patient does not affect the treatment of another) and for when events that might occur are not recurrent. In a decision tree, there is a distinction between a decision node and a chance node. A decision node is a point where a choice is made by the decision maker (typically a physician or patient). For example, for a woman with stress incontinence, the choice to operate (yes or no) would be represented with a decision node. A choice must have at least 2 mutually exclusive options; though a choice involving more than 2 options are possible. This means that a woman could not choose both an operation and no operation. A chance node is a point where chance determines what happens next. For example, if surgery is chosen, then there is a chance that the surgery will not be successful and a chance that it will be successful. The point where these two alternatives might occur is represented by a chance node. As can be seen from this case the two alternative changes must be mutually exclusive, and collectively be exhaustive (the surgery will either work or it will not). Collectively the probability of these two events happening must sum to 1).

In addition to chance and decision nodes, a decision tree also includes terminal nodes. These nodes are the final outcomes (the payoffs) for the pathway taken (e.g., cured/not cured, cost). What outcome is chosen will depend upon the type of economic evaluation conducted (see Section IV).

Once the structure of the decision tree has been defined then the next step involves identifying probabilities at each chance node. These data could come from a single empirical study or they might come from the published literature. In both cases consideration needs to be given as to whether these data are appropriate. Where data are obtained from the literature this should be systematically identified with clear inclusion and exclusion criteria applied so that problems of distorted assembly are avoided. In addition, where possible, the probabilities data on the distribution around these probabilities should be sought. For example, for surgery the probability of success might be 58% with a 95% CI 51-68%. If surgery were being compared to medical management, then the probability of success might be similarly estimated or if data from a trial or meta-analysis were available then a relative effect could be taken from there so that the probability of success for medical management is the probability of success for surgery multiplied by the relative effect size.

Once probabilities are assigned then values for both costs and outcomes must be assigned. These are measures of cost and effects must be assigned to the nodes. The effect measures used can be ones consistent with any of the forms of economic evaluation set out in Section III. With costs, effects and probabilities assigned, one can then "run" the decision tree. Running the model involves starting at each terminal node and working left or backwards. In the example below, the expected value for the surgical survival node is 3.8 QALYs (see Figure 1). A similar approach is used to work out the expected values for each of options that are decided between at the decision node.

5.2.2. Markov models

A decision tree can get very complicated if we need to consider costs and effects over time for a complex and changing condition. A person, for example, could get surgery for stress incontinence, but over time, we need to include the potential for surgical failure. One common approach to capture this is to use a Markov model. In

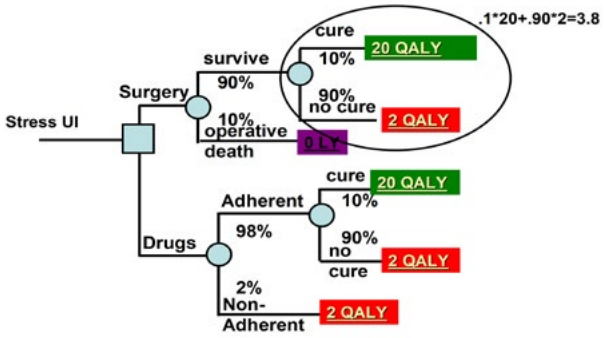

Figure 1: Example of a decision tree for the comparison of surgery with drug therapy for stress urinary incontinence

a Markov model, the pathways of care and changes in health over time for a cohort of patients is described as a set of mutually exclusive health states that the individual can move over time. The duration of time considered by the model is called the time horizon and it should be as long as necessary to capture all impacts on costs and effects. For this reason, a lifetime time horizon is often adopted. At least one of the states is what is called an absorbing state – that is a state the individual can enter but cannot leave. Commonly in Markov models, death is represented as an absorbing state.

Some aspects of the Markov model construction are similar to a decision tree. Setting up the model is quite similar. One must identify the health states and the transition probabilities. What is quite different is that one must determine the cycle length—the rate at which you allow people to change states. The cycle length should be a clinically meaningful period of time and this choice is also frequently affected by the availability of data. There may be publications showing annual failure rates for surgery and so one could choose an annual cycle. Given that the cycle length might be lengthy, it is sometimes quite appropriate for states to have decision trees embedded within them to capture the impact of transitory events e.g., infections, or to determine what future events are possible.

For each state within the model both costs and effect measures are assigned. Costs reflect the care given during time spent in that state and effect measure may reflect events that occur in that state or may be represented by a health state utility. The model works by

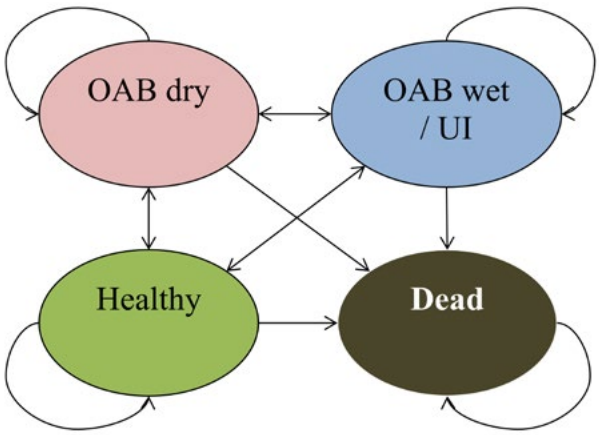

Figure 2: Example of a Markov model for use when evaluating treatments for overactive bladder

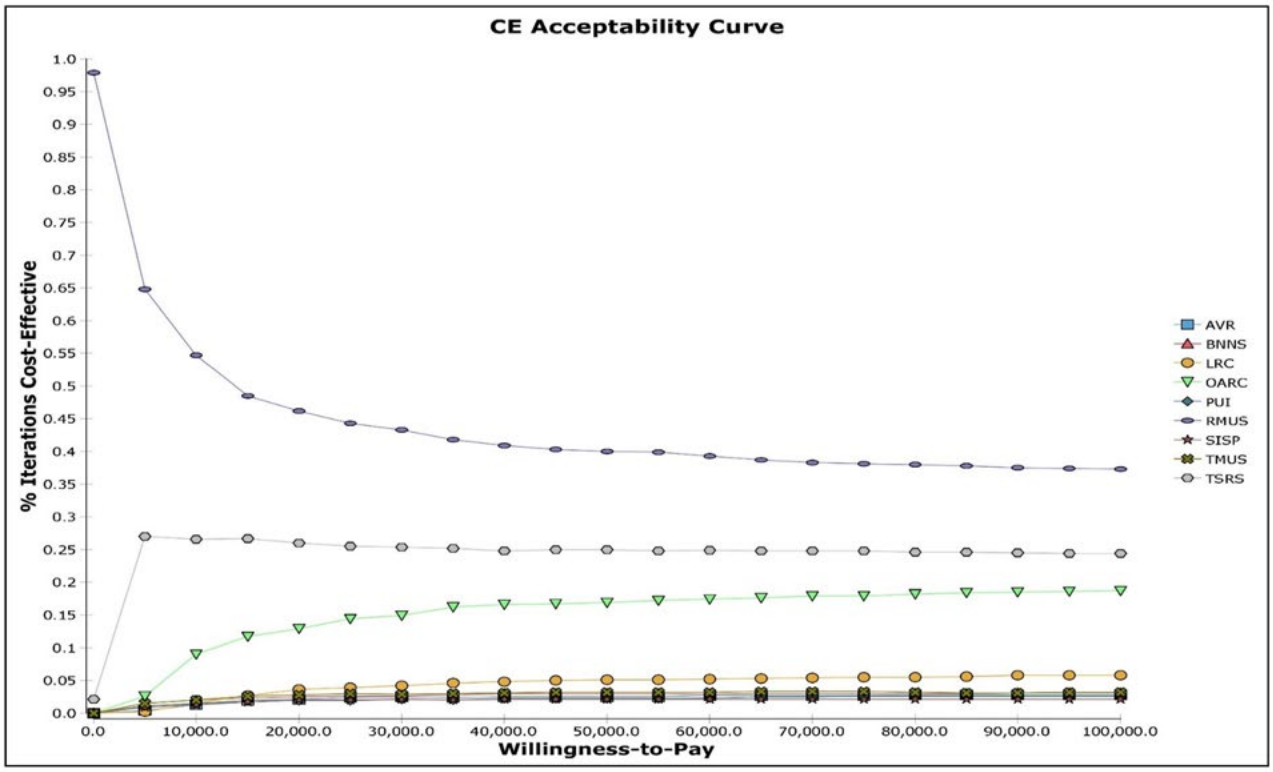

Figure 3: Cost-effectiveness acceptability curves for the nine strategies: lifetime time horizon

making calculations for each cost and effect measures for each cycle and summing these together to produce a cumulate estimate of cost and effects over the time horizon modelled. Figure 2 shows a very basic four-state Markov model for people with overactive bladder. At each time point, a person has to be in one (and only one) of the states. But at the end of each cycle, the individual can move to another state, shown with arrows, depending on the possible states and a probability. If the person dies, they enter and cannot leave this health state.

5.2.3. Microsimulation models

In a Markov model one important assumption is that the models are memoryless. That is prior treatment and events do not influence the success or otherwise of future treatments. One way around this is for the model to include sequences of events in what are called tunnel states. For example, if after surgery a person could have repeat surgery the costs and outcomes for that second (or third, etc) surgery can be modelled as a separate set of states. This can quite quickly become very complicated. In such circumstances an alternative is to model a set of individuals. Each individual moves through the model one at a time and accumulates their own unique history (an example of this form of model is that by Javanbahkt and colleagues modelling surgical treatments for SUI described in Section 4.3.2 below).

5.2.4. Discrete Event Simulations

Discrete event simulations address some of the challenges that face Markov models and microsimulations. They allow for nested, interdependent events and can be especially useful when considering situations where an individual is asked to queue or wait for treatment or where the use of care by one person may restrict the access (or perhaps outcomes of care) of others. Discrete event simulations have not been widely used to study pelvic floor and bladder issues.

6. SENSITIVITY ANALYSIS

Regardless of whether the type of economic evaluation is a CMA, CEA, CUA, etc. or a within trial or model-based analysis all economic evaluations should include sensitivity analysis. Sensitivity analysis can be used to vary one or more parameters at a time to assess the effect of these changes on the output. One and two-way sensitivity analyses are useful for identifying the relative leverage across the parameters.

For the decision model to include uncertainty, a probabilistic sensitivity analysis is required. This involves running Monte Carlo micro-simulations where transition probabilities are chosen at random from a distribution. These Monte Carlo simulations run cohorts of patients through the model many times. The results yield information on the expected values as well as the uncertainty around that expected value. These complex models can be built in Excel, but some people prefer specialized software such as TreeAge. Over the past decade, there has been considerable discussion on how to best present results from decision models. Readers will probably encounter cost-effectiveness acceptability curves (CEACs), which present CEA results with uncertainty (Fenwick & Byford, 2005). An example of a CEAC is shown in Figure 3.

7. ELEMENTS OF A SOUND ECONOMIC ANALYSIS

Economic evaluation readers need to know that the methods employed in the study are appropriate and that the results are valid to establish that the results are useful in their decision-making context. This section draws on a list of the elements of a sound economic evaluation described in Drummond et al (29) and the BMJ guidelines(55) for submitting and reviewing economic papers. For those preparing economic evaluations we refer readers to the CHEERS checklist for the reporting of economic evaluations(56). It may not be possible for every study to satisfy all the points, but the systematic application of these points enables readers to identify the strengths and weaknesses of an economic evaluation (Box 3).

8. IMPLEMENTATION SCIENCE

Implementation scientists are focused on reducing gaps in the delivery of evidence-based care. They test strategies to reduce these gaps. Some tweaks, such as shortening the time horizon and changing the perspective from societal to payer, helped, as was noted in the 2016 CEA Panel(58). The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) developed a budget impact analysis (BIA) that is designed to examines the costs for the decision maker. Increasingly BIA and other economic tools are being used in implementation science, but these analyses differ from the traditional CEA.

BIA was developed to inform a decision maker, often a hospital director, on the budgetary ramifications for a decision(59,60). A BIA will often focus on the decision maker's costs over a short time frame (e.g., 1-3 years). Other parameters in the model, such as patient characteristics or input costs, can also be tailored specifically for the decision maker. Making decisions based solely on a BIA can lead to suboptimal societal results(61) but it may lead to an optimal decision for the hospital director.

Economic evaluation in implementation science is a rapidly evolving area as researchers test alternative strategies to improve the quality of care. These strategies include creating educational material, obtaining leadership support, finding additional funding, and using an internal facilitator (62). They are also highly heterogenous in their resource intensity. One of the challenges is being able to differentiate the cost of using different implementation strategies from the cost of evidence-based treatment. In general, the decision maker needs information on costs because they can identify how these costs change over time with the phase of deployment (e.g., initial adoption versus sustained use)(63,64). Economic evalua-

1. Research question
It is important that the study has a well-defined question, posed in an answerable form. The question should clearly identify the alternatives being compared and the perspective (see Box 1) from which the comparison is to be made.

2. Clear description of competing alternatives
A comprehensive description of the competing alternatives is essential for the readers to judge the applicability to their own setting. This can help assess whether any costs or outcomes have been omitted from the analysis (see also point 4 below).

3. Establish the effectiveness of alternatives
How has the effectiveness of the alternatives compared been assessed? Evidence on effectiveness may come from a single study such as a randomised trial or from a systematic review of several clinical studies and used in an economic model (see Section III.5).

4. Identify all important and relevant costs and outcomes
The study should also ensure that all the important and relevant costs and outcomes for each alternative have been identified.

5. Measure cost and outcomes in appropriate units prior to valuation
Once the important costs and outcomes have been identified they must be measured in appropriate physical and natural unit e.g., number of pads used.

6. Value cost and outcomes appropriately
The sources and methods of valuation of costs and outcomes should be clearly stated to ensure that they are credibly valued (see Section III.3.1). The approach used to estimate costs and outcomes has to be clearly described. This includes all sources of costs and utilities.

7. Adjust cost and outcomes for differential timing
The costs and outcomes need to be adjusted for differential timing as they might not all occur at one time point (see Section III.3.3).

8. Perform incremental analysis of costs and outcomes (see Section III.2.2)
If one intervention is more effective and more costly than another then an ICER should be calculated. Interpretation of the ICER is based on what is the maximum acceptable value for a unit of effectiveness, such as a QALY, this value varies from country to country.

9. Perform sensitivity analysis (see Section III.6)
Every evaluation will have some degree of imprecision or other form of uncertainty. Briggs et al (2000)(57) identified several types of uncertainty. To explore the impact of this uncertainty sensitivity analysis is performed.

10. Presentation and discussion of study results
Presentation of the economic evaluation should include all the issues of concern to users.

Box 3: Key features to consider when reading an economic evaluation

tions are increasingly common in implementation science and there is a growing literature to guide researchers interested in implementation issues (65-67) (Wagner, 2020; Wagner, Dopp, et al., 2020; Wagner, Yoon, et al., 2020).

IV. SUMMARY OF RECENT ECONOMIC EVALUATIONS

1. URINARY INCONTINENCE

1.1. Non-surgical interventions for urinary incontinence

1.1.1. Behavioural therapies

Women may prefer conservative/behavioural therapy, at least as a first-line treatment, because it is non-invasive with few adverse side effects. Conservative/behavioural therapy, (hereafter referred to as behavioural therapy) covers a class of techniques for preventing incontinent episodes through behaviour change. The most common behavioural treatment is pelvic floor muscle training (with or without biofeedback) (68)(10).

There is considerable variation in behavioural techniques and their adjuvant use of professional staff. Some modalities use intensive, one-on-one clinician-led training with direct verbal feedback often involving physical examination of the pelvic floor, while other options are more focused on group training or self-care techniques. The self-made techniques are the most useable options for the incontinent women. The level of intensity is important as it not only affects the effectiveness, but it also affects the cost of the intervention, with more intensive interventions generally being more effective and more expensive than less intensive options.

Since the last edition three economic evaluations in the use of PFMT were identified. Hagen et al (2020) (69) compared basic versus biofeedback-mediated intensive pelvic floor muscle training (biofeedback pelvic floor muscle training) for women with urinary incontinence. The results indicated that at 24 months, biofeedback pelvic floor muscle training was not significantly more expensive than basic pelvic floor muscle training, but neither was it associated with significantly more quality-adjusted life-years. The probability that biofeedback pelvic floor muscle training would be cost-effective was 48% at a £20,000 willingness to pay for a quality-adjusted life-year threshold.

In the second study Sjostrom et al (2017)(70) performed a cost-utility analysis of SUI treatment with the app, Tät (pelvic flow exercises for women), compared with no treatment. They estimated that the extra cost per QALY for the app treatment was €7615.5, and the sensitivity analyses indicated a potential range of −€2425.7 to €14,870.6 and they concluded that self-management of SUI with an app for PFMT is a cost-effective first-line treatment alternative. In a third study Simpson et al (2019)(71) performed a cost-utility analysis of nonsurgical treatments; pelvic floor muscle therapy (PFMT), a disposable tampon-like device (Impressa), a self-fitting intravaginal incontinence device (Uresta), and a traditional incontinence pessary for stress urinary incontinence (SUI) in healthy adult women with a health system perspective over a 1-year time horizon. They concluded that their findings favoured PFMT as the most cost-effective nonsurgical treatment option for SUI.

A brief economic commentary was presented in an update of the Cochrane Review on this topic(68) based on the data available (31 trials involving 1817 women from 14 countries. Trials were of small-to-moderate size, with follow-ups generally less than 12 months and many were at moderate risk of bias). The review of effects showed that PFMT can cure or improve symptoms of SUI and all other types of UI. It may reduce the number of leakage episodes, the quantity of leakage on the short pad tests in the clinic and symptoms on UI-specific symptom questionnaires. The brief economic commentary summarised the existing economic evaluations and it suggested that in terms of cost-effectiveness PFMT looks promising.

1.1.2. Pharmacotherapy for incontinence

Although pharmaceutical companies must show that a new drug is safe and efficacious prior to approval and marketing, the requirement for evidence of cost-effectiveness (i.e., whether the new drug is cost-effective compared to another treatment), varies from country to country. For example, the U.S. Food and Drug Administration does not require economic data in its review of a new drug but leaves economic questions to the purchasers (e.g., insurance companies, government purchasers or individuals). Similarly, in other countries the European Medicines Agency in the European Union and the Medicines and Healthcare products Regulatory Agency in the UK also do not require evidence of cost-effectiveness. However, in many of these countries an extra 'national' agency does make judgements about cost-effectiveness. An example of this is the National Institute for Health and Care Excellence (NICE). NICE require all drugs (and other therapies) to be evaluated using a standard reference case methodology. With this methodology a therapy is not recommended if the incremental cost per QALY is above £20,000 unless there are other reasons e.g., fairness or end of life of care arguments. This threshold has not changed for several years and hence in real terms it is reducing (because of the effects of inflation). There is also some pressure to reduce this threshold because it appears higher than the value placed on a QALY in real world decisions(72). In Australia, manufacturers likewise must prove cost-effectiveness, but there is no explicit threshold to be listed on the Pharmaceutical Benefit Scheme (whereby patients pay a subsidized cost for the drug). However, only therapeutic efficacy and safety must be shown for it to be available in Australia as a non-subsidized "private" prescription. Many purchasers (as in Australia) have formularies or lists of medications that they are willing to pay for, and the economic evaluation is frequently part of the request to place the new drug on the formulary. The same situation exists, for example in the Czech Republic. In the next sections, we review the literature since the prior Committee publication in 2016 on the economics of drugs for incontinence and overactive bladder.

We identified no cost-effectiveness articles related to pharmacotherapy for stress urinary incontinence (SUI) in the past 3 years since the prior ICI report in 2016. This is consistent with the lack of available pharmacological therapies for stress incontinence. (NOTE: Duloxetine is approved only by the European Medicines Agency, an Agency of the European Union, for depression, anxiety and diabetic peripheral neuropathy.)

For urge urinary incontinence/over-active bladder evaluations please see Section IV.2.1.

1.2. Containment products

Data on the overall cost of incontinence/containment products such as pads utilized in the US is over 1 billion US dollars. There is no precise indication of the real place for absorbent products in the management of urinary incontinence, regardless of the aetiology of the incontinence or the clinical context (73). Nevertheless, sometimes, it is not possible or appropriate to promote continence, and

the focus shifts to managing incontinence to enable the person to maintain dignity and avoid the complications of poorly managed urinary incontinence(74).

For the current update no economic evaluations were identified in this area. Given the many different designs that are available, their different suitability's for the type of incontinence and the characteristics of the person using them, this represents a significant evidence gap. This gap is compounded when it is noted that given the numbers that suffer from incontinence the use of pads and other continence products is substantial. From a cost perspective in many countries these are available over the counter without prescription and without reimbursement(73). This means that the costs fall on individuals and their families, many of whom may already be suffering significant financial hardship. Prescription for incontinence products is available in some countries such as the UK and the Czech Republic although, access to this prescribed care may be limited.

1.3. Surgical interventions for stress urinary incontinence

The review of economic evaluations of surgical interventions for stress urinary incontinence from across the world is hampered by the variability in health care delivery systems and variability in costs(75)**.** A recent systematic review of economic evaluations focusing on the cost estimates illustrated the hetrogeneity in costs that existed between studies conducted in 13 countries(76). A second systematic review (77) reviewed 26 economic evaluations, of which 13 were model-based analyses. This review found that MUS and colposuspension (open/laparoscopic) were the most frequently assessed procedures over one and five years. The identified studies suggested that MUS and single-incision slings are among the most cost-effective. However, caution needs to be exercised when interpreting reviews of economic evidence. It is for this reason that the guidance from Cochrane on the synthesis of economic evaluations emphasises that the focus of the review is to understand the causes of heterogeneity rather than come to a single precise estimate of cost (or cost-effectiveness) that is not applicable to anyone(76).

In terms of new economic evaluations there have been four evaluations which have been published. Of these, 3 related to surgical treatments of SUI in women and one related to surgical treatments of incontinence post-prostatectomy. With respect to surgical treatment of SUI, the first of these was by Lier et al. (2017)(78) who compared TOT with TVT as a surgical treatment of SUI in 195 women for 5 years, in Canada**.** TOT saved an average of $2368 and gained 0.04 QALYs when compared against TVT which suggested that TOT is potentially more cost-effective than TVT.

In the UK the cost-effectiveness of nine common surgeries for SUI was evaluated as part of a comprehensive health technology assessment (77). The surgeries considered were: Retropubic mid-urethral slings (MUS)/ TVT against; transobturator MUS (TOT), traditional sling, single incision sling, open retropubic colposuspension, bladder neck needle suspensions laparoscopic colposuspension, anterior vaginal repair, and urethral bulking agents. They utilized a Markov microsimulation model from the UK NHS perspective over 10 years and lifetime time horizons(79). Evidence on effects came from over 120 trials combined using network meta-analyses. Other data came from existing economic evaluations(80), other focused searches. The study suggested that retropubic mid-urethral slings would be the most cost-effective option for SUI treatment. Sensitivity analysis showed that complication rates and relative treatment effectiveness appeared to have the largest effects. They suggested that further long-term research of initially appearing cost-effective procedure (e.g., retropubic-MUS) and complications management might confirm the safety, effectiveness and cost-effectiveness of such interventions.

In the third study Electrical Muscle Stimulation (EMS) was evaluated for the treatment of SUI amongst women in the UK (81). Over the lifetime of women, EMS results in reduction of costs by £250 and £327, and an increase in 0.03 and 0.13 QALYs in the "cure" and "improvement" analyses, respectively. In a probabilistic sensitivity analysis EMS cost-effectiveness is greater than 74% at a cost per QALY threshold of £20,000, the threshold level adopted by NICE in the England.

With respect to surgery for incontinence post prostatectomy, a Canadian-based group(82) utilized a Markov model to evaluate the surgical options. Artificial urinary sphincter was concluded to be more cost-effective than male slings over one year. Similar conclusions were drawn when the analyses were replicated for five- and ten-year' horizons.

2. URGE URINARY INCONTINENCE/OAB

2.1. Pharmacotherapies

In contrast to stress urinary incontinence some economic evaluations were identified in the treatment of overactive bladder (OAB). OAB is a symptom-driven condition and in identified studies the costs of physician visits and incontinence pads were included in nearly all analyses. However, the wider impacts such as OAB associated depression and nursing home costs were rarely included, despite being large cost drivers in cost of illness studies.

Since the last consultation two studies have compared mirabegron versus antimuscarinics drugs(18,83). Arlandis-Guzmán(18) and colleagues modelled the two treatments over a 5-year time horizon, for the Spanish Health Service. The incremental cost per patient with mirabegron 50 mg compared with tolterodine was €196. Taking a wider societal perspective gave an incremental cost of €157. The gain in QALYs with mirabegron compared with tolterodine was 0.0127 QALY. Consequently, the incremental cost per QALY with mirabegron versus tolterodine was €15,432 and €12,425 for health service and societal perspectives respectively. The probability that mirabegron would be cost-effective at a willingness to pay threshold of €30,000 was: 70% (health service) and 71% (societal) versus tolterodine. Other drugs were also compared with mirabegron. For these comparisons mirabegron had the following probabilities of being cost-effective; 94% (health service and society) versus solifenacin 5 mg; 84% (NHS) and 85% (society) versus solifenacin 10 mg; 96% (health service and society) versus fesoterodine 4 mg; 98% (health service) and 99% (society) versus fesoterodine 8 mg.

The second study was conducted in Japan. In this study, mirabegron 50 mg was reported to be cost-effective compared to treatment with antimuscarinics(83). Over a 5-year time horizon mean QALYs were 3.860 for first line mirabegron and 3.839 for first line tolterodine. Costs per patient were ¥526,191 and ¥472,390 for first line mirabegron and tolterodine respectively. This resulted in an incremental per QALY of ¥2,565,927 for first line mirabegron compared with first line tolterodine. This value is below the willingness-to-pay threshold of ¥5 million per QALY used in Japan. In more severe states, the incremental cost per QALY however exceeded ¥5 million.

A further three studies did not compare specific treatments rather they compared treatment by pharmacotherapy with non-treatment. To do this they used a range of different study designs. None of these studies were explicitly described as economic evaluations but for each the results could be reinterpreted as cost-consequence analyses. These studies all used non-randomised designs which may be prone to selection biases. Therefore, care has to be taken not to over interpret their results.

A cross-sectional study using data from an internet-based questionnaire of a nationwide sample of 75,000 adults (US National Health and Wellness Survey) evaluated the impact of treating urge and mixed UI. It was used to look at OAB treatment users compared with non-treatment users (i.e., those who self-reported that they never used treatment and whose condition reportedly interfered with life activities or was difficult to manage) (84). Outcome measures included healthcare utilization and work productivity and activity impairment questionnaire-based scores. Direct and indirect costs were estimated using labour and medical expenditure data sources ($2008). Treatment (vs. non-treatment) users were more likely to be female (81% vs. 70%), older (mean = 63 vs. 53) and reporting more moderate-to-severe OAB (71% vs. 53%; all $p < 0.05$). Adjusting for covariates, treatment users had significantly lower activity impairment, more provider visits and higher total direct costs ($27,291 vs. $21,493) per year. Though this is a non-randomised design and as such prone to selection biases, it is suggestive that treatment for UUI/MUI may help with symptom management and lessen activity impairment but at higher costs compared to never users.

A study, performed by a pharmaceutical company, concluded that OAB treatment resulted in cost savings from the US payer perspective compared to no OAB pharmacotherapy for vulnerable elderly OAB patients(85). Costs of treating OAB with fesoterodine compared to no OAB pharmacotherapy were assessed using a decision analytic cost model. Implicit in this model were estimates of effectiveness. Vulnerable elderly OAB patients were defined as age ≥65 years with 2-15 UUI episodes/day and at risk of deteriorating health by a score of ≥3 on the Vulnerable Elders Survey (VES)-13. Fesoterodine treatment response was defined as no UUI episodes after 12 weeks of treatment and assumed that was maintained up to one year. OAB-related costs included OAB drug costs, healthcare resource use (inpatient hospitalization, outpatient visits, and physician office visits), and OAB-related co-morbidities (falls/fractures, urinary tract infections, depression, and nursing home admissions; $2013). It was reported that treating OAB patients could save $1616 per patient vs. no OAB pharmacotherapy. Costs were most sensitive to changes in fesoterodine efficacy followed by the annual costs of inpatient hospitalization. This analysis did not include cognitive impairment, assumed a low prevalence of UUI (13.5%), used a high probability treatment response (51% no UI episodes at week 12).

A further Spanish retrospective study looked at the cost-effectiveness of treatments for 3094 actively working patients initiating first treatment with antimuscarinics (fesoterodine, solifenacin or tolterodine) from 31 primary care centres (86). The study compared fesoterodine versus solifenacin and tolterodine. Adherence (medication possession ratio) was 90%, 87% and 86%, respectively). Treatment persistence was 40% vs. 35% and 34%) and days of sick leave were 5, 10 and 9 days. Cost per patient after correcting for covariates were €371, €703 and €683 in €2014; all $p < 0.05$). While it is not clear how sick leave and productivity were assessed, the results suggest that initiating treatment with fesoterodine to treat OAB (compared with solifenacin or tolterodine) had fewer days of sick leave, lower loss of productivity and was lower in cost.

2.2. Surgical interventions

Since the last consultation four economic evaluations have been published that have considered surgical interventions for OAB. One compared OnabotulinumtoxinA (Botox) 100 U with best supportive care from a UK context (87). Two compared Botox with anticholinergics from a US perspective(88,89)and one compared Botox with sacral neuromodulation using data from nine U.S. centres(90). For the comparison of Botox and best supported care, a Markov model with a 10 year time horizon was adopted. It was reported that Botox lowered total costs and resulted in better quality of life than best supportive care alone. The incremental cost per QALY was less than £20,000 90% of the time in the probabilistic sensitivity analysis conducted(87).

The first of the two studies that compared Botox against anticholinergics found that over a two year follow-up that Botox as a first line of treatment had the highest quality-adjusted life year (QALY) but was more costly that than non-selective anticholinergics(89) but selective anticholinergics were more costly than Botox. Botox was also found to be cost-effective when the costs of any further treatments when initial treatment has failed were included or excluded. The second multicentre considered costs and QALYs for 231 women over a one year follow up(88). The study reported no evidence of a difference in QALYs and costs (i.e., the study was underpowered to detect differences).

The last economic evaluation compared Botox with sacral neuromodulation using data from nine U.S. centres(90). QALYs were reported as comparable but sacral neuromodulation procedures was more costly than Botox, $35K vs $7,460 over a two-year analysis, and $36K vs $12K over a five-year analysis. Based upon these data sacral neuromodulation was highly unlikely to be considered cost-effective compared with Botox.

3. PELVIC ORGAN PROLAPSE

With regard to studies that assessed different management strategies for pelvic organ prolapse (POP) six studies were identified. Two were based on comparison of pelvic floor exercises with other non-surgical treatments and three of the identified studies were economic evaluations of surgical interventions for POP. Three of the identified studies were carried out alongside clinical trials, three studies utilised an economic decision model and one used a within trial approach and a decision model to consider the outcomes at different time horizons.

3.1. Non-surgical interventions for pelvic prolapse

Two studies were identified that considered non-surgical interventions for pelvic prolapse and both of these were within trial economic evaluations and both reported results for a CEA and CUA. Panman et al 2016 (91) compared the use of PMFT with pessaries in woman over a two-year period. Cost-effectiveness was reported as the incremental cost per point improvement on the PFDI-20. The cost-utility analysis reported the incremental cost per QALY, though the sources of the utility values were unclear. The additional cost to improve one point on the PFDI-20 in the pessary group compared with the PFMT group was $77 (USD 2014). The authors inappropriately reported a negative ICER for both the CEA and CUA (which is not readily interpretable). On average however the use of pessaries was more costly but no more effective. A second study by Panman et al (2017) (92) compared PFMT management with watchful wait-

ing. The same cost-effective and cost-utility outcomes as Panman et al (2016)(91) were reported. In the CEA, the incremental cost per unit improvement in PFDI-20 for PFMT compared with watchful waiting was €43 (Euros 2013). For the CUA, the incremental cost per QALY for PFMT compared with watchful waiting was €31,983. Statistical imprecision was explored using bootstrapping. These data suggested that there was a 55% probability that PFMT would be considered cost effective (this form of analysis requires that the probability be estimated relative to a threshold value for the decision-makers willingness to pay for a QALY. However, the threshold value was not stated.

Due to the nature of reporting or the findings themselves the evidence supporting PFMT vs either pessaries or watchful waiting is far from compelling. For example, for the comparison with watchful waiting drawing a firm conclusion based upon the data would be like basing a conclusion on the toss of a coin.

3.2. Surgical interventions for pelvic prolapse

Five economic evaluations comparing surgical interventions were identified. Of these Glazener et al (2017)(93) compared mesh inlay interventions for the treatment of primary and recurrent prolapse in two concurrently conducted randomised trials. A within trial cost utility analysis was undertaken. This analysis took a UK NHS (health service) perspective with participant costs included in a sensitivity analysis. Follow-up was over two years. For those with primary prolapse, standard repair which involved fascia being separated from the vaginal wall and the fascial defect plicated (sutured or buttressed) was compared with standard repair including a biological graft inlay and standard repair with a non-absorbable or combined mesh inlay. When the analysis sought to make the best use of available data and missing data were imputed using appropriate techniques it was found that at a cost per QALY threshold of £30,000 standard repair had a 52% probability of being cost-effective. Synthetic mesh and biological repair had probabilities of 29% and 20% respectively. There were significant patient costs incurred. These included: time spent travelling to and from appointments, time on sick leave and private treatments. However, the inclusion of these costs did not affect the overall conclusions. The results of the primary surgery were extrapolated beyond the trial time horizon to 5 years using a Markov model. In this model, a woman could move between various states of prolapse repair or complications. Standard repair was estimated to be less costly and marginally more effective than either the synthetic or biological mesh. When the decision-maker was willing to pay a maximum of £30,000 per QALY the probability each treatment would be considered cost-effective was 22%, 57% and 21% for standard repair, synthetic mesh and biological graft, respectively.

For recurrent prolapse standard repair was compared to standard repair with a non-absorbable or combined mesh inlay and standard repair with a mesh kit procedure. The probabilities that each treatment was cost-effective at a £30,000 per QALY threshold was: standard repair (32%); mesh inlay (19%) and mesh kit (49%). As for repair of primary prolapse there were significant patient costs, but these were evenly distributed across the groups. The authors conclude that there was no compelling evidence for the use of mesh for recurrent prolapse repair, unless there is significant failure of standard repair over a longer term follow up than the 2 year period reported in the study.

Hemming et al (2020)(94) compared two surgical interventions in the management of both uterine and vault prolapse. Two within trial cost-effectiveness analyses were carried out with a surgical intervention for vaginal hysterectomy in both groups. The uterine group compared uterine preservation with hysterectomy and the vault group compared transvaginal vault surgery and abdominal vault surgery (colposuspension). With respect to the uterine trial, the result of the within trial evaluation, showed additional costs for the uterine preservation group with no significant difference in the amount of QALYs gained at 12 months. The inclusion of costs borne by the trial participants did not impact these conclusions. Extrapolating these results over the patient's lifetime using a Markov model gave similar results to the within trial analysis. The results of the vault surgery trial concluded that abdominal vault repair incurred significant costs but with no evidence of additional QALYs when compared with transvaginal vault repair. Conclusions remained consistent across the sensitivity analyses conducted.

Ohno et al 2016(25) also compared surgical treatments for prolapse in a model-based cost utility analysis from a societal perspective. Despite the authors taking the societal perspective, costs which were reported were only health care costs. This model compared abdominal sacral colpopexy (ASC) against sacrospinous ligament fixation (SSLF). The form of decision model was not described but health service costs were derived from Medicare data. QALYs were derived using utilities based on the HUI3 data taken from the National Population Health Survey (95). The model considered post-operative SUI, recurrent pelvic organ prolapse, and post-operative dyspareunia. All participants in the model were assumed to have a baseline utility of 0.93 (i.e., almost full health prior to surgery). ASC was estimated to be both more costly and more effective than SSLF with an incremental cost per QALY gained of $24,574 (USD 2013), lower than the proposed threshold of $50,000 per QALY. In sensitivity analysis, the conclusions were found to be sensitive to cost of the surgery and the post-operative rate of SUI. No probabilistic sensitivity analysis was performed which means it is uncertain how imprecise the conclusions are.

A further model based CUA was conducted by Slade et al (2020) (96). This model made use of data from a network meta-analysis in a Markov model from a UK NHS perspective. The utilities used were taken from Glazener et al. (2017). Anterior colporrhaphy (AC) was the dominant strategy being the least costly and the most effective. Although the results of the meta-analysis found that there was greater effectiveness with biological and synthetic mesh, this is offset by an increased likelihood of complications. The authors note that complications were often poorly reported and more studies about the longitudinal effects of both biological and synthetic mesh are warranted.

Whilst a number of different studies compared the different surgical approaches to the management of prolapse, Wyman et al (2020) (97) investigated the cost and benefits of the use of preoperative pelvic magnetic resonance imaging (MRI) to identify women with a high risk of surgical failure. A CEA based upon a decision tree model was carried out from a third-party payer perspective. It was estimated that imaging increased cost by $400 (USD 2014) compared with no use of routine MRI-based screening but also led to a 17% higher likelihood of success after the initial surgery. This results in an incremental cost per surgical failure of $2298. The results of the probabilistic sensitivity analysis conducted showed that the probability that imaging would be cost-effective would be 50% at threshold of $7100 or more. The reason this threshold was chosen was not clear.

Summary and Conclusions:

With regard to PMFT interventions there is limited evidence with some methodological and reporting limitations in the identified studies. Further evaluations which explore a longer time horizon and full

exploration of uncertainty would fortify these conclusions. The evidence for surgical management of prolapse is limited with several economic evaluations falling short of generally accepted reporting of methods. Nevertheless, two robust and well-designed studies, Glazener (2016)(93) and Slade et al (2020)(96), found that mesh interventions were not likely to be cost effective. Future research of both longitudinal clinical outcomes and economic evaluations with full probabilistic sensitivity analysis will be beneficial in the understanding of the best surgical techniques to manage pelvic organ prolapse. There is early evidence in relation to the effectiveness of preoperative imaging, but this also requires further high-quality economic evaluations to draw firm conclusions.

4. FAECAL INCONTINENCE

4.1. Evaluation and testing

Faecal incontinence is a diagnosis that can be made on clinical history alone, however, patient reported symptoms are a poor indicator of underlying pathophysiology. Diagnosis is best made by a focused and appropriate evaluation. Costs incurred for evaluation may range from transportation to the healthcare facility to that of conservative or surgical treatments. While the costs of evaluation have been assessed no economic evaluations were identified that compared alternative modes of clinical evaluations and testing.

4.2. Conservative therapies

While it may be feasible to provide the relative costs of conservative treatments (e.g., behavioural modification, scheduled toileting and dietary fibre supplementation), cost-effectiveness still needs to be evaluated. Unfortunately, no economic evaluations were identified since the last consultation.

4.3. Medications

Pharmacoeconomics remains a constant challenge and of increased interest. With advent of newer medications, there may be cost savings in the newer drug versus the older drug, reduction of hospitalizations, or reduction in costs associated with managing adverse side effects of older drugs(98). Again, no economic evaluations were identified since the last consultation.

4.4. Advanced therapies

Patients may fail to respond to conservative therapy and require more advanced or surgical therapy such as vaginal bowel devices, stem cell therapies, anal slings, neurostimulation, bulking agents, radiofrequency, sphincter repair, sphincter replacement, or faecal diversion. These newer therapies are beginning to surface. Only one economic evaluation was identified since the last consultation. Hounsome et al (2018) (99) compared sacral nerve stimulation and percutaneous tibial nerve stimulation for faecal incontinence using a decision analytic model. The analysis was run over a 5 year time frame. Percutaneous tibial nerve stimulation prior to sacral nerve stimulation compared with delivering sacral nerve stimulation straight away was both more effective and less costly in all scenarios. The probability of this strategy being cost-effective was around 80% at £20,000–£30,000 per quality-adjusted life-year (QALY).

V. SUMMARY AND FUTURE RESEARCH PRIORITIES

Since the last ICI several high-quality economic analyses have been published. This chapter has focused on what are called full economics evaluations. The chapter has not considered so called partial economic evaluations – these studies consider costs alone or effectiveness alone. The reason for this is that full economic evaluations are the only studies that provide information about efficiency.

Despite extensive searching there were several areas where no new published studies were identified. One of these was pharmacotherapy treatments for stress urinary incontinence and this is consistent with the lack of pharmacological therapies for stress incontinence. There were economic evaluations identified in other areas. Three studies were found in the use of PFMT in the treatment of urinary incontinence. A brief economic commentary was included as part of an updated dated Cochrane review on this topic. This brief economic commentary suggested that in terms of cost-effectiveness, PFMT looked promising. This commentary did not subject any of the identified economic evaluations to critical appraisal. However, a study conducted alongside a large RCT reported that that biofeedback mediated PMFT was unlikely to be cost effective in a UK setting.

The majority of studies identified related to surgical or pharmacotherapy for urge incontinence/OAB interventions. For surgical intervention for stress urinary incontinence 4 studies were identified. Of these, 3 related to surgical treatments of SUI in women and one to surgical treatments of incontinence post-prostatectomy. One economic evaluation was conducted alongside a randomised controlled trial and the others were model based. A robust model-based study reported that results suggest that retropubic mid-urethral sling (retro-MUS) is the most cost-effective surgical intervention over a 10-year and lifetime time horizon and highlighted the need for further long-term research. There was only one study that looked at the cost-effectiveness of slings in the treatment of male incontinence and evidence suggests that the AUS was more cost effective however, these results need to be interpreted taking into account that although the study was based on the best available evidence, there is a lack of long-term data on the clinical effectiveness of slings in the treatment of male incontinence.

Several studies were published that compared pharmacotherapies for OAB. The type of analysis conducted varied considerably, but the reporting of the type did really correspond to the type of analysis conducted. For example, three studies did not compare specific treatments rather they compared treatment by pharmacotherapy with non-treatment. None of these studies were explicitly described as economic evaluations but for each the results could be reinterpreted as cost-consequence analyses. This goes against previous recommendations of the committee that researchers correctly label their studies to avoid confusion.

Since the last consultation four economic evaluations have been published comparing onabotulinumtoxinA (Botox) compared with best supportive care or anticholinergics or sacral neuromodulation. The results suggest that Botox is a cost-effective treatment for urge urinary incontinence compared to these treatments. varied depending on comparator even though there was some evidence that there did not appear to be in the differences in QALYs therefore the results were mainly driven by the costs of Botox.

Several studies were identified in the management strategies for the Pelvic organ prolapse (POP); Two of these studies looked at non-surgical interventions and four considered surgical interventions. The reporting of the non-surgical studies meant that the evidence was not compelling. Likewise, some of the economic evaluation evidence for surgical management of prolapse fell short of generally accepted reporting of methods. However, two robust and

well-designed studies found that mesh interventions were not likely to be cost effective. Only one economic evaluation was identified for management of faecal incontinence, and it was model based.

As noted in earlier consultations the requirements of reimbursement agencies and guidelines for economic evaluation publications have been the drivers for the improvement of the quality of the identified studies. With respect to the economic evaluations identified there have been some very high-quality studies reported. It was however disappointing to see some examples of poor practice still being published and there is still room for improvement in conduct and reporting of economic evaluations. Overall, in most of the areas considered in this chapter there is need for more primary collection of quality of life as well as long term follow up data.

Most studies included quality of life measures and incremental cost-effectiveness ratios (ICER) and reported the willingness to pay threshold. For all areas future research should seek to capture the full impact of the interventions considered over time and more fully address both statistical and other forms of uncertainty using sensitivity analyses. Many studies identified were piecemeal in that they did not consider all relevant alternatives. This indicates that there is a need for more and better large-scale modelling studies based upon best available evidence.

A further limitation relates to the application of economic evaluation methods. The studies identified estimated cost-effectiveness for the average patient. This is common practice, but such studies are not sufficient to inform decisions about adoption of interventions. Economic evaluation in implementation science is a rapidly evolving area as researchers test alternative strategies to improve the quality of care. One of the challenges identified in implementation science is the ability to differentiate the cost of using different implementation strategies from the cost of evidence-based treatment. There is a growing literature to guide researchers interested in implementation issues.

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Takahashi, Satoru (Japan)

COMMITTEE 22

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I. INTRODUCTION

This chapter summarizes important new aspects of research arising from data and discussion as a product of this consultation. This chapter includes issues inclusive of recommendations for ongoing and future research focus related to prevention, improved elucidation of mechanisms of causation of disease, personalised medicine, and topical areas of research focus related to specific pelvic floor conditions.

This report stresses the need for clear and consistent use of definitions with approved terminology, as well as published guidelines arising from International Continence Society (ICS) and other major professional societies and consensus groups. Previously the Oxford Centre for Evidence-based Medicine Levels of Evidence and Grades of Recommendation (http://www.cebm.net/levels_of_evidence.asp) have been used for this purpose however the addition of clear and consistent methods of evidence classification as defined by the GRADE system will be highlighted and strongly recommended for inclusion.

1. SCIENTIFIC INTEGRITY, RIGOR, REPRODUCIBILITY IN BIOMEDICAL RESEARCH

Good research practice mandates the determination and definition of the experimental or research topic.

(1-18) Increasingly, meta-analytic reviews provide a background and foundation to potential subsequent clinical research projects. The Cochrane Incontinence Group (http://healthsci.otago.ac.nzldsm/wch/obstetrics/cure) provides a summative review of pelvic floor topics. The prospective formulation of the rationale, objectives and hypotheses for a proposed study may be constructed on this basis. Critical to study design is a consideration of the power of the study and subsequent termination of sample size necessary to answer statistically driven conclusions. (19) The study design should provide the highest quality of evidence to test the given hypothesis in the most thorough and robust manner. Clinical practice and clinical research often overlap. Recommendations as to optimal integration of the two are extant and lucid. (20 -24) There should be clear understanding on both parts of the clinical researcher and the patient/subject as to the differentiation of standard and routine clinical care as opposed to formal clinical research systematic investigation leading to generalizable knowledge. (25)

The U.S National Institutes of Health (NIH) convened a joint workshop in 2014 in collaboration with the Nature Publishing Group and Science, and produced detailed guidelines pertinent to research integrity and data reporting inclusive of: statistical analysis, transparency in reporting, data and material sharing, and consideration of refutations. Also included was a consideration of image-based data (i.e. immunohistochemistry or western blots) and biological materials which must be detailed in order to ensure reproducibility of design and interpretation (i.e. antibodies, cell lines, and animals).

The incorporation of new technologies in benign urologic research including artificial intelligence (AI), social media, and genetic engineering all pose important ethical questions. Regarding AI, researchers must be willing to provide full disclosure regarding any algorithmic code that underlies research decisions (26). For social media research, privacy concerns and unintentional biases are important to consider as highlighted by a recent, retracted article entitled, “Prevalence of unprofessional social media content among young vascular surgeons.” (27) The study was highly criticized for its bias against young women surgeons and for targeting private social media accounts in the name of research. (28) In terms of genetic engineering, the use of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology, and new abilities to alter the human genetic code either in embryos or adult humans must be applied with extreme care and consideration of underlying ethical issues. (29)

2. RESEARCH ETHICS

Medical research is founded on the highest ethical basis. This ethical foundation arises from experiences that have arisen from prior endeavors with both positive and negative implications for the current and future status of basic and clinical research endeavors.

The Belmont Report entitled „Ethical Principles and Guidelines for Protection of Human Subjects of Research“ outlines critical aspects of research and was summarized in the prior edition of this chapter. (30) These principles include Respect for Persons, Beneficence, and Justice and are critical aspects of ethical research. Studies must be free of coercion, undue investigator interference, and risks otherwise unintended including physical, emotional or psychologic trauma.

Criteria defining ethically based research include: clearly defined study aims, prospective planning, data base registration, and feasibility, and there should be a reasonable assumption that new knowledge will be provided at the end of the study; as well as reasonable and achievable study goals which will advance knowledge. (20,30-32)

Ethical approval is a critical procedural aspect of research and requires Institutional Review Board (IRB) approval for human subject research protocols. Additionally, informed consent is an absolute ethical requirement for human subject research and must contain three elements: 1) it must be voluntary, 2) it must provide a full disclosure of relevant information including risks, benefits, and alternatives, and 3) it must be presented to an individual or surrogate who has clear decision-making capability. Autonomy is a critical aspect of informed consent and should be easily understandable and meaningful to potential participants. (32 -34)

Informed consent should include the type of study, associated randomization, and inherent risks of the trial. The document should include a statement allowing the subject to decline participation with no attendant consequence to any ongoing medical care and whether or not remuneration is provided. If an adverse event occurs during the study and is related to the study, a statement as to risk mitigation should be included. (32,33)

An obligation to disclose relationships with industry and financial disclosures related to supplemental personal income exists as part of the informed consent process. (32-36) Institutional contracts and oversight are critical for study integrity. The U.S. National Institutes of Health (NIH) provides clear guidance as to this process. (37,38)

II. EVIDENCE

1. BACKGROUND

To many currently practicing clinicians, evidence-based medicine (EBM) may seem to be well established in undergraduate and postgraduate teaching, and in the methods that guideline bodies use to reach recommendations, but it remains a young and dynamic field. The concept of clinical epidemiology was only introduced in the 1930's; formal teaching of critical appraisal of medical literature began in the 1960's; and even the term "evidence-based medicine" was coined as late as 1991, by Gordon Guyatt at McMaster University. (39) The core concept of EBM has been to use the current best evidence from clinical research to improve the care of individual patient. (40) The foundations of EBM were built on an understanding that there was a hierarchy of clinical evidence, with some study designs, and some individual studies producing more credible evidence than other. (41)

Evidence-based clinical practice guidelines play a critical role in guiding decision-making at the point of care and should therefore be developed to the highest standards. (42) The earliest editions of the ICUD's books, including this work on urinary incontinence, used essentially narrative summaries of a body of evidence, to reach four strengths of recommendation for each intervention or test: "highly recommended, recommended, optional and not recommended." From around 2002 onwards, corresponding with the 2nd through 6th editions of this text, it was recognised that these different strengths of recommendation should be backed by a systematic rating of the quality of evidence. The ICUD adopted, with minor modifications, the widely used Oxford Centre for Evidence Based Medicine system, (43)incorporating both a hierarchy of levels of evidence, and a subsequent grade of evidence. These grades (A to D) were based on a narrative assessment of the highest level of evidence reported, and the consistency of evidence at that level.

Subsequent to the publication of the 6th edition of this work, a worldwide consensus has emerged for a shift to a more transparent system for evaluating evidence and reaching recommendations about that evidence. This system, known as Grading of Recommendations Assessment, Development and Evaluation (GRADE) (44) has been found to be reproducible (45) and been widely adopted including by specialty guideline bodies including the American Urological Association (AUA), European Association of Urology (EAU) and international and national general guideline bodies including Cochrane, the WHO, and NICE. The consistent use of the same framework across different guideline developers is a positive development that should facilitate collaboration and resource sharing. (46)

In this summary of current methods for EBM in incontinence, we first give an overview of general considerations when evaluating a body of evidence focusing on the different domains by which GRADE judges the certainty of evidence; we then conclude with a brief overview of how the GRADE system moves from assessment of evidence to make guideline recommendations. For further reading, one of the best resources for understanding how to apply the principles of evidence-based medicine is the JAMA's Users' Guide series, in particular the articles on therapy and prevention. (47,48) There are also many EBM resources specifically for urologists. These include the Users' Guide to the Urological Literature series, (49) as well the Evidence-based Urology In Practice series, (48) that explains these principles using urology-relevant examples.

2. RATING THE CERTAINTY OF EVIDENCE

GRADE stands in contrast to some prior systems such as that by the CEBM in Oxford that it does not appraise individual studies, (44) but a body of evidence as summarized in a high quality systematic review.(50) Critical aspects of a high-quality systematic review should be governed by the A MeaSurement Tool to Assess systematic Reviews Assessment (AMSTAR)-2 criteria. (51) These include an a priori protocol, ideally registered in advance, a comprehensive search strategy, performance of key steps independently and in duplicate by two or more investigators as well as the use of a system like GRADE to rate the certainty of evidence. Unfortunately, many systematic reviews published in the urological literature are of low methodological quality. (52)

2.1. The importance of a clear question

Guideline panels seek to develop actionable, evidence-based recommendations to support clinical decision making at the point of care. To do so, it is important that the panel has clearly articulated what clinical question the recommendation is meaning to address. (43,52) Any question addressing clinical management should follow the following format and include four components: Patients (P), the intervention (I), a comparator (C) and the relevant outcomes (O) of interest. For example, a guideline panel on prostate cancer seeking to address the role of Retzius-sparing for the surgical management of clinically localized prostate cancer, may formulate the following question: In patients with clinically localized prostate cancer, how does a Retzius sparing approach compared to a non-Retzius-sparing approach with regards to urinary continence as well as the risk of serious surgical complications, recurrence free survival and disease specific survival. Components of this question in the so-called PICO question will then also guide an information specialist in developing a comprehensive search strategy to identify all relevant studies. (53)

2.2. Addressing the importance of outcomes

An important aspect of GRADE is its focus on outcomes that are of direct importance to the patient. (52) This is relevant, since clinical research studies oftentimes focus on endpoints that are easy to measure but are not of direct interest to patients. Examples include PSA levels suggesting biochemical recurrence after treatment for clinically localized prostate cancer and DEXA bone density scores; these are surrogates for disease specific survival and fractures, respectively. GRADE emphasizes that guideline recommendations should be based on outcomes that are of direct patient importance, rather than on surrogates. In settings where no evidence is available to inform these patient important outcomes, information on surrogate outcomes can be used to indirectly inform how these outcomes may be impacted. We will discuss this later under the domain of indirectness.

To identify which outcomes are most patient important, the guideline panel thus should assemble a comprehensive list of outcomes that are potentially impacted. (52) Importantly, they should include both outcomes that reflect a potentially desirable effect but also those that reflect a potentially undesirable effect, for example drug-related adverse events. Based on this comprehensive list, the panel should go through a prioritization process during which outcomes are rated on a scale from 1-9. On the scale, scores from 7-9 characterize outcomes of critical importance for decision making. Ratings of 4-6 are outcomes that are important, but not critical. Ratings of 1-3 items that are considered not critical and not important and therefore are of limited importance. Ultimately, outcomes that fall into the latter

category are omitted from the evidence summary that is compiled as the basis for the panel deliberations. The overall certainty of evidence rating that characterizes a recommendation is ultimately determined by those outcomes that are deemed as critical; this will be discussed further in this text.

2.3. Judging the certainty of evidence in the context of guideline development

GRADE makes a distinction between how the certainty of evidence is established in the context of a systematic review versus in the context of a clinical practice guideline. (54,55) For the latter, the certainty of evidence reflects the extent to which confidence in an estimate of effect is adequate to support recommendations. Therefore, it is context specific. It also requires some judgment as to what effect size represents a clinically meaningful effect.

2.4. Domains that impact the certainty of evidence of randomized control trials

Historically, rating systems have placed an undue emphasis on study designs alone. Whereas GRADE also begins with study design, with randomized control trials starting off as high certainty evidence and observational studies as providing lower certainty evidence it recognizes that under certain circumstances, well-done observational studies may provide stronger evidence then evidence drawn from the body of randomized control trials. (54) It has clearly defined five criteria that may lower the certainty of evidence from randomized control trials (as well as three criteria that may increase the certainty of evidence from observational studies reviewed below).

2.5. Study limitations

This domain of study limitations captures the major limitations that have historically been referred to as risk of bias. (56) GRADE recognizes that the confidence that we can place on recommendations decrease if the underlying studies lack important methodological safeguards against bias. These include appropriately randomized patients with allocation concealment to guard against selection bias, blinding of patients and personnel to guard against performance bias, and blinding of the outcome assessments to guard against detection bias. In addition, large losses to follow up present the risk of attrition bias and failure to report outcomes (typically those for which no effect was observed) may amount to selective reporting bias. In addition, the analysis of superiority studies should be performed as intention to treat. Shortcomings in the methodological quality of randomized controlled trials are very common and therefore frequently prompt downgrading the certainty of evidence.

2.6. Inconsistency

In a systematic review, the authors will seek out in aggregate the results of studies that all address the same PICO. Therefore, one would expect the results of all the studies to be similar. However, it is not uncommon for there to be considerable heterogeneity or variability in the results as reflected in differing estimates of treatment effect. Potential explanations for this variability include clinical differences in populations (for example, different disease stages), in interventions (for example drug dosages), comparators (for example usual care or placebo) and/or in different ways of assessing the same outcome (for example, some studies using validated and others non-validated instruments to assess quality of life). In addition, studies may differ in the methodological rigor with which they were conducted (for example, some studies blinded outcome assessors and others did not). Lastly, some degree of variation can be explained due to chance variation. Whenever there is considerable variability that cannot be explained due to chance, systematic review authors should seek to explain this variability. Ideally any hypothesis they explore, should be defined a priori. Ultimately, if no good explanation is identified for the observed inconsistency between studies that contributed to a pool effect, GRADE recommends rating down for inconsistency. (57)

2.7. Indirectness of evidence

The domain of indirectness can be categorized into two different types. (58) First, there may be no direct head-to-head comparisons between two types of interventions but each of these interventions may have been compared to placebo or to sham surgery. Whereas the findings of such studies, may still allow for important inferences about the relative effectiveness of these two interventions, we would be less certain of these results if they had been compared in the setting of one trial. Secondly, there may be important differences between the intended population, intervention, comparator, or outcome of interest as defined in the PICO, versus that of the available body of evidence. For example, in the absence of clinical trial evidence in children, it may be reasonable to apply study results from adolescents; however, the underlying degree of confidence that we can place in the treatment effects would be lower.

2.8. Imprecision

This GRADE domain relates to the issue of small sample sizes, low event rates and wide confidence intervals. (59) If the confidence interval of the pooled effect size includes values that would lead to a different interpretation of the evidence, GRADE would recommend that you rate down the certainty of evidence. A related concept in this context is also the optimal information size (OIT), which relates to the required sample size that a single adequately powered randomized control trial would require.

2.9. Publication bias

It is a well-established phenomenon that positive studies that demonstrate that a new intervention performs better than an established intervention (or placebo) are met with greater interest by the urological community then negative studies that failed to do so. This often results in publication in higher impact journals, more rapid acceptance, increased dissemination in the form of secondary publications, as well as editorials and exposure in social media. Meanwhile, negative studies may only be presented as abstracts at meetings, or not at all made public. Therefore, when reporting bias is strongly suspected, either from a funnel plot, or for example when published evidence is limited to a small number of trials which are all published by industry, GRADE would recommend to rate down for this reason. (60)

2.10. Domains that impact the certainty of evidence of observational studies

For many important questions in urology, the available evidence is limited to (comparative) observational studies. In most cases, the resulting evidence will be of low or very low certainty. However, in unusual circumstances, they may produce moderate or even high-quality evidence. The most practically relevant scenario is when methodologically strong observational studies that are not compromised by risk of bias yield large or very large and consistent estimates of the magnitude of the treatment effect. In those situations, although the observational studies are likely to overestimate the true effect, the weak study design is unlikely to explain all the apparent effect. (61) One example, may be the effect of androgen ablation in patients with newly diagnosed metastatic prostate cancer with neurological symptoms due to cord compression. Although the impact of immediate castration has never been studied in the setting of a randomized control trials, the dramatic effect of treating patients would allow us to be confident that it is indeed effective. The two other criteria that will at times allow us to be more confi-

dent in the results of observational studies relate to the existence of a dose response gradient, or the situation in which all plausible biases would decrease the magnitude of an effect.

2.11. Evidence profiles and summary of findings tables

GRADE evidence profiles and summary of findings tables represent two structured approaches to present a summary of evidence to a guideline panel. (62) They differ in the degree of detail that they provide. An evidence profile includes detailed information about the certainty of evidence assessment; specifically, it will inform the user which specific domain contributed to the rating down (or up) of the certainty of evidence, if applicable. The summary of findings table omits that information. Both representations share many characteristics. These include explicit information about the number of included studies, participants, relative and absolute effect size estimates as well as the rating of the certainty of evidence with foot notes that explain how the authors arrived at a given rating. These types of evidence summaries, typically a summary of findings table, are foundational for the deliberations of a guideline panel.

3. USING EVIDENCE TO MAKING RECOMMENDATIONS.

One important prerequisite for the process of making recommendations is to establish an overall certainty of evidence. This is necessary because any given recommendation is expected to impact all outcomes simultaneously. As per GRADE, the overall certainty of evidence will usually be based on the lowest certainty of evidence for any outcome that was deemed to be critical. For example, if there is moderate certainty of evidence for a certain desirable effect of an intervention yet the certainty of evidence describing an undesirable effect of that same intervention is not well established, then the resulting overall certainty of evidence should be low.

3.1. Strength of recommendation

The strength of a recommendation reflects the extent to which we can be confident that the desirable effect of an intervention outweighs the undesirable effects; in other words, that the patient is likely to experience a net benefit. (63) Importantly, GRADE only has two categories of recommendation which are strong or weak (which may also be called conditional). Strong recommendations are appropriate when the panel members, based on the available evidence and a series of structured judgements they have made, are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects. Weak recommendations are appropriate when the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident. GRADE also recognizes that there is a subset of recommendations, so-called good practice statements, that panel may perceive to be important to communicate but that should not be graded. (64,65) Lastly, there is no category of "expert opinion" in GRADE, since this usually refers to indirect, oftentimes poorly documented observational or even anecdotal evidence that has not been well reported (66); however there are strategies in how guideline developers can nevertheless move forward in making evidence-based recommendations. (67)

GRADE operationalizes what a given recommendation of a certain strength should mean to patients, clinicians, and policy makers. The implications of a strong recommendation are:

- For patients: Most affected individuals in the same setting would want the recommended course of action and only a small proportion would not. A discussion of the intervention should be offered.
- For clinicians: Most people should receive the recommended course of action.
- For policy makers: The recommendation may be adopted as a policy (or performance measure) in most situations.

Meanwhile, the implications of a weak recommendation are:

- For patients: Most affected individuals in the same setting would want the recommended course of action but many would not.
- For clinicians: Although we expect a net benefit if a patient follows a weak recommendation, different choices may be appropriate for different patients. Shared decision-making will be important to help each patient arrive at a management decision consistent with his or her values and preferences.
- For policy makers: These recommendations are usually not suitable as policy of performance measures. It may require considerable debate and involvement of stakeholders.

3.2. Factors that determine the strength of a recommendation

GRADE has defined four major determinants of the strength of recommendation as well as three additional considerations. (67)

Balance between desirable and undesirable consequences

This represents a judgment on part of the panel members to what extent the aggregate of potential benefits of an intervention weigh up against the potential downsides of an intervention, based on the best estimates of those consequences as summarized on the summary of findings table. For example, a new chemotherapy regimen for metastatic renal cell carcinoma may extend overall survival but come at the price of reduced quality of life. Panel member deliberations would likely center around the relative weighting of these outcomes and the magnitude of the resulting net benefit (or harm). These considerations become even more complex when several outcomes contribute to both desirable and undesirable effects. When advantages and disadvantages are closely balanced, a weak or conditional recommendation would be appropriate.

Certainty of evidence

The overall certainty of evidence is the second determinant of the strength of recommendation. The more uncertainty there is about the magnitude of the benefits and harms of an intervention the less appropriate it would be to make a strong recommendation for or against the particular course of action. Therefore, outside of five paradigmatic circumstances that GRADE has described, an overall low or very low certainty of evidence calls for the resulting recommendation to be a weak or conditional recommendation.

Patients' values and preferences

The third factor that impacts the strength of recommendation is the uncertainty about or variability in patients' values and preferences. (68) Ideally, a systematic review of high-quality studies that a been performed to elicit these values and preferences would help inform this domain. However, such high-quality studies often do not exist and therefore the panel members' perception of these values and preferences and the variability stands in. To the extent that we are uncertain about the values and preferences of the target audience of a given guideline, or there is considerable variability of these values and preferences, a weak or conditional recommendation will be appropriate. (69,70)

Resource utilization

Although many guideline developers may choose not to perform a formal cost effectiveness analysis, general considerations about

costs, both direct and indirect and the total budget impact of a given recommendation are important.

The greater the incremental cost from a given intervention, the less appropriate a strong recommendation will be made.(71)

Importantly, costs of drugs and surgical procedures will often vary widely across the marketplace making it important for guideline developers to define the setting.

Equity, acceptability and feasibility.
These are additional considerations that may be relevant for the panel deliberations. If a given intervention would reduce equity, this may be reason to formulate a weak or conditional, rather than strong recommendation. The same goes for concerns about acceptability of an intervention among stakeholders, and the feasibility of implementing a recommendation in a given jurisdiction.

3.3. The GRADE evidence to decision framework
Historically, panel deliberations supporting many guidelines have not been transparent and reproducible. To address this issue, GRADE has developed an evidence to decision framework that facilitates a structured decision-making process to support and document the final recommendation that a panel arrives that. Doing so, increases confidence in the final product and should also improve recommendation uptake. The evidence to decision framework includes all the above domains and takes the panel through a process of deliberation and judgments to ultimately reach a strong or weak/conditional recommendation. (64,72) Of note, GRADE discourages the potential option of "no recommendation can be made" since patients, clinicians and policy makers ultimately do need to make a decision. One approach is to specify under which circumstances a given recommendation may be appropriate. For example, for patients with a renal stone who are candidates for both ureteroscopy and shockwave lithotripsy, the panel may make a weak/conditional recommendation for shockwave lithotripsy in patients wishing to minimize the perioperative risk (but it willing to accept a higher retreatment rate).

3.4. Wording of recommendations
Once a recommendation has been made, it should be clearly articulated. Therefore, GRADE recommends for panel members to use standardized terminology to express a given type of recommendation. (63,73) For strong recommendations, the suggested wording is "the panel recommends"; for weak recommendations, the suggested wording is "the panel suggests". Organizations using GRADE to develop guidelines may deviate from the suggestions, but consistency in signaling a given strength of recommendation will be important. In addition, GRADE recommends that recommendations that are intended to express that something should not be done use the wording "the panel recommends against" or the "the panel suggests against", rather than stating "the panel does not recommend" or "the panel does not suggest", since this wording is less direct and explicit. (74)

3.5. Conclusion
GRADE provides a methodologically rigorous and transparent framework for summarizing and rating the certainty of evidence and for arriving at guideline recommendations based on this evidence. Moving from evidence to recommendations requires several judgments on part of the panel members. Although GRADE cannot assure that these judgments are appropriate, it makes these judgments both explicit and transparent, and thereby the ultimate recommendation reproducible.

III. FOCUS AREAS

1. PREVENTION AND INTERVENTION RESEARCH

Research in prevention of urinary incontinence continues to evolve. Modifiable risk factors of pelvic floor disorders, inclusive of transitional age issues, aging related disorders and the lack of understanding of what represents a healthy bladder and the individual behavioral, interpersonal and environmental factors that contribute to bladder health all need further investigation. (75)

In 2015, the NIH launched the Prevention of Lower Urinary Tract Symptoms (PLUS) research consortium to provide the foundational evidence to support future prevention intervention studies. This group has subsequently produced seminal papers related to a variety of impacts on voiding status and pelvic health issues. This network has produced numerous well-conceived trials which have advanced knowledge of lower urinary tract conditions inclusive of: the design of the Prevention of Lower Urinary Tract Symptoms Bladder Health Instrument (PLUS-BHI) (76), the transdisciplinary approach to promoting bladder health across the stages of life as standardized by the consortium (77), and progress in reporting for consortium creation and shared mission with mutual decision-making. (78)

2. GENOMICS, PROTEONOMICS, TRANSCRIPTOMICS, METABOLOMICS – PERTAINING TO INCONTINENCE AND ASSOCIATED INTERVENTIONS.

"Omics" studies have the potential for comprehensive assessment of a biological system, and the integration of "omics" technologies is known as systems biology. Genomics, the measurement of all common genetic variation, and proteomics, the measurement of expression of all proteins are the two most developed aspects of this family of therapeutics and diagnostics. The use of the "omics" suffix has now been expanded to include all kinds of biological molecules and subtypes of molecules, but the most common additional applications include transcriptomics, the measurement of total gene expression, and metabolomics, the measurement of all metabolites. The potential of these technologies to impact personalized medicine and also to understand individual variation is vast.

2.1. Genomics
Genome wide association study (GWAS) has revolutionized the study of the genetics of common diseases. GWAS identifies genetic regions or loci associated with a trait, with the first identified gene being that for macular degeneration. GWAS is a cornerstone of the Wellcome Trust Case Control Consortium study. This includes studying type 1 diabetes, type 2 diabetes, coronary heart disease, hypertension, bipolar disorder, rheumatoid arthritis, and Crohn's disease. All of these diseases are common, with genetic, environmental, and lifestyle risk factors impacting presentation and natural history. (79,80,81,82)

For most common diseases, there may be hundreds of gene variants, each with inducible and suppressive effects, for which conventional GWAS is not sensitive enough to detect differences. Two

significant limitations of GWAS exist. One major limitation is that GWAS cannot fully explain the observed heritability of complex conditions. (82,83,84) Even with large sample sizes ,GWAS is currently not able to uncover the full genetic architecture of a condition. The second major limitation is that GWAS is inconsistent for identifying causal variants.(84)

Many single nucleotide polymorphisms (SNPs) identified in GWAS are intergenic, but even identification of genie SNPs may not directly help to uncover the underlying biology. GWAS, when used to assess genetic loci for incontinence, has not identified any specific risk loci.(85,86) This situation is likely to change as the size of the incontinence GWAS consortia grows.

2.2. Transcriptomics

Total gene expression has been performed using cDNA microarrays, which provide for simultaneous measurement of active mRNA expression for all known and putative genes and transcripts in a cell or tissue at any given moment.

This technique has been used extensively for the study of bladder carcinomas. (87) A number of studies have been limited by whole genome expression in cultured human detrusor smooth muscle cells (88, 89) or in cultured human urothelial cells, (90,91) rather than in vivo. Using urinary sediment as the source of material may over-represent senescent or apoptotic cells. (92) Transcriptome data from healthy portions of the bladder for patients undergoing cystectomy has also been measured either using microarrays (93) or more recently RNA sequencing (94), with the latter experiment now publicly available. (95) RNA sequencing has numerous advantages over microarray, including that it can capture expression of unknown mRNAs, and their variants, whereas microarrays are limited to detection of known sequences. To our knowledge, RNA sequencing has not been used in functional urology.

Only two studies have applied whole genome arrays to benign bladder biopsies. Both evaluated interstitial cystitis. (96,97) Both studies attempted to differentiate expression associated with ulcerated and non-ulcerated areas of the bladder in interstitial cystitis.

2.3. Proteomics and Metabolomics

The expressed proteins in a cell or tissue is considered the proteome, whereas the metabolome encompasses only the smaller molecules less than 1 kDa in size as identified with spectroscopy. Biomarker discovery is dependent on these two fields, specifically in urine. Many existing biomarkers in both urology and gynecology are themselves proteins (e.g. PSA and CA125). The numeric amount of human proteins is thought to be more than 250,000 human proteins and there are believed to be around 5,000 small metabolites. Research using these tools in pelvic floor disorders remains limited. Understanding of the urinary tract microbiome has substantially evolved due to advancements in these areas. (98,99,100)

2.4. Limitations of "omics" Research

Incontinence is an archetypical example of a common complex disease, with multiple subtypes and an array of complex potential causes. It has a wide range of environmental and lifestyle risk factors, that might obscure attempts to identify meaningful biological differences. Stress and urgency incontinence overlap much more commonly than expected by chance, suggesting that they might have common environmental or genetic risk factors (101), but it is not a trivial problem to correctly assign women as having stress, urgency, or mixed incontinence either on the basis of symptoms (102) or laboratory testing.(103) Thus any "omics" study of incontinence faces substantial problems with case ascertainment, and potential problems with misclassification bias, which might further obscure biological signals. Although these technologies can be applied to any common trait, they been most successful for conditions with tightly defined pathology. Incontinence, as a symptomatic condition, certainly does not have a single clear pathogenesis, and the subtypes of incontinence have multiple potential causes. (104)

The common pitfalls of clinical research described above tend to be magnified in "omics" research. Two particular problems need to be planned for in the design of all "omics" studies, both relating to the lack of specific hypothesis. "Omics" research seeks to define differences in any of a large number of molecules between cases and controls, or between different experimental conditions. For some "omics" technologies, formal consensus has been reached regarding adjustment of significance to account for the huge number of simultaneous measurements. For all "omics" studies very careful consideration of sample size is needed at the planning stage to account for loss of power from multiple comparisons.

The ability to replicate "omics" results is another concern. A risk of false positive results confounding issues compounded by effect size errors exists in "omics" studies.{ (105,106) However, the potential for "omics' investigative methods to elucidate complex disorders of aging or condition specific disorders such a fibrosis associated with external toxins has recently been demonstrated to be robust and reproducible. (107,108,109)

IV. BASIC SCIENCE RESEARCH

Drawing from the human ethical oversight construct, the development and implementation of a similar process to ensure animal welfare is now common practice and required at all research institutions conducting research with animals. In 1986, the term IACUC (Institutional Animal Care and Use Committee) was coined in the Animal Welfare Act where the composition of each institution's IACUC committee was delineated. Each IACUC must ensure the use of animals for research is performed in a humane manner compliant with federal guidelines and regulations.

1. LABORATORY ANIMALS AND RESEARCH

Advancement of modern medicine, including Functional Urology, is greatly accelerated by the judicious use of laboratory animals, acting as an essential tool for testing scientific hypotheses, deepening our understanding of the mechanisms of disease and eventually leading to the development of novel therapies. Scientists are directly responsible for the welfare of the animals used in experiments and are guided in their activities by the national and international laws and regulations, protecting the animals and ensuring the implementation of 3R principles of animal research (Replace, Reduce, Refine). 3R Principles represent a responsible approach to animal experimentation. The goal is to replace animal experiments whenever possible, while keeping the number of animal experiments as low as possible and only use the necessary number of animals. Refinement of laboratory practices and procedures is vital to ensure that the distress inflicted upon the animals is as low as possible. In addition, the newest changes in the EU regulation (EU Directive 2010/63) emphasize the intrinsic value of animals and introduce Animal Welfare Bodies for assessment of all animal license applications prior to submission to the governmental organs. The concept of transparency of animal research is very important, as most

science is funded by the public and is accountable to the society. The US Animal Welfare Act requires that all research is approved by the duly appointed Institutional Animal Care and Use Committee (IACUC). India also has elaborated the regulations, including Prevention of Cruelty to Animals Act 1960 and The Breeding of and Experiments on Animals Rules 1998 with newest amendments up to the Bill 2017. China, which uses approximately 20 million animals per year, follows its own nation-wide animal protection law, however, lack of harmonization with existing international regulations singles out animal research in this country, and hinders effective international collaboration in experiments involving lab animals.

Publication of results involving animal research is another area undergoing continuous change, after a survey of 271 publications carried out in 2009 revealed lack of consistency and identified a number of issues that need to be addressed in order to improve experimental design and reporting in publications describing research using animals (110). This led to publication of the original ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines in 2010, and the current updated version ARRIVE 2.0 appeared in 2020 (111). These guidelines are a checklist of information to be included in publications describing animal research. Reporting animal research in adherence with the ARRIVE guidelines 2.0 ensures transparent and thorough reporting. This enables readers and reviewers to scrutinize the research adequately, evaluate its methodological rigor, and reproduce the methods or findings. Most journals require the authors and reviewers alike to ensure implementation of the ARRIVE checklist, which includes reporting the study design, sample size, inclusion and exclusion criteria, randomization and blinding, outcome measures, statistical methods, the detailed information on the used experimental animals and experimental procedures, and reporting the results.

2. LOWER URINARY TRACT DYSFUNCTION (LUTD)

Using animal models in Functional Urology has a long history. Laboratory animals helped to elucidate the mechanisms of bladder dysfunction, attributed to different diseases, and to establish new approaches to therapy, which can be subsequently translated to humans. These studies and the rationale for the use of laboratory animals have been thoroughly reviewed in several excellent recent publications (112 – 116).

Several rodent models of bladder dysfunction have been developed using rats, mice, and guinea pigs to study voiding and storage function in normal conditions and in various disease models using cystometry. While rodents are cheap, and offer other advantages including possibility of genetic manipulation, it should not be forgotten that the mechanisms of micturition are different between mice and humans: rat micturition requires a pulsatile activity dubbed “milking action’’ of the urethra; rat, mouse and guinea pig bladder contraction is mediated primarily via ATP, not acetylcholine as in humans. Nevertheless, cystometry in rodents continues to be used and improved, transitioning from anesthetized to awake animals for both UDI (urodynamic) and EUS-EMG (117) to achieve the results comparable to human urodynamic investigation. Micturition in free moving animals was traditionally monitored by the spot assay, which has recently been improved by using Micturition Video Thermography (MVT) – a fully digitalized non-invasive void spot assay reported in 2019 (118). Imaging technology is being continuously applied to control voiding events in combination with catheter implantation followed by UDI, and recently, a closed-loop wireless system with an implantable device wrapped around the bladder and measuring changes in resistance during bladder filling and emptying was used in freely moving rats (119). Similarly, high frequency ultrasound proved to be an effective method for assessing bladder and urethral measurements during urinary function in mice (120).

Rodent models of bladder dysfunction employ either direct changes (injury, stimulation, etc.) to the bladder, its blood supply or peripheral innervation, or injuries to the spinal cord, or brainstem, leading to changes of lower urinary tract function. Neurogenic bladder dysfunction was studied in models of Parkinson’s disease, stroke and Multiple Sclerosis in experimental autoimmune encephalomyelitis mice. Additionally, many transgenic mouse disease models can develop LUTD, and be used to delineate or validate the involvement of particular molecules and signaling pathways in disease development (121,122).

Bladder function in rodents can be investigated with optogenetic methods, which are increasingly applied to elucidate the role of selected structures (smooth muscle cells, peripheral nerves, defined areas of CNS) in bladder contractility and responses to stimuli. Optogenetics uses light-responsive proteins (opsins) to activate defined cell populations. Using transgenic mice or viral expression vectors to deliver activating and inhibitory opsins, membrane potential of the bladder smooth muscle cells was modulated to regulate the contractile behavior of the bladder (123). Optogenetic silencing of nociceptive primary afferents was shown to reduce evoked and ongoing bladder pain (124), or to activate the sciatic nerve similar to neuromodulation (125). This approach was instrumental in studying the subtypes of neurons from Barrington’s nucleus which control the bladder and sphincter function (119). A further advancement of this approach was the development of a fully implantable, soft optoelectronic system for wireless, closed loop optogenetic modulation of bladder function to control inhibitory opsins expressed virally and by bladder sensory afferents (120). Although such systems are still a long way from the translational applications in human trials, being able to reduce neural activity and facilitate bladder storage function by delivering a corrective signal opens an exciting new field in Functional Urology.

Non-rodents are also being used to study bladder dysfunction, including feline spontaneous (interstitial) cystitis, which was previously extensively studied. Recently, however, several transgenic mouse models have been developed as an alternative, including URO-OVA/OT-I mice, a transgenic autoimmune cystitis model that spontaneously develops bladder inflammation (126). More transgenic mouse models are being evaluated for bladder function, and new genes regulating voiding are being discovered, such as the recently described acyloxyacyl hydrolase (AOAH) (127). Therefore, it is likely that the use of large animals will further decrease. The notable exception are pigs: micturition volume and frequency of Göttingen minipigs are comparable with that of humans, making them the better choice for translational research in fields such as urology, neurology and nephrology (128). Minipigs are big enough to allow telemetric monitoring following implantation of transmitters (telecystoscopic monitoring) and can be used for testing devices suitable for human application, such as the recently reported Bladder Pill, a wireless intravesical device for real-time bladder pressure measurement (129). Minipigs are also used for drug testing, and toxicological evaluation, both relevant for urological application. High costs of maintenance and generally low number of used animals are the disadvantages of this species compared to mice, however, the advent of transgenic pigs (130) might offer new possibilities for their use in Functional Urology.

3. PELVIC FLOOR DYSFUNCTION

Animals models to study pelvic floor disorders (131,132) and their treatment (133) are advantageous as they allow for a focused evaluation of specific factors without involvement of interfering co-factors. On the other hand, most animals are quadrupeds with a different pelvic floor muscle construction including a tail, a different load distribution on the pelvic floor and a different birth process and hormonal changes.

3.1. Pelvic floor anatomy

In quadrupeds, the bulk of weight is perpendicular to the spine so that the pelvic organs are supported mainly by bony structures, whereas in bipeds the pelvic floor supports the pelvic organs. In addition, in quadrupeds the tail movements are dependent on the levator ani. Rodents have a similar pelvic floor structure and function of the vaginal connective tissue to humans, making them a preferred model for evaluating connective tissue support. Rats seem to have a more histologically comparable pelvic floor to humans than mice and rabbits. Rabbits due to the large surface of the abdominal wall are a good model to test the biomechanical behavior of implants (134). Sheep are a large animal option with a similar anatomy of the pelvic organs and a three-level support similar to what has been described by DeLancey in humans. The main difference being a lack of obturator internus muscle, sacrospinous ligaments and a different shape and orientation of the pelvis (135). Pigs, like sheep have a similar anatomy to humans, but both need space to be boarded. Non-human primates (NHP), of which squirrel monkeys are the best studied, are most similar to humans but have the obvious limitations such as long-life cycle, expertise needed to handle them, and ethical constraints.

3.2. Estrous cycle and length of gestation

Rodents have a regular and short estrous cycle and length of gestation. Rabbits do not have an oestrus cycle, ovulation is induced by coital vaginal stimulation. Sheep have an oestrus cycle of 17 days and 147-day gestation period. Ewes can have prolonged labor and relatively large fetuses. NHPs again are very similar to humans. Squirrel monkeys, besides similar anatomy and estrous cycles also have large fetuses relative to the maternal pelvic outlet and long labor (136). None of these animal models develop menopause.

There are various models of pelvic floor dysfunction. Denervation by pudendal nerve crush has been used to stimulate urinary and fecal incontinence in rats and to evaluate therapeutic approaches and neuroregeneration (137). Unlike humans where the pudendal nerve innervates the M. pubocaudalis and iliocaudalis, atrophy of these muscles could only be induced by damage to the LA nerve in squirrel monkeys (138). Vaginal delivery can be simulated by distending a balloon in the vagina with different volumes and for different durations causing mechanical stretch and hypoxia (138). Iatrogenic menopause is generally induced by ovariectomy as most animals used for research purposes do not develop menopause (139). Findings are inconsistent most likely due to the difference in age at the time of ovariectomy and the interval to measurement. Aging itself however, natural or accelerated, leads to a drop in oestradiol underscoring the interaction between age and hormonal changes in animals (140). Various genetically manipulated mouse models have been developed to study the effect of changes in pelvic floor connective tissues on pelvic floor function (141-145).

Research in human tissue for pelvic floor dysfunction is hampered by the prolonged natural history of disease and the difficulties associated with obtaining human tissue. Various animal models in different animals and using different techniques have been developed, each with unique advantages and disadvantages. Careful selection, well designed and powered studies and consistent reporting are imperative to minimize the number of animals used and optimize outcome and forward our knowledge on pelvic floor dysfunction.

V. TRANSLATIONAL CONCEPTS

Translational research involves results and findings obtained from multiple sources including the basic science laboratory, clinic and community environments and developing these datasets into interventions benefiting the health of individuals and the public. Translational developments may span diagnostics, therapeutic, behavioral , and psychologic interventions. (146)

Translational research is a critically important link between the bench and the bedside. Unfortunately, only about 2 percent of the current US federal funding goes to translational research. The translation of basic biological discoveries into clinical applications that improve human health is an intricate process that involves a series of complex steps: the discovery of basic information about the pathogenesis of a disease; an assessment of whether that information has the potential to lead to a clinical advance; development of candidate diagnostics, devices or therapeutics; optimisation of the candidates in preclinical settings; regulatory assessment of the data to determine use for human use; testing in human clinical trials; application for approval for widespread clinical use; and ultimately, the assessment of approved diagnostics, devices, and therapeutics during widespread use in real-world settings. (147) Initiatives to integrate the public and private sectors led to the formation of the National Center for Advancing Translational Sciences (NCATS) at the US National Institutes of Health in 2012. NCATS research projects and initiatives focus on addressing scientific and technical challenges to reduce and remove obstructions in the development of new treatments and tests that will ultimately improve human health. The aim of NCATS is to catalyse the scientific community to propose implementation projects including therapeutic target validation, chemistry, virtual drug design, preclinical toxicology, biomarkers, efficacy testing, phase zero clinical trials, drug rescue and repurposing, novel clinical trial design and post-marketing research. With translational research, the focus is on the result, not the process. However, the impact of experimental methods differences, species response variances, or aging related dysfunction must be considered in the intrepretation of the results derived from translational analyses. (148)

VI. CLINICAL RESEARCH

1. STATISTICAL METHODS AND STUDY CONDUCT

Many definitions for „clinical research“ have been proposed. The National Institutes of Health (NIH) currently defines clinical research as research with human subjects that is:

Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects.

Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.

1.1. Outcomes Research and Health Services Research

Patient-oriented research encompasses many study designs, from cross-sectional questionnaire studies to large-scale clinical trials. The NIH defines a clinical trial as, „A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.“ Clinical trials of an experimental intervention may be done in a small group of people to determine a safe dosage range and identify side effects (Phase I), in a larger population to determine efficacy and further evaluate safety (Phase II), in a very large population to compare effectiveness with other standard or experimental interventions and to collect information that will allow the interventions to be used safely (Phase III), and to monitor the effectiveness and safety of the approved intervention in the general population after it has been marketed (Phase IV)

Conducting clinical research is challenging. An Institute of Medicine workshop identified several key challenges as follows (149):

1. Prioritising of clinical research questions
2. The divide between clinical research and clinical practice
3. Globalisation of clinical trials
4. The cost of clinical trials
5. Narrow incentives for physician participation in clinical research
6. Shrinking clinical research workforce
7. Need to navigate administrative and regulatory requirements
8. Recruitment and retention of patients

The next section focuses on some challenges that are of particular relevance to studies of urinary incontinence and pelvic organ prolapse.

1.2. Inclusion and Exclusion Criteria

Inclusion criteria are often narrow; while results derived from a homogenous pool of participants is more likely to demonstrate a difference from an experimental intervention, the results also may be biased and applicable only in this homogeneous population (150), causing translation to generalized practice to be problematic. Narrow-inclusion criteria also may hamper the ability to meet recruitment goals. But, while broad inclusion criteria yield more generalizable results, these may also make it harder to attribute statistical significance to the intervention under study.

Inclusion criteria which focus on the condition for which the trial is providing intervention must be considered in concert with the consideration of the primary outcome measure. If an inclusion measure defines “disease,” it is essential that the outcome measure does not include this same measure or cut-point as “success.” It is also important to note that a given condition, such as stress urinary incontinence, will be present or absent depending on which outcome measure is used to define it. Investigators should avoid using one outcome measure to exclude women from a study and then a different outcome measure defining the same condition as the primary outcome measure.

Exclusion should emphasize criteria to reduce risk to potential participants, and, especially in longer-term studies, to reduce those factors that could hamper the potential for follow-up. It is important to include individuals in whom the treatment would likely be used once widespread. For example, in testing a new drug for urgency incontinence, that is excreted by the kidneys, it is important to exclude people with high serum creatinine levels, but equally important to include older individuals with multiple comorbidities in specific studies, as these are also likely to benefit from a drug for urgency incontinence once released. However, certain exclusion criteria may purposefully exclude certain common conditions (such as poor glycemic control) to potentiate safety associated with clinical trial interventions.

1.3. Blinding (Masking)

Controlled clinical trials require blinding of both investigator and site personnel and the subject (participant). Participant blinding is feasible in many types of trials (pharmaceutical trials) but may not be possible in trials of some surgical procedures, behavioral or physical therapies, or health care delivery methods. In these studies, the only possible blinded person is often the assessor. Thus, a third-party independent assessor may be required to optimize site blinding. It may be advantageous for the clinical staff to be aware of the assignment to allow them to monitor the health and safety of individuals, since the potential effects of the treatment (side effects) will often be known in advance. Single blinding ameliorates biased reporting of symptoms and/or side effects by participants. However, clinical staff can influence data collection and change other aspects of participants’ care when they know which study treatment subjects are receiving. It should be noted that blinding is not impossible in all surgical trials and should be considered when possible

1.4. Randomization

Stratified randomisation ensures equal distribution of subjects with a particular characteristic in each group when blocking is employed within strata. This is particularly important if certain participant characteristics are likely to influence the outcome. For example, in incontinence research, variables such as prior failure of therapy, degree of pelvic organ prolapse or severity of incontinence might be considered important enough to stratify at randomisation, because unequal distribution of variables important to the outcome may create headaches during the data analysis. Increasingly, demographics are being considered as critical elements in stratifaction of study populations.

The gold standard in analysing randomised trials is by intention-to-treat, according to the group to which subjects were randomised, regardless of the extent of compliance with the intended treatment. Appreciable loss to follow-up in a trial (which is not the same as adherence with intended treatment, lack of efficacy, or the observation of adverse events) may present serious problems both in terms of generalizability of the findings to the wider population and, in the case of differential loss to follow-up across treatment groups, to the validity of the comparisons. Results should always be accompanied by a full and clear description of how the analysis handled deviations from intended treatment and missing outcome measures. Missing outcome data may also affect study conclusions. (151) Sensitivity analyses can be used to test the exclusion of, or assumptions about, missing values; practical examples of such analyses are becoming more common. (152) Also, the use of last observation carried forward (LOCF) may be used in certain circumstances when subject withdrawal is problematic, however in regulatory approval trials, this technique is not optimal.

2. PROTECTION OF SUBJECTS AND INFORMED CONSENT

Ensuring participant safety is paramount. An independent data safety monitor (DSM) or data safety monitoring board (DSMB) is important to evaluate the study on an ongoing basis to determine early evidence of significant harm or benefit. (153,154) Depending on the size, complexity, and risks of a trial, the DSMB is comprised of experts needed to monitor interim data to ensure the safety of the participants. The DSMB should be established prior to initiation of the trial. In addition to reviewing results of the study for safety monitoring they may evaluate interim analyses to ensure that a treatment is not producing unacceptable levels of side effects and/or efficacyc . (153) Clinical events committees (CEC) may also be used in clinical trials as another oversite group to assist in unbiased, third party assessment of adverse events and other clinical reports arising from trials, especially those evaluating device interventions.

2.1. Analysis

High quality data management is key to providing valid and ethical research results. (155) The analytical plan should be consistent with study aims and the a priori analytical plan should be included at the time of the protocol entry into a clinical trials registration system. (156) Stopping rules or boundaries are established to assess-if the study should continue or be terminated due to futility (that is, no conclusion will be drawn due to low enrollment, few outcome events, or high drop out rates etc.), reaching an endpoint, or identifying increased risks. Guidelines for stopping the study should be agreed upon, prior to the start of the trial. Interim analyses (in particular those based on efficacy) will have implications for the study power. Specialist statistical advice and support will be essential to address these issues, (157) Investigators must not be aware of the results of interim analyses, however, since this may cause bias by influencing how vigorously any given patient is recruited into or followed up in the study, and most importantly, runs the risk of a type 11 error (i.e. mistakenly concluding benefit when there is none). Nevertheless, emergency procedures for unblinding a patient‘s allocation are required in case of a severe side effect or concomitant serious illness where knowledge of treatment assignment is essential for patient management and safety. (157)

3. CHALLENGES IN CONDUCTING TRIALS IN DEVELOPING COUNTRIES

Conduct of clinical trials in developing countries presents ethical, organizational, cultural and infrastructural challenges to researchers, pharmaceutical companies, sponsors and regulatory bodies.(A balance between managing these challenges while yet conducting the trials is important so that research can be encouraged and supported in order to bring maximum public health benefits to these communities, often underrepresented in research. Difficulties, as outlined by authors of an investigator-initiated trial, include “obtaining valid informed consent, ethical compensation mechanisms for extremely poor populations, poor health infrastructure and considerable socio-economic and cultural divide_s (158). Other challenges include appropriate linguistic translations of forms and support documents, access to care at the conclusion of the trial, administrative bottlenecks, equitable investigator (as well as participant) compensation, difficulty in obtaining skilled researchers, and regulatory bodies with different standards from those of developed countries.

3.1. Trial Registration and Data Sharing

The International Committee of Medical Journal Editors (ICMJE) initiated a policy in 2005 requiring investigators to enter information about trial design into an accepted clinical trials registry at or before the time of first patient enrollment. (159) This requirement, adapted by many journals, aims to restrict the practices of selective publication and selective reporting of research outcomes, as well as to prevent unnecessary duplication of research effort. The ICMJE accepts registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) or in ClinicalTrials.gov. The ICMJE encourages registration of research with non-trial designs, such as observational studies, but does not require it at this time. The ICMJE also encourages posting of clinical trial results in clinical trial registries but does not require it; such posting is not considered a prior publication if the results are limited to a brief abstract or tables.

Standards recommended by ICMJE are frequently adapted by medical journals and therefore play a major role in guiding research conduct. Thus, it is of interest to note that at the time of this writing, the ICMJE posted proposed requirements for sharing clinical trial data and is inviting public feedback. In an editorial, the Committee notes that “there is an ethical obligation to responsibly share data generated by interventional clinical trials because participants have put themselves at risk” (160).The ICMJE recommendation continues: “As a condition of consideration for publication of a clinical trial report in our member journals, the ICMJE proposes to require authors to share with others the de-identified individual-patient data (IPD) underlying the results presented in the article (including tables, figures, and appendices or supplementary material) no later than 6 months after publication.” The proposal also requires that authors outline a detailed plan for data sharing at the time of clinical trial registration. Nuances of data sharing should be considered in planning clinical trials (for example, in the consent process, participants must be asked to provide consent to have de-identified data shared publicly). Investigators should stay abreast of changes in this rapidly evolving area.

Many funding agencies around the world require publications resulting from such funding to be deposited in an open repository, so that they are freely available to all. In general, authors submit the post-print (the manuscript after peer review and acceptance but before copy editing, formatting or other journal-specific tasks) to a repository accessible online without charge. A large number of journals now assist the author by automatically depositing the published content into a repository such as PubMed Central.

3.2. Reporting Research Results

The investigator has an ethical responsibility to take responsibility for all aspects of the research, ensuring that the work is done rigorously and to maintain the integrity of the research. Investigators should adhere to published standards in reporting their research results, in order to maximise quality and transparency. Further, most journals require this. Adherence to these guidelines and the use of flow diagrams in particular is associated with improved quality in reporting of RCTs. (161) The “Enhancing the QUAlity and Transparency of health Research” (EQUATOR) Network project (www.equator-network.org) provides a continuously updated platform of the many different guidelines now available for reporting the design, methods and results of different study types. The most commonly used guidelines for clinical research are listed below:

- Consolidated Standards of Reporting Trials for randomized clinical trials (162)
- Strengthen the Reporting of Observational Studies in Epidemiology (163) Of note, these guidelines do not pertain only to

prospective cohort studies, as sometimes assumed, but also to cross-sectional, case-control and retrospective studies.
- Standards for Reporting of Diagnostic Accuracy (164) : for studies about the accuracy of diagnostic tests.
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (165): for systematic reviews
- Standards for Quality Improvement Reporting (166)

3.3. Study Conduct and Statistical Methods

The role of quality RCTs as providing the strongest level of evidence in incontinence research should be fully acknowledged by researchers, for studies about quality improvement in health care the following guidelines and consensus statements are informative:
- Excellence (SQUIRE) (166)
- Standard protocol items for clinical trials (SPIRIT) - this is an excellent resource in planning a clinical trial. (167)

To improve guidelines adherence, a checklist accompanies each guideline. It is crucial that the reporting guidelines be considered during the planning phase of the study in order to ensure that all key elements are collected as required.

Most of the guidelines contain additional separate items for certain types of studies. In this section, we use the CONSORT guidelines as an example. CONSORT includes additional guidelines for reporting parallel group randomised trials, pragmatic trials, non-inferiority and equivalence trials, and cluster randomized designs. (168) The statement includes a checklist of items that covers a comprehensive set of characteristics of a clinical trial. These include clear statements about the objectives of the trial, intended study population, planned comparisons and justification for any subgroup or covariate analyses. The method and unit of randomisation should be stated. For all trials, specifications for the sample size calculation (primary outcomes, target differences, etc.) should be stated and justified. In addition, the precision actually obtained in a study must be presented. This requires confidence intervals as well as the observed p-values, at least for primary outcomes but preferably for all outcomes. The principal confidence intervals should be for comparisons between the groups, rather than for differences in the outcomes within the trial groups. (157,169,170) Results should include a trial flow diagram, with numbers and reasons for the exclusion of eligible subjects, the number randomized and subsequent losses to follow-up. (171) Protocol deviations should be described and explained. (172)

Harms of the trial should be described for each treatment group. Finally, the discussion should include a brief summary of the trial‘s findings, possible explanations for the results, interpretation of the findings in light of the literature, limitations of the trial including internal and external validity, and the clinical and re search implications of the study. (173) Some guidelines also include specific information that must be included in publication abstracts. These are particularly important to follow, given that many readers rely solely on the abstract for their interpretation of a study.

4. SPECIAL CONCERNS FOR SPECIFIC STUDIES

4.1. Systematic Reviews

Systematic review remains perhaps the most formalised part of epidemiology, with a wealth of available guidance for the correct conduct and reporting of reviews (164, 174-178) , and the creation of recommendations based on the evidence. (176) Without transparent reporting of systematic reviews, it is difficult for editors and readers to judge the quality of a review. One fundamental step that is frequently overlooked is prospective registration of the review protocol in a database such as PROSPERO. The types of studies included should be pre-specified, along with all planned outcomes and analyses.

Searches should encompass a range of sources, perhaps including Medline, EMBASE and CINAHL. Importantly, as many studies never reach publication, efforts should be made to search the grey literature. It is almost always helpful to directly contact primary study authors for clarifications, additional information about methodology, and even additional data or analyses where necessary.

The screening and data extraction process should be planned in advance, and all reviewers should be trained to use the data forms, to achieve a high level of consensus. All screening and data extraction should be performed independently and in duplicate. Reference lists should be hand searched for all included articles, applying the same standardised screening process, as this can pick up additional relevant studies.

Statistical methods are equally formalized for metaanalysis. Fixed effects models (Mantel-Haenszel weighting) (179) should be used for meta-analyses with only two studies, or for three or more studies and low heterogeneity, but otherwise random effects models (Dersimonian and Laird) weighting should be used. (175)Assessments of risk of bias in primary studies, and for the meta-analysis as a whole (177), are important particularly when formalising recommendations based on the pooled evidence, and should follow the most relevant scheme for the types of studies included. (178)

4.2. Quality Improvement Studies

The SQUIRE (2.0) guidelines facilitate performance, analysis, and publication of quality improvement. (166) SQUIRE 2.0 is the inclusion of a glossary of key terms to help standardise definitions and clarify the use/misuses of commonly employed phrases in the quality improvement literature. Terms such as „intervention,“ „opportunity costs,“ „process,“ and „systems“ are clearly defined. The guidelines also present information about context (interpreting the work within its own unique environment), and studying the intervention (evaluating the generalisability of the intervention as opposed to simply performing or doing it). The guidelines are presented in a printable 18-item table that takes potential quality improvement investigators through a step-by-step process for performing and publishing their work from abstract to conclusion.

4.3. Observational Studies Using Routinely Collected Health Data

Observational studies using routinely collected health data obtained for clinical and administrative purposes (often referred to as „database studies“) are increasingly common, given the increased availability of health administrative data, disease registries, electronic health record data repositories, public health reporting data, etc. The major advantage of these studies, that the data are already collected often on millions of people, is also the major drawback: Because the data were collected without a specific a priori research goal in mind, the database may lack key information needed. Further, the information collected, especially in administrative data collected for billing purposes, may not be accurate; validation is often required. However, the potential of such databases to enable efficient and cost-effective research is substantial.

The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement is an excellent resource for investigators planning and reporting such studies. (180) Below we summarize, based on this statement, some of the key recommendations for investigators planning studies using routinely collected health data. Further detail is available in the full report.

- Clarify whether the analyses were exploratory or confirmatory, and indicate whether the hypotheses were generated before or after data analysis.
- For studies that involve linkage of databases, display in detail the data linkage process.
- Explicitly state the methods used to identify study subjects, including whether identification is based on single codes, algorithms (combinations of records or codes), linkage between databases, or free-text fields.
- Provide a complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers.
- Describe data cleaning methods at different stages of the study (for example, how were missing data and repeated measures handled?)
- Clearly define how the final study population was derived.
- Consider potential sources of bias: „(1) codes or algorithms to identify study populations, outcomes, confounders, or effect modifiers (misclassification bias); (2) missing variables (unmeasured confounding); (3) missing data; and changes in eligibility over time“. (180)

Unmeasured confounding is particularly problematic in these types of studies. The fact that an outcome was assessed in a very large population cannot make up for the absence of an important potential confounder in the database. The investigator is better off looking elsewhere to answer the research question at hand. Another problem frequently arising in studies using large databases are changes in composition of the database population or coding practices over time. Such changes challenge the integrity of temporal comparisons using the dataset. Finally, some journals require that the author attest to the reliability and validity of key variables used in a database before they will consider publication of these studies.

5. EXPERIMENTAL DEVICES AND MATERIALS

Surgical research presents unique challenges to efforts at optimizing patient care. It is important to create a pathway for real advances while simultaneously protecting patient safety. When new procedures are substantially different from prior operations there should be a broad-based preliminary exploration leading to a comparative trial if warranted. At the same time, many minor modifications of surgical procedures are inappropriate for randomized trials and if required, surgical progress would be slowed. (181)

It has been argued that the first patient in whom a procedure is performed should be randomized. (183,183) Alternatively, it has been suggested that case series for new procedures are allowed until the procedure finds its intended use and to avoid doing studies while those performing the procedures are on the „learning curve“. Typically, new surgical procedures for incontinence have been reported as case series. (184,185) Pilot and feasibility studies are necessary, providing sufficient methodological evidence for the further randomized trials. They can also provide the lowest level of evidence for treatment effects and justify for the trials. However, in some situations, case series may be „harmful“. An accumulation of „positive“ case series may present a premature certainty about benefits of a procedure and make it even more difficult to perform randomized trials. (186,187) Influential members of the surgical community may endorse a new procedure and if the procedure is considered better it may be difficult to get surgeons and patients to randomize or a trial may appear to be unethical with a „proven“ procedure. (182)

Therefore, devices often are widely adopted by clinicians based on anecdotal data, marketing, or small case series. This raises a unique problem for trials in this area: 1) Surgeon buy-in can be difficult to obtain as some surgeons („early adopters“) may perceive that the newest therapy is best and thus be unwilling to randomize patients to receive the traditional therapy, 2) Other surgeons („late adopters“) may perceive that the data available do not support use of the newest therapy and thus be unwilling to randomize patients, 3) Patients may be unwilling to be randomized to traditional therapy because they are influenced by marketing forces propelling the newest devices to the forefront, and 4) Device companies frequently modify their materials or technique recommendations; therefore, by the end of the 3-5 years it typically takes to complete the earliest outcome assessment for a surgical randomized trial, the device tested is no longer the same as the device used in the trial. Thus, the results may be discounted as being no longer applicable.

An important area of concern in surgical and device studies is patient recruitment procedures. The protocol should detail the procedure for selection of consecutive patients who meet the inclusion criteria. All situations in which a patient meets the inclusion/exclusion criteria but is not offered enrolment by the investigator should be documented. The number of patients who decline enrollment should be stated, along with the reasons. It is vital that clinician researchers do not „cherry pick“ from their patients, that is, that they do not limit recruitment to those patients considered to have the greatest chance of cure or lowest chance of risk. The study population should be as generalizable as possible. There should be a complete accounting of all participants in the study including the reasons for subject withdrawal. Participants must be well informed about what is known and not known about devices or procedures being tested. They should not be led to assume that because a device is on the market, it is „safe and effective“, as gaining knowledge about this is the purpose of the trial.

Randomized controlled trials (RCTs) have long been recognized as the gold standard for assessing the efficacy of clinical interventions, valued for their statistical rigor and mechanisms to avoid bias (188) . However, clinicians increasingly recognized the limitations: each patient had unique pathological findings, each surgeon had different skills, and each operation involved countless choices about anesthesia, premedication, surgical approach, instrumentation, and postoperative care, all of which defied the standardization that clinical trials required. In recent years, the significance of real-world study (RWS) in clinical research has gradually been realized (189). Real world evidence (RWE) in medicine means evidence obtained from real world data (RWD), which are observational data obtained outside the context of RCTs and generated during routine clinical practice (189). It is derived from a number of sources that are associated with outcomes in a heterogeneous patient population in real-world settings, such as patient surveys, clinical trials, and observational cohort studies. RWS that can sustain follow-up observation after the completed RCT research holds important significance. However, it should be emphasized that RWS must be fit for purpose, and it cannot replace RCT (190).

6. SURGICAL INTERVENTIONS

Cross-sectional studies of surgical procedures by type can provide estimates of prevalence, variation by age, race, and region as well as morbidity and mortality. (191,192) This type of information raises important health policy questions regarding physician practices, patient preferences for incontinence treatment, and differential access to, and the utilization of care. Observational studies can provide important information about effectiveness and complications of surgical procedures, and also are very helpful in designing and selecting potential randomized clinical trials.

The randomized controlled trial is the accepted „gold standard“ for research of treatment effects. In all surgical specialties, there has been growing concern regarding the limited number of randomized controlled trials for surgical procedures, poor methodological standards in those that have been performed, and a perception that surgeons are reluctant to rigorously test new surgical interventions. (182,186, 193,194)

The body of literature of surgical randomized trials in pelvic floor disorders is increasing. Modern trials are beginning to overcome historical limitations including insufficient sample sizes, lack of blinding of the participants and/or individuals assessing the outcomes, short follow-up, inclusion of limited number of surgeons only, poor description of the technique, and lack of standardized outcome measures. Multicenter treatment networks appear effective in overcoming some of these limitations. Differential drop out after randomization (or for cohort studies, after the intervention} can introduce bias. Randomization can occur in the operating room after the patient was anaesthetized, reducing this risk. (195,196)

For studies of specific surgical procedures, the technique should be described in such detail that it could easily be reproduced in another study. Standardization of the procedure may vary depending on the research question. (197) Surgical trials using a small number of highly skilled surgeons are analogous to medical trials where only compliant patients are randomized, reflecting efficacy of the procedure in an ideal setting. It may be more generalizable to a mixture of skill level among surgeons in the community, and so reflect effectiveness of the procedure in usual practice. (187)

Masking (blinding) of participants as to their assigned intervention and those assessing the outcome is particularly important for surgical trials for incontinence because there may be enthusiasm by the patient or surgeon for a new procedure, many outcomes are based on the patient‘s own assessments such as symptom and quality of life scores, and the intervention is primarily for improvement of symptoms. (181)

Organizations and treatment networks have been established to address many issues related to surgical interventions. Examples include the UK National Institute of Clinical Excellence (NICE www.nice.org.uk), the Australian Safety and Efficacy Register of New interventional Procedures- Surgical (ASERNIP-S www.surgeons.org/asernip-s}. The NICE and ASERNIP-S provide systematic reviews of new operations, assessment of effectiveness, and recommendations that the technique has sufficient data for widespread use, or that the techniques appear unsafe, or that further research are required before its widespread usage.

The need for more surgical randomized trials is well recognized, and in recent years, the number of surgical trials has grown. When it comes to surgical treatment, most RCTs have a high or ambiguous risk of bias, especially selection bias. Due to the nature of the operation, it is not feasible to blind participants and staff (198). Recently, RWS has gradually become a hot research method by strictly standardizing the design, measurement and analysis of clinical big data (199). It allows for surgeons to evaluate the surgical procedures in a larger population and provided high-quality evidence in the true clinical situation.

7. RESEARCH PRIORTIES FOR SURGICAL AND DEVICE TRIALS

An agreed and standardized technique for the surgical procedure or device application should be clearly defined

The safety and serious side effects of new operations or devices, especially implantable devices and biologic materials, must be completely defined with adequate follow-up so that risks can be weighed against efficacy. At a minimum, this requires more use of large scale, independent, prospective, multicenter cohort studies when RCTs are not practical.

Valid informed research consent is required in all trials of research surgical interventions; this research consent is separate from the main surgical consent.

Whenever possible, randomization for surgical trials should occur at the time of surgery to minimize dropouts and switch of procedure

Reports of successful treatment should be limited to subjects with a minimum (not mean) of one-year follow-up and should include a patient perspective measure. Specific assumptions about subjects lost to follow-up should be stated.

Long-term follow-up of RCT cohorts in an observational cohort is recommended

8. RESEARCH PRIORTIES FOR PHARMACOTHERAPY TRIALS

Although many randomized clinical trials (RCTs) of pharmacotherapy for urinary incontinence have been published in recent years, a great deal more remains to be learned (200). In addition to conventional clinical trials of oral drug therapy for urinary incontinence, novel clinical trials of botulinum toxin injection to bladder wall (201,202) and autologous stem cell transplantation to urethral submucosa (203) have emerged in recent years.

The trials have been mostly limited to 8-12 weeks of treatment giving little information about long-term safety and efficacy of therapies. Inclusion criteria are often stringent, such that the study population of healthy middle-aged people bears little resemblance to the patients for whom providers wish to prescribe medication. There is less than adequate information about special patient groups-men, children, neurogenic patients, and especially the frail elderly. Because incontinence induces such an impact on the older population, well-designed studies to define the utility and safety of drug therapy are greatly needed in this group.

Anticholinergics are commonly used for the treatment of overactive bladder (OAB). In the elderly population, this can add to an individual’s anticholinergic load. There are increasing data suggesting that a high anticholinergic load increases the risk of cognitive adverse

events and the development of dementia in the elderly (204). The further studies focused on the anticholinergic load in frail elderly with OAB are needed (205).

Another issue of special relevance in trials of pharmaceutical agents is the controversy regarding placebos in clinical trials. Regardless of whether a drug is effective or not, simply giving a drug to a patient may produce a beneficial response. To assess if a drug has an effect over and above the placebo response, it is usually tested against an inactive substance (placebo). In incontinence studies, the placebo effect may be quite large, anywhere from 30-50% in recent published studies (206). In order to account for this, investigators and regulators have generally demanded a placebo arm in most clinical trials of medication. While this may be acceptable to participants for short trials, it is neither ethical nor feasible to withhold treatment for longer periods of time. Recently, a clinical trial using stem cells where a conventional treatment set as a control group has been enrolled, but these trials are still few. Further, clinicians and patients generally want to know how a new drug compares with established treatment. Masking, while desired in all types of trials, is especially important in pharmacological trials. Further, it is feasible to do in such trials (as opposed to surgical or conservative interventions, in which masking may not always be possible) and thus should be prioritized. However, the identical appearance of two pills does not guarantee that participants will be unaware of group assignment. Side effects common with anticholinergic therapy, such as dry mouth, may unmask participants. Studies should assess the degree to which masking was successfully maintained.

New clinical trials have emerged, including stem cell transplantation and intravesical injection of botulinum toxin, which are different from the conventional oral drug therapy. Little is known about the safety, efficacy and tolerability of drug therapy beyond 12-week trials. High anticholinergic load may induce cognitive adverse events in frail elderly with OAB. Placebo has a role in the improvement of urinary incontinence, supporting the need for placebo control in RCTs.

Research Priorities

As effective drug therapy is available for most forms of incontinence, active drug comparator arms are recommended for most trials.

Long-term follow-up of RCT cohorts in an observational cohort is recommended. -

Further studies focused on the anticholinergic load in frail elderly with OAB are recommended. -

9. COST ANALYSIS

Economic and health policy outcomes are gaining increasing importance, as policy makers deliberate the values of different therapies. The financial burden on the health care system, the patient and patient's family of various treatment options makes cost an important outcome to measure. We recommend that cost analyses be planned with clinical studies whenever possible. Costs may be influenced by economic and political factors that are subject to change at any time; however, when basic units of work, time, and resources are carefully defined, models of costs remain useful even if market forces change in an unforeseen manner.

In health and medicine, economic analyses are descriptive and/or comparative. Descriptive data include the socioeconomic cost caused by the disease and its current treatment, whereas comparative data provide an economic evaluation of different treatment strategies and interventions where costs are compared to health outcomes.

There are several relevant types of cost analysis, some of which require a high level of expertise to conduct:

- Cost of illness analysis (COi) typically quantifies the burden of medical expenses (direct costs) and the resulting value of lost productivity (indirect costs) attributable to a specific condition such as an illness or injury (207,208).
- Cost effectiveness analysis (CEA) measures the costs and consequences of two or more diagnostic or treatment pathways related to a single common effect or health outcome. It then summarizes the results in ratios that demonstrate the cost of achieving a unit of health effect for different types of patients and for variations of the intervention. (209,210)
- Cost utility analysis (CUA) is a form of cost effectiveness analysis in which particular attention is paid to the quality of health outcome related to treatment. In CUA, health effects are expressed in terms of quality-adjusted life years.
- (QALYs). (211) A QALY is a measure of health outcome that assigns to a given period of time a weighting that corresponds to the health-related quality of life during that period, and then aggregates these weights across time periods. The QALY is important because it considers both quantity and quality of life.

Cost benefit analysis estimates the net social benefit of an intervention by comparing the benefit of the intervention with the cost, with all benefits and costs measured in dollars. Health outcomes are converted into monetary values using „willingness to pay" (the value an individual would pay for reduction in illness severity) or „risk of death" or „human capital" methods (an individual's value to society based on productivity or future wages). (197,207)

For a further discussion of these concepts please see Chapter 21 (Economics of Urinary and Faecal Incontinence, and Prolapse).

Research Priorties

Cost analysis should be incorporated into clinical studies whenever possible. (210)

10. BEHAVIORAL AND PHYSIOTHERAPY TRIALS

The lack of consistent terminology severely hampers the ability to build a body of literature about conservative interventions. The terms „behavioral therapy," „lifestyle intervention," „conservative treatment," „non-surgical treatment," „physiotherapy," „biofeedback and pelvic floor muscle exercise" are often used interchangeably and incorrectly to describe both the same, and different interventions. While such therapies are discussed elsewhere in this consultation, we here advance this committee's opinion about appropriate terminology, consistent with the most recently updated terminology manuscript. (212)

According to the Oxford Advanced American Dictionary the term behavioural is „the way someone behaves, especially towards other people", and behavioural science is the study of human behav-

iour. We recommend that behavioural science be limited to studies that evaluate how people do or do not behave as desired.

Lifestyle modification interventions for UI are discussed elsewhere in this consultation and have traditionally included diet modification, intake of caffeine and carbonated soft drinks, fluid restriction, weight loss, smoking cessation and advice of increasing general physical activity level. Behavioural science can be used to understand how and why people change lifestyle to, for example, adhere to exercise and weight loss programs, but it should not be used as term to replace specific therapies such as physiotherapy or pelvic floor muscle training.

Physiotherapy refers to assessment, prevention and treatment given by an authorised physiotherapist (ICS physiotherapy committee www.icsoffice.org). It involves "using knowledge and skills unique to physiotherapists" and "is the service only provided by, or under the direction and supervision of a physiotherapist" (WCPT 1999). This implies that the term physiotherapy should only be used in trials where the professional providing the intervention is a physiotherapist. We recommend describing the actual intervention instead of using the term physiotherapy: e.g. pelvic floor muscle training with or without biofeedback, electrical stimulation, pelvic floor muscle training with vaginal cones or resistance device etc. This accurately describes the intervention and is neutral towards the administering professional. Publications should report the actual profession of the interventionist (e.g., physiotherapist, general practitioner, urogynaecologist, urologist, midwife, nurse, fitness instructor), rather than using the vague term, "therapist."

Biofeedback: Biofeedback encompasses "a group of experimental procedures where an external sensor is used to give an indication on bodily processes, usually in the purpose of changing the measured quality". (212,213) Biofeedback equipment was developed within the area of psychology, mainly for measurement of sweating, heart rate and blood pressure under different forms of stress. Today, a variety of biofeedback apparatuses are commonly used in clinical practice to assist with PFMT, and the biofeedback can be either visual, auditory or both. In many textbooks the term "biofeedback" has been used to classify a method as different from PFMT. However, bio feedback is not a treatment on its own. It is an adjunct to training. For example, it may measure the response from a single PFM contraction or provide visual feedback during attempts to relax the muscles. Hence, a more precise terminology is PFM training or relaxation with or without biofeedback.

Many different assessment methods can be used to provide biofeedback. These include: manometry measuring urethral, vaginal and anal squeeze pressure, dynamometry, surface, wire and concentric needle EMG, ultrasonography and MRI. (214,215) In addition to traditional biofeedback apparatuses, other instruments can offer valuable feedback. Vaginal and anal surface EMG, urethral, vaginal or anal squeeze pressure measurements, ultrasound and MRI can all be used to make the patients more aware of muscle function, and to enhance and motivate patients' effort during training. (216)

Conservative interventions/treatments: Conservative interventions include all of the above, and this term includes everything except medication and surgery. (214,215) As several studies have found that more than 30% of women with pelvic floor dysfunction are not able to perform a correct PFM contraction at the first consultatiocn. (217-220) It is mandatory to report how ability to perform a correct contraction was assessed before commencing an exercise trial. Also, in electrical stimulation research one should report in which way response to the stimulation was assessed.

Although there is level A, grade 1 evidence for some of the conservative interventions such as PFMT for SUI and POP, a variety of new conservative methods to treat the condition are frequently suggested in clinical practice and in the literature. These new methods are often presented as being effective but are usually only based on a hypothesis based on theories, data from small experimental laboratory studies/small clinical series, or associations found in large epidemiological studies. If the clinicians like the approach, it soon enters clinical practice and textbooks without any further critical testing. (221) A model for how new therapies ideally should enter clinical practice has been proposed((222). In this model, the new idea should go through at least several stages before they enter practice:

- Clinical observation and laboratory studies
- Clinical exploration
- Pilot studies
- Randomised controlled trials
- Refinement, e.g. dose-response issues
- Active dissemination of the method if it has proven to be effective

It is important that the patients participating in the 3 first stages before the RCT are given full information that they are participating in an experimental treatment, and that the clinician does not know if this new approach is effective. The patients also need to be informed if there are other proven effective treatments available.

10.1. Reporting of Trial Characteristics

In addition to reporting the specific type of intervention (e.g. PFMT with biofeedback compared to PFMT alone or electrical stimulation) and the profession administering the intervention, the intervention needs to be described in such detail that other investigators can reproduce the intervention. This includes:

- Ability to perform a correct PFM contraction.
- Frequency: number of home training sessions and supervised training sessions (e.g. every day, 3 times/week)
- Number of repetitions and sets (e.g. 12 sets x 3 times/ day)
- Duration: length of each training session (e.g. 20 minutes), and duration of the total training period (e.g., 3 months, 6 months)
- Intensity: In exercise science, this is usually reported as % of one repetition maximum for strength training. In pelvic floor muscle training it is often described as attempts to reach maximum contractions or utilizing submaximal contractions. Another description of intensity is the holding time in seconds, e.g.: 6-8 sec
- Adherence: the degree to which participants follow the prescribed protocol, usually reported as a percentage of the total possible.
- Educational material provided, such as apps, DVDs, brochures and booklets should be described. (223)
- Assessment: All devices used for assessments (e.g. manometers, dynamometers, ultrasound and EMG) must be described in detail, and their responsiveness (ability to detect small changes), reliability and validity should be reported{. (225)

10.2. Adherence vs. Effectiveness

It is important to note that adherence is not the same as the effectiveness of a program, as it is possible to have high adherence, but still little effect of training. (225) Hence, when reporting the effect of conservative interventions, it is ideal to also measure the exposure variable that the treatment is expected to change (e.g. muscle strength, ability to relax etc.). This variable should not be

confused with the primary or secondary outcomes of the intervention (e.g leakage measured with pad testing, number of leakage episodes or Qol).

In many areas of conservative interventions there are high quality RCTs, systematic reviews and meta analysis showing statistically significant and clinically relevant differences between the intervention and the untreated control group or other interventions. Of conservative therapies, PFMT for SUI/MUI has the strongest evidence to support its use; further, the more intensive the program (more supervision, higher dosage of training) the better the effect. In addition, there is also 1A evidence/recommendation for PFMT to be first line treatment for POP (see chapter ICI Conservative Treatments in Adults). Therefore, when comparing new methods and innovations with established PFMT, it is important to compare the new intervention with the current best evidence, meaning the effective arm of the reported RCTs. Unfortunately, it is common to compare new methods with an ineffective training protocol, thereby overestimating the effect of the new method and claiming that it is equal to or better than "the old method". When comparing different methods, the dosage also needs to be the same in both treatment arms (e.g. when comparing PFMT with and without biofeedback, the number of supervised sessions, length of the sessions, frequency of home treatment and duration of the intervention must be the same). In a multicenter RCT comparing the exact amount of exercise dosage and attention by the therapist between PFMT with and without biofeedback, there was no additional effect of adding biofeedback on long-term continence outcomes. (226)

10.3. Adverse Events and Cost

There are few adverse effects or complications reported after conservative interventions, but they do exist, (e.g. in electrostimulation),(227) and adverse effects or lack of adverse effect, and inconvenience to the patients should be reported. Although seldom harmful, conservative treatments are time-consuming and can be costly for participants and paying parties because of the need for close follow up during the interventions. Cost effectiveness studies are crucial to fully understand where conservative therapies fit in the treatment armamentarium. (228)

10.4. Outcome Measures

The need for use of responsive, reliable and valid outcome measures in research is covered elsewhere in this chapter. The RCTs published in conservative treatment have applied a plethora of outcome measures, making systematic reviews and metaanalysis difficult or impossible to conduct. Therefore, in future research it is important to use established and recommended outcome measures. In addition to description and use of responsive, reliable and valid primary and secondary outcome measures, future studies should include description and assessment of adherence to the intervention protocol, measurement of the independent variable (the intervention; e.g. strength training, relaxation training) and measurement of the possible underlining mechanisms of how the treatment works. It is usually not possible to blind the participants or those providing the intervention, but the assessors of outcome should always be blinded to group allocation.

10.5. Specific and Non-Specific Effects

There have been some concerns that the effect of conservative treatments can be attributed to non-specific effects such as the extra attention of the therapist. The role of the therapist is to educate, motivate and empower the patient to be able to perform the actual program, secure high adherence, and minimize participant drop out. In patient-reported outcomes and reports on quality of life, it may be difficult to separate the effect of the attention and the actual effect. However, the effect of the attention is less likely to affect outcomes such as muscle strength, urodynamic assessments, pad testing and morphological changes measured by ultrasound and MRI. Investigators blinded to treatment allocation should conduct all assessments in order to minimize bias. The logistics of this should be addressed during the planning phase of the study. In a high quality RCT, Dumoulin et al address the problem of attention in physiotherapy research. (228) Women with persistent SUI, three months after childbirth were randomized to either two different training regimens or a control group receiving relaxation massage for the back and limbs for the same amount of time as the supervised pelvic floor muscle training groups. 70% were cured on pad-testing in both treatment groups while there was no effect on urine loss in the relaxation massage group. Participants in the massage control group had improvement in disease specific quality of life.

10.6. Power Calculations and Number of Participants

Some of the RCTs on conservative treatments are flawed by small sample sizes, this being especially evident in electrostimulation studies and may account for negative effects caused by type II errors. It is important that future studies use results of previous published studies to make appropriate power calculations that incorporate estimates of dropouts and loss to follow-up to decide the optima! number of participants needed. Recruiting large numbers of participants may come at the expense of the rigor of the intervention. (229) Weak interventions (e.g. non-optimal training dosages or suboptimal electrostimulation parameters) are unlikely to be effective and do not yield the true effect of an intervention. In meta-analyses, adding RCTs with large sample sizes but weak and ineffective interventions can dilute the effect of smaller RCTs with higher methodological and interventional quality (229)

10.7. Long-Term Studies

Challenges in long-term follow-up studies include cross over to the more effective treatment after cessation of the original RCT, co-interventions during the follow-up period, recurrent events (e.g. new pregnancy}, competing events (other diseases leading to incontinence) and loss to follow up. For conservative interventions it is expected that any training effect will diminish over time if no maintenance training is conducted or the pre- or co-contraction of the pelvic floor muscles has not resulted in morphological changes to the pelvic floor during the original trial. [230] Nevertheless, of the 19 long term follow-up studies reported by Bø & Hilde five studies reported sustained success rates (ie, percentage remaining

free of UI at long-term follow-up), which were between 41% and 85%. Surgery rates in the long term varied between 5% and 58%. (231) In order to control for as many of the above-mentioned factors as possible, it is recommended that the long term follow up study should be planned together with the original RCT. (232) Loss to follow-up and adherence to the protocol during the follow-up period must be reported. (221,222,224,226-229,233)

Research Priorties For Conservative Treatment Trials

- Use correct terminology to describe the intervention.
- Report details of ability to perform correct contraction, dose-response issues and adherence.
- Use recommended outcome measures with high responsiveness, reliability and validity.
- Compare new methods with the best available intervention.

- Use power calculation in planning of the study. Avoid large sample sizes and weak (ineffective dosages) interventions.
- For long-term follow-up studies report cross over, co-interventions, recurrent and competing events, adherence in the follow-up period and loss to follow-up

11. RESEARCH PRIORTIES FOR SPECIAL PATIENT GROUPS

11.1. Men with LUTS

When considering men with LUTS, one must consider some unique factors that may influence urinary tract symptoms independently of any intervention, and so confound any data. These are the presence of the prostate gland that can cause bladder outlet obstruction (BOO), and the rarity of sphincter incompetence except in men who have undergone surgery for benign or malignant prostatic disease. For short term outcomes after intervention studies, these factors are unlikely to be relevant, but longer term follow up, and large observational or epidemiological studies· may need to take these factors and changes over time into account when analyzing data. The prostate gland may complicate research outcomes as a result of outflow obstruction (either at baseline, or development of a new problem during follow up studies). Also, for patients with prostate cancer (either at the time of enrollment, or during follow up of longer studies), it is likely that both the disease, and the treatment given (surgery or radiotherapy) may alter urinary tract function and symptoms independently of any intervention in the study and thus confound the outcomes. , Overall, about 2/3 of men with LUTS have urethral obstruction and over 50 % have detrusor over-activity, although a much smaller number have urinary incontinence due to detrusor overactivity. (234) If prostate size is considered to be a variable that could affect outcomes, measurement of prostate volume should be made before and after treatment. The method used to measure volume and its reliability and validity should be provided if available or their absence indicated. Any associations between outcomes and change in prostate size should be tested for using appropriate methods and reported. Consideration should be given to stratifying participants by prostate volume when there is suspicion that response to therapy may be size dependent.

Insofar as about 2/3 of men with LUTS have bladder outlet obstruction (BOO), any research protocol in men should consider inclusion of a method to screen for it. At the least, maximum free urinary flow rates and measurement of post-void residual urine should be recorded before and after treatment and the effect of therapy on these parameters should be documented simultaneously with assessment of the primary outcome variables. Synchronous pressure-flow studies are generally desirable and should be included whenever feasible. Several pressure-flow nomograms have been proposed to diagnose obstruction in men. It is important to specify which if any nomogram is being used; the ICS nomogram is recommended. (235)

Research Priorties In Men

- Measurement of prostate size should be performed before and after treatment (at the same time as continence outcome measures where possible) whenever prostate size is considered to be a potentially important variable, or to change during the intervention and follow up.
- Maximum free flow rate and measurement of post-void residual urine should be recorded pretreatment and the effect of therapy on these parameters should be documented simultaneously with assessment of the primary outcome variables.
- Participants should be stratified by prostate size at randomisation when size is considered to be a potentially important determinant of treatment outcome.
- Clinical evaluations of different male UI products, including strengths, limitations and efficacy in clinically relevant subgroups.

11.2. Women with LUTS

11.2.1. Hormonal effects:

Our knowledge of hormonal influences on the lower tract remains limited. Randomised clinical trials and prospective cohort studies have demonstrated that hormone replacement therapy (HRT) does not improve or may worsen incontinence. (236-238) It therefore seems appropriate that information about menstrual and hormonal status should be an integral part of the baseline history. New studies designed to examine the influence of hormones on incontinence (if considered ethical by an appropriate review board) should include details of hormonal status (premenopausal, postmenopausal without HRT, post-menopausal with HRT), the route and type of HRT (oestrogen only, combined sequential, combined continuous), and whether or not oophorectomy has been performed.

11.2.2. Obstetric History:

The influence of vaginal childbirth on the structure and function of the female pelvis is the focus of much recent and ongoing research but the complex interactions remain incompletely understood. While it is clear that childbirth, and particularly vaginal childbirth increases the risk of incontinence and pelvic organ prolapse, the potential effect of further childbirth on previous or current treatments of incontinence (especially surgery) has yet to be determined.

Potentially confounding variables include: number and route of deliveries (vaginal/Cesarean), use of forceps or vacuum, infant birthweight and head circumference, duration of second stage of labor, use of episiotomy and any vaginal or perineal trauma, and epidural anesthesia. The importance of these variables will depend upon the specific study design; for randomized studies the allocation process should balance these between groups, but consideration should be given to stratifying or minimizing the randomization against one or more of these important factors, depending on the exact intervention. For epidemiological or observational research each of these factors should be collected and included in univariate and multivariate analyses.

Research Priorties in Women

- Specific information about menopausal status, hysterectomy, parity/obstetric history, and hormonal status should be included in baseline clinical trial data and controlled for in specified analyses in the research protocol.
- High quality, symptom and bother scores (e.g.,ICIQ-FLUTS, KHO, PISQ, ICIQ-FLUTSsex) validated in women should be employed when assessing outcomes
- Standardised assessment of pelvic organ prolapse (by POP-Q) should be performed before treatment and at the time of oth-

er outcome assessments in alL research where prolapse and continence outcomes are being assessed.

- Criteria for cure/improvemen/failure from incontinence treatment should be defined in the protocol based on patient perception as well as objective and semi-objective instruments such as validated questionnaires, diaries and pad tests.

- Assessment of the impact of treatment on sexual function should be performed with other outcome assessments when appropriate.

11.3. Frail older and Disabled Men and Women

There are a number of unique and pertinent research issues for this population. In the frail elderly, important variables include:

- Demographic information: Advancing age, white race, and women (238-240) are associated with an increase risk of incontinence and each of these variables should be adjusted for in most analyses.
- Medical Conditions: Medical conditions related and unrelated to the lower urinary tract have been shown to increase the risk of incontinence in older women and are especially important to assess in the frail older population. (240-244)
- Prior hysterectomy has also been suggested as a potential risk factor for incontinence in older women. (244,245)
- Medication Inventory: Certain medications may exacerbate incontinence and therefore a complete medication inventory is essential. (244,246 – 249)
- Physical function: Mobility is often impaired in the frail elderly and impacts urinary control (250), therefore mobility should be assessed using validated instruments such as the Bartel Orcats or AOL scales. (250,251) Data on walking aids or wheelchairs, gait speed, and manual dexterity may also be collected.
- Cognitive function: Cognitive function impairment and/or dementia increase the risk of incontinence. (252) The Mini-Mental Status Scale Examination (253) assesses global cognitive function, and the Confusion Assessment Method (CAM) is a standardized assessment for delirium. (241) A battery of neuropsychological tests to measure subtle impairments in cognitive function include the Buschke Selective Reminding Test (verbal learning and memory) (254) the Digit Symbol (incidental memory, visual scanning and motor speed)., (255) and the Trails A (attention and visual).

Outcome measures should be selected for applicability to the frail elderly. Commonly used self-reported measures of frequency of urinary symptoms, severity, or level of bother may not be possible in the cognitively impaired frail elderly patient. Similarly, voiding diaries that have been shown to be valid and reliable in assessing urinary frequency, nocturia, and incontinence episodes by type may not be feasible or reliable (256-258). Motivated and trained staff, caregivers, or family members may be able to adequately collect diary data; however, this has not been validated.

In nursing home or inpatient settings, wet checks by staff at set intervals have been used in a number of studies. There are limitations to the measurement including visually determining what is “wet” because of new absorbent materials and staff reports not always being reliable or valid, due to under-reporting(.(259,260)

To overcome the limitation of defining magnitude of incontinence and under reporting, 24-hour pad weight tests may be used. (261,262) Pad weighing tests and wet checks are feasible and can provide important outcome data if staff is well trained and checks are often. I (262) New outcome measures specific to the frail older population such as increased socialization or decreased caregiver burden need to be developed.

12. RESEARCH PRIORTIES FOR STUDIES OF NEUROGENIC POPULATIONS

Neurogenic lower urinary tract dysfunction (NLUTD) is defined as a bladder disorder secondary to a known neurological lesion, disease or condition. This broad definition includes a very heterogeneous constellation of neurological disorders and syndromes making the clinical diagnosis of neurogenic bladder (NGB) difficult in many cases. Classification of NLUTD has three primary aims – to aid in discriminating or identifying an unknown underlying neurological disease process, to characterise the nature of the dysfunction so as to develop a treatment plan, and to assess the risk of secondary effects (e.g. on the upper tract) which may influence the necessity and aggressiveness of treatment. The latter two are clearly relevant to research in neurogenic incontinence and must be reflected in study design and patient description.

It is difficult to find a classification system for NLUTD that serves both clinical and research demands that is satisfactory for each of the three aims. The published NLUTD classification systems have been reviewed in detail in textbooks. Both the disease process and the site of the neurological lesion(s) are relevant in the study of NLUTD, yet even this informationis inadequate to predict the functional lower urinary tract deficits for an individual patient. There is no one method that meets the broad needs of classification in this group. Typical or classic cases are often well described but it is especially difficult to describe mixed and incomplete lesions. Historically, classification systems oversimplify or become extremely complex to apply in routine clinical practice.

A new classification system has been proposed by Powell to better define the neurogenic lesion or condition affecting lower urinary tract function and thereby help direct treatment. (261)The SALE (Stratify by Anatomic Location and Etiology) classification system for NLUTD is based on seven categories (six anatomical/aetiological and one future biomarker), each having a neurological defect (upholds basic definition) in a distinct anatomic location. The system incorporates the presence or absence of bowel dysfunction and autonomic dysreflexia. The proposed classification divisions would benefit research stratification including supra-pontine, pontine, supra sacral, sacral, lower motor neuron/neuropathy, and syndromes with no definitive neurological lesion detected thus far.

According to the European Association of Urology guidelines for managing the neurogenic bladder, primary aims for treatment (also research) include protection of the upper urinary tracts, improve urinary continence, restore function and improve quality of life when possible.. (264) Despite proper classification and guideline adherence, it must be acknowledged that the complexity of neurological diseases and variations in individual behaviour almost always call for a customised approach to therapy, further complicating research in the neurogenic patient. All of these factors may complicate study design as it becomes difficult to create workable inclusion and exclusion criteria that apply to other than a narrow segment of the neurogenic population. Ideally a broad population of potentially relevant participants would be enrolled in research studies with full characterisation of both the neurological condition and the nature of the lower urinary tract dysfunction so as to allow for subgroup

analysis. The new SALE system may provide a better classification scheme for NLUTD.

Study planning is being undertaken with the cooperation of urologists, neurologists, and other clinicians, who have a specific interest and special training in the neurogenic patient. Baseline data collected by history in subjects with neurogenic lower urinary tract disorders should include:

- bladder volumes by diary or examination (maximum voided or catheterised volume, post voiding residual urine, total capacity);
- mechanism of bladder evacuation: normal (volitional), spontaneous involuntarily („reflex“), Crede, sterile intermittent catheter (SIC), clean intermittent catheter (CIC), intermittent catheter by second person, or suprapubic or urethral catheter;
- use of external appliances (e.g., diaper or pad use, condom catheter, urethral catheter, suprapubic tube);
- the typical time span of continence (continence interval) following last bladder evacuation and maximal continent bladder volume.
- bowel function, sexual function, and specific neurologic deficits
- the evolution of the condition of (changes in) the upper tract should be included in the outcomes evaluation of treatment for NLUTD.

Where possible these factors should be controlled for in analyses and stratified for in randomisation for interventional studies, or patients with certain factors should be excluded. The details will depend on the research question to be asked.

12.1. Outcome Measures for NLUTD

Follow-up recommendations for patients with NLUTD are based on long-standing evidence suggesting increased risk of bladder cancer as well as upper tract deterioration in this patient population. A study of cancer-specific mortality in a population of U.S. Veterans with Spinal Cord Injury demonstrated up to 70% greater bladder cancer specific mortality in patients with SCI as compared to those without the condition. In a study by El Masri regarding the issue of cystoscopic surveillance, the author stated, „Since the second world war, integration of urological surveillance and timely intervention in the management of patients with SCI has reduced morbidity and mortality prolonging survival.“ (265) However, despite this observational data, strong evidence regarding the type and timing of surveillance in patients with NLUTD is lacking.

Several organizations have set out to improve outcomes by creating evidence-based guidelines for follow-up and surveillance. Some of the more publicized of these include:

- European Association of Urology (EAU): „Guidelines on Neurogenic Lower Urinary Tract Dysfunction“. (266)
- United Kingdom: National Institute for Health and Clinical Excellence (NICE) „Urinary Incontinence in Neurological Disease: management of lower urinary tract dysfunction in neurological disease“. (267)
- U.S. Veteran‘s Health Administration Handbook on Spinal Cord Injury and Disorders (SCI/D) Systems of Care. (268)
- American Urological Association (AUA) and Society for Urodynamics Female Pelvic Medicine and Urogenital Reconstructiuon (SUFU): Guidelines for Urodynamics (269)
- The AUA/SUFU Guideline on Adult Neurogenic Lower Urinary Tract Dysfunction: Diagnosis and Evaluation (270)
- The Consortium for Spinal Cord Medicine „Bladder Management in Adults with Spinal Cord Injury“. (271)

A comprehensive review of these guidelines is beyond the scope for this chapter; however, key areas included renal function testing, imaging, cystoscopy, and urodynamics. The most aggressive surveillance protocol came from the EAU guidelines that recommended yearly renal function testing, imaging every 6 months, and urodynamics at least every 1-2 years. The NICE guidelines recommended ultrasound surveillance every 1-2 years, consideration of urodynamics for high-risk patients, and that surveillance cystoscopy should not be performed. The newest AUA/SUFU guidelines recommend against surveillance cystoscopy in patients with NLUTD and chronic indwelling catheters based on two recent meta-analyses (272,273). The variability in these guidelines, which are derived mainly from poorly done observational studies and are consensus based, speaks to a pressing research need for the ICI to encourage long-term evidence-based studies on outcomes in patients with NLUTD and how these are affected by different forms of surveillance and management.

Measuring quality of life outcomes in the NLUTD population has often lagged behind other lower urinary tract disorders due to the heterogeneity of the neurological conditions that are often grouped together (i.e. spinal cord injury with multiple sclerosis). Several patient-reported outcome measures (PROMs) have been specifically designed for measuring the quality of life in patients with neurogenic bladder. Costa and associates described the Qualiveen in 2001 to measure the quality of life in patients with spinal cord injury and it has been validated and is available in English, French, Dutch, Spanish and Italian. Clark and Welk contributed an excellent review of 16 PROMs for assessment of quality of life and symptoms in neurogenic bladder patients. (274,275). Selection of the appropriate PROM for measuring quality of life outcomes is essential for clinicians and researchers working with the NLUTD population.

The following summary highlights recommendations for research in the key areas of this Consultation.

13. RESEARCH PRIORITIES

13.1. Pathophysiology of NLUTD

- An area of priority for research is the development of a more directly informative classification system which would include anatomical location and aetiology in association with corresponding urinary, faecal and neurological symptoms, information from clinical neurophysiological testing and urodynamic abnormalities as well as prognostic biomarkers. As such, the classification would describe a patient suffering from NLUTD and simultaneously inform about the most appropriate treatment, follow-up regimen, and long-term prognosis
- The thalamus may be a promising target for the development of new therapies for lower urinary tract dysfunction. Further investigation on this matter is needed before its potential role can be elaborated.

13.2. Diagnostics

- Additional studies are needed to establish neurological populations and absolute indications for the use of invasive urodynamics in NLUTD as a primary assessment tool and as specialized assessment tool as well as establish its best application for follow-up of treatment modalities
- Research to establish what is ‚urodynamic safety‘ in NLUTD, preferably by population studied
- Identify clinical predictors of urodynamic findings in NLUTD
- Further development of patient reported outcome measures needed in NLUTD

- Further research into neuroimaging and its association with clinical neurourological practice
- Further development and standardisation are needed for the use of electrosensation tests to assess their role as a clinical test
- Research to produce high level evidence to define UTI's in neurological patients
- Need more evidence for the use of prophylactic antibiotics to reduce symptomatic urinary tract infections after invasive UDS

13.3. Management of NLUTD

- Research into mechanisms and prognosis of the development of bladder cancer in patients with NLUTD
- It is currently not possible to state whether any IC method or catheter type is advantageous due to the poor quality of available studies. Further research on the topic is strongly recommended

13.4. Pharmacotherapy for NLUTD

- Further research is needed to establish the efficacy and safety of the newer antimuscarinics in NLUTD, long-term outcomes and safety, the efficacy and safety of mirabegron in NLUTD, as well as combination treatments
- Oral and intravesical cannabinoid agonists have shown promising results either in clinical or preclinical studies, and should be further investigated for optimal balance between efficacy and safety in NLUTD
- Further research needed on pharmacotherapy for detrusor-sphincter dyssynergia, sphincter deficiency and detrusor underactivity

13.5. Minimally Invasive Treatments Botulinum Toxin A

- Further research is needed on long-term outcomes and safety, administration techniques, the bio-equivalence of the various preparations, the concomitant use of anticholinergic drugs or 3-agonists, mechanisms of action, and wider effects
- Future research should also focus on PROs and patient satisfaction, tolerability issues, alternative techniques of application, ways to minimise posttreatment voiding dysfunction in patients who void freely
- Larger studies in select patient populations are also recommended

13.6. Electrical Neuromodulation

- Further studies on chronic pudenda[nerve stimulation must be carried out to identify the best stimulation parameters and to verify the long-term results in patients with inadequate bladder emptying due to DBND, either as a first-line procedure or as a complementary approach to DBND recognised following permanent urethral stenting. Further studies are needed
- Bladder augmentation using biomaterials or tissue engineering is promising, but the preliminary results need to be confirmed by larger studies
- IVES is a viable option to induce/improve bladder sensation and to enhance the micturition reflex in patients with incomplete central or peripheral nerve damage, but corroborating controlled evidence is needed
- Research to establish indications for sacral neuro-modulation in the care of DSD in neurological urinary dysfunction.
- Effectiveness of tibial nerve stimulation (transcutaneous, percutaneous, and implantable)

13.7. Specific Neurological Conditions

There is a need for robust epidemiological research, insight into mechanisms, studies on utility of diagnostic tests, assessment of urinary tract risk factors, and randomized trials to assess benefits and harms of therapy for specific neurological diseases. Urinary and faecal incontinence both suffer from limited high-quality research, and fecal incontinence in particular.

Priority Research Topics include investigations into:

- Systematic cataloguing of the specific brain centres pertinent to lower urinary tract control, and how they are at risk in given neurological diseases
- How medications for LUTS may influence specific neurological diseases or associated dysfunctions (e.g. blood pressure control)
- The clinical relevance of functional brain imaging to clinical management
- Indicators of neurological presentation or progression that may be first evident in urological clinics
- Outcomes for interventions for smooth sphincter dyssynergia

VI.I Research Priorties in Faecal Incontinence

- Develop and test interventions for promoting care seeking and self-management of fecal incontinence (and associated odour and urgency)
- Develop and test interventions for increasing coping skills and health literacy related to faecal incontinence for patients and family caregivers
- Evaluate tailoring the management of faecal incontinence based on patients' goals, peer support, and the use of current technologies such as mobile devices for delivering management and support interventions to patients and family caregivers
- Collect data on faecal incontinence whenever practical as part of research on urinary incontinence
- Develop techniques for diagnosing faecal incontinence and its aetiologies using new and available diagnostic technologies
- Develop user-friendly measures and instruments for quantifying the severity of faecal incontinence and other components of anal incontinence separately and in total
- Investigate the epidemiology of the different types and subtypes of bowel and anal incontinence
- Well-designed and adequately-powered studies are needed to evaluate fecal incontinence treatment modalities currently available including:
- Effectiveness of lifestyle modifications including weight loss, exercise, diet and eating pattern modifications, and supplementing dietary fibre as an adjuvant or combined strategy
- Comparative effectiveness trials of instrumented biofeedback training versus neuromodulation

14. RESEARCH PRIORTIES IN POPULATIONS AFFECTED BY BLADDER PAIN (INCLUDING INTERSTITIAL CYSTITIS)

The pathogenesis and pathophysiology of IC / BPS remains unknown. Diagnosis should be obtained by excluding diseases that can be confused with symptoms and no curative treatment exists (276-281). Recent studies suggest that the pathophysiology of Hunner type IC (HIC) and non-Hunner-type IC (NHIC)/BPS is significantly different (282) and the former is characterized by pancystitis,

frequent clonal B-cell expansion and epithelial denudation. Therefore, IC/BPS may be categorized by the presence or absence of Hunner lesions, rather than by clinical phenotyping based on symptomatology (281,282). Basic research and clinical trials should be conducted separately for each. Research recommendations are:

- Research that focuses identify bladder-specific pathology, a bladder pain syndrome-specific biomarker
- Develop a simple, non-invasive diagnostic tools for HIC and BPS.
- Research that focuses identifying specific pathology (the pathogenesis of a B-cell population abnormality in Hunner lesions) and biomarkers for HIC and NHIC/BPS.
- Standardize the manners of hydrodistension.
- Research to develop a curative treatment for HIC and BPS.
- Establish patient databases in different region and conduct longitudinal follow-up to understand the natural history of the disease and to examine the differences in disease natural history among regions.
- Develop a simple, non-invasive diagnostic test for BPS
- Research that focuses identify bladder-specific pathology, a bladder pain syndrome-specific biomarker
- Broaden the research scope to improve symptom-based classification to identify the degree of bladder and non-bladder symptoms.
- Establish patient databases in different regions and conduct longitudinal follow-up to understand the natural history of the disease and to examine the differences in disease natural history among regions
- Develop a practical multi-disciplinary care model and test it in various settings.
- Develop an easy-to-use tool for non-specialists to readily identify co-morbid conditions that may impact on the need for additional consultation and suggest specific treatment pathways.

15. RESEARCH PRIORTIES IN PELVIC ORGAN PROLAPSE

The effect of pelvic organ prolapse on lower urinary tract function remains poorly understood. Pelvic organ prolapse may potentially affect lower urinary tract function by obstruction of the urethral outflow, and thereby mask sphincter weakness (so called “occult” stress incontinence). Emerging evidence suggests that prolapse may contribute to the symptoms of OAB and correction of the prolapse may modulate these symptoms. Thus, it is important to include assessment of pelvic organ prolapse in incontinence research on women. A validated assessment method for prolapse should be used to identify the stage of prolapse; the Pelvic Organ Prolapse Quantification System (POP-Q)(9) is recommended. Research protocols should be developed, either excluding women with prolapse severity beyond a specified stage, or the analysis plan should include stratification for stage of prolapse in randomisation, and adjustment for prolapse stage in any analysis. For larger studies where regression analyses are planned, stage of prolapse should be considered a mandatory factor for inclusion. Prolapse should be graded at the same time as the outcome assessment for incontinence and LUTS is performed.

POP may induce a various type of lower urinary tract symptoms (LUTs); not only storage symptoms but voiding symptoms, according to the types and severity of POP (276,277). Although POP surgery generally improves LUTs, overactive bladder (OAB) may persist and/or de-novo stress urinary incontinence (SUI) may occur after surgery (276, 278, 279). Also, there is a risk of voiding dysfunction after POP surgery and its incidence varies depending on types of surgical procedure and baseline patient characteristics. (276, 280-29

Further research is required in areas of the management of LUTS in patients with POP and the assessment of LUTs before/after various types of POP surgery (including transvaginal mesh surgery and laparoscopic/robot-assisted sacrocolpopexy) as below. Especially, long-term follow-up of LUTs and other adverse events (including chronic pain and mesh extrusions) in cases treated with transvaginal mesh surgery is required.

Significant further research is required in most areas of the surgical management of prolapse including but not limited to:

- Uterine prolapse and its various treatment options
- Surgery for recurrent prolapse
- Identifying risk factors for recurrent prolapse
- Re-evaluation of prolapse quality of life questionnaires to ensure they are sensitive to change
- The utilization and incorporation of tissue engineering in pelvic organ prolapse surgery
- Impact of POP surgery on bladder overactivity.
- Impact of POP surgery on urinary voiding dysfunction
- Impact of rectocele repair on symptoms of obstructed defaecation and fecal incontinence
- Impact of various types of POP surgery on OAB.
- Impact of various types of POP surgery on SUI.
- Impact of various types of POP surgery on urinary voiding dysfunction.
- Impact of rectocele repair on obstructed defecation and fecal incontinence.
- Long-term follow-up of LUTs and other adverse events (including chronic pain and mesh extrusions) in cases treated with transvaginal mesh surgery.
- Re-evaluate prolapse quality of life (P-QOL) questionnaires to ensure they are sensitive to changes after treatment.
- Identifying risk factors and predictors for persistent/de-novo incontinence after POP surgery.

16. RESEARCH PRIORTIES IN MINORS (CHILDREN, ADOLESCENTS AND TRANSITIONAL SUBJECTS)

The conduct of clinical research in children is no more difficult than in adults, as parents and caregivers are often motivated and eager to participate. Four overriding issues separate pediatric research from the general recommendations. First, developmental physiology and psychology varies widely within the group referred to as children who undergo many different stages: newborns, infants, toddlers, preschoolers, school age children, adolescents and young adults. They not only differ from older adults, but also undergo rapid developmental changes within a short time. Because children are growing, any treatment, especially pharmacological and surgical therapy, may affect them profoundly in the long term. On the other hand, treatment in children can be more effective than in adults precisely due to this developmental flexibility. A specific aspect is the close interaction between the developing central nervous system and peripheral organs such as the bladder. In addition, the interaction between the urinary and gastrointestinal system plays a special

role in this age group. Second, compliance with therapy requires the inclusion of parents, as children and even adolescents depend on caregivers to administer treatment in most studies. Third, reporting of symptoms and outcomes requires the assessment by both parents (proxy) and children. Symptoms reported by a caregiver may not be interpreted in the same way as the child, which is important to consider. Finally, the issue of informed consent is complex with children, but this has been settled by legal requirements in most countries.

Urinary incontinence in children falls into four main categories: organic, i.e. neurogenic (myelomeningocele and other less common neurogenic etiologies) or structural; nocturnal enuresis, which can be either mono-symptomatic or polysymptomatic; non-organic daytime urinary incontinence, including detrusor overactivity, voiding postponement and dysfunctional voiding without neurological disease. This issue of age groups is most crucial in children with myelomeningocele. These children are often on medication beginning at a very young age and continuing for many years; the long-term safety of medications in children must be established in all age groups. We recommend that clinical studies have long-term (five years or more), open label extension arms to monitor safety, particularly focusing on normal growth and development and the effects on treatment of liver and central nervous system function. Therapy for other causes of incontinence in children tends to start at a later age, i.e. the definitional age of incontinence (5 years).

Assessment of compliance with therapy is always difficult and can also be so with children. Compliance with voiding diaries, a significant issue in the adult population, has to be monitored to achieve reliable results. The social and family interactions between the child and parent or caregiver, as well as own behavioral issues and disorders, can influence the accuracy of data collection and treatment compliance, both positively and negatively.

Outcome measures have been developed in children as in adults. Validated, age-specific symptom and disease-specific quality of life instruments are available for most chronic disease for the pediatric population, as well as generic instruments. Early efforts in this area have been reported for dysfunctional voiding and daytime incontinence. Invasive urodynamics can be used when deemed appropriate (specifically in the neurogenic population). but is usually not required in non-organic incontinence.

- Long-term follow-up is of critical importance in the paediatric population in order to ascertain the effect of a treatment on normal growth and development.

Broadened the research scope to improve symptom-based classification to identify the degree of bladder and non-bladder symptoms.

- Establish patient databases in different regions and conduct longitudinal follow-up to understand the natural history of the disease and to examine the differences in disease natural history among regions
- Research is needed to develop standardized outcome measures including validated, age specific symptom and disease-specific quality of life outcome measures.
- Research of problems specific to different age groups is needed. Especially, incontinence in preschool children and in adolescents is needed.
- The transition and transfer from pediatric to adult care should be studied and evidencebased recommendations should be formulated.
- Develop a practical multi-disciplinary care model and test it in various settings.
- Develop an easy-to-use tool for non-specialists to readily identify co-morbid conditions that may impact on the need for additional consultation and suggest specific treatment pathways.
- The specific incontinence problems of young adults aged 18-21 years need more attention in research.
- Incontinence in children and adults with special needs is a neglected part of research and clinical care. These include individuals with intellectual disability, specific syndromes, autism spectrum and other disorders.
- The interaction between brain and bladder and/or gut needs to be studied with new functional and structural imaging techniques of the CNS.
- Treatment studies of daytime urinary inconti nence, including pharmacotherapy and urotherapy, are needed.
- The correlates of sleep in children with nocturnal enuresis needs to be elucidated in more detail.
- Life span, longitudinal epidemiological studies from childhood to adulthood in a prospective design are required to procure representative data.

17. RESEARCH PRIORTIES IN BASIC SCIENTIFIC RESEARCH

- Integrate data from reductionist experiments to inform the formulation of better systems-based approaches in the investigation of the pathology of the lower urinary tract (LUT), the genital tract (GT) and the lower gastrointestinal tract (LGIT) through:
  - the development of animal models that accurately describe human pathological conditions, including the greater use of large-animal models
  - the better use of reverse translational approaches for linking animal models to the human disease.
- Encourage greater emphasis on basic research to characterise tissues receiving relatively little attention: ie the lower gastrointestinal tract; the bladder neck and urethra; the ureter, pelvic floor musculature
- Generate research programmes for foetal and neonatal research in LUT and LGIT function.
- Use genome-wide bioinformatics and population health surveys to generate testable hypotheses regarding the physiological and pathophysiological functions of the LUT, GT and LGIT.
- Generate improved experimental approaches to investigate the pathophysiology of the LUT and LGIT by:
  - the use of human tissue from well-characterised patient groups.
  - the development of emerging areas such as: tissue engineering; proteomics and metabolomics
  - increased collaborations between biological, physical and mathematical sciences.
- Develop centers of excellence or consortia of excellence in LUT, GT and GIT research
- Integrate expertise from university departments, academic medical units and industry
- Encourage translational approaches to research.
  - develop inter-institutional research-training programs to allow new researchers the opportunity to better interact and exchange ideas.

- Additional emphasis on the importance of research to medical trainees and science graduates through:
  - establishing research training as a corecomponent of post-graduate clinical development
  - increased access to support funds, especially scholarships and personal awards
  - organisation of focused multidisciplinary research meetings, either stand-alone or as dedicated sessions during national and international conferences
  - greater interaction between medical centres and Higher Education Institutions (HEIs).
  - allowing researchers-in-training better access to international meetings through reduced registration charges and improved travel grants.
  - inclusion in clinical meetings of point-counterpoint session(s) with both basic science and clinical viewpoints.
  - development of research fora for exchange of ideas between active researchers and industry.
  - lobbying research funding organisations about the medical and social importance of LUT and LGIT disorders.
- Increase emphasis on research into LUT and LGIT in HEIs through greater representation on grant-funding agencies

VII. CONCLUSIONS

The 2021 Consultation expanded and focused on specific areas which were summarized by the 2016 committee and working document. This committee places significant emphasis on the needs for standardization of data aggregation, interpretation, analysis, reporting and summary presentation with grading of evidence. The meaningful advancement of research in the focus areas of this consultation, should be promoted with lucid research question and hypothesis. Once the research focus is identified, careful design, conduct and analysis of the research study is paramount. Prompt dissemination with appropriate data sharing is strongly recommended to benefit affected individuals and the broader research community. Data registries and multi-institutional collaboratives will improve the potential ability for the acquisition of large and generalizable data sets which can be used for basic, translational, and clinical trials which will help to address population-based conditions and diseases.

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2023

7TH INTERNATIONAL CONSULTATION ON INCONTINENCE

RECOMMENDATIONS OF THE INTERNATIONAL SCIENTIFIC COMMITTEE

EVALUATION AND TREATMENT OF URINARY INCONTINENCE, PELVIC ORGAN PROLAPSE AND FAECAL INCONTINENCE

A. Wagg, P. Abrams, K-E. Andersson, M. A. Averbeck, L. Birder, D. Bliss, L. Cardozo, D. Castro-Diaz, F. Cruz, D. de Ridder, S. de Wachter, R. Dmochowski, C. Dumoulin, M. Fader, E. Finazzi Agrò, C. Fry, H. Goldman, P. Hanno, V. Khullar, T. Kessler, M. Kilonzon, C. Knowles, E. van Laeke, C. Maher, I. Milsom, K. Moore, C. Murphy, A. Rantell, E. Rovner, D. Robinson, S. Salvatore, A. Wein
and the members of the committees

INTRODUCTION
The 7th International Consultation on Incontinence took place online in November 2021 and was organ-ised by the International Consultation on Urological Diseases and the International Continence Society (ICS), to develop consensus statements and recommendations for the diagnosis, evaluation and treatment of urinary incontinence, faecal incontinence, pelvic organ prolapse and bladder pain syndrome. Oppor-tunity for discussion was offered both in real time and asynchronously, by the use of question and answer fora, enabling attendees to comment upon presentations and pose direct questions to the committees, resulting in refinement and modifications where necessary

The consensus statements are evidence based following a thorough review of the available literature and the global subjective opinion of recognised experts serving on focused committees. The individual com-mittee reports were developed, and peer reviewed by open presentation and comment. The Scientific Committee, consisting of the Chairs of all the committees then refined the final consensus statements. These consensus statements will be periodically re-evaluated in the light of clinical experience, techno-logical progress and research

Co-sponsored by
International Consultation on Urological Diseases (ICUD)
International Continence Society (ICS)

In collaboration with
Major international associations of urology, gynaecology and urodynamics
and other medical associations

RECOMMENDATIONS OF THE INTERNATIONAL SCIENTIFIC COMMITTEE

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1. DEFINITIONS

The consultation agreed to use the current Interna-tional Continence Society definitions (ICS) for lower urinary tract dysfunction (LUTD) including incontinence, except where stated. These definitions were published in the journal Neurourology and Urodynamics (2002; 21:167-178 and 2006; 25: and can be viewed on the ICS website: www.ics.org

The following ICS definitions are relevant:

LOWER URINARY TRACT SYMPTOMS (LUTS)

LUTS are divided into storage, voiding and post micturition symptoms.

Urinary incontinence is a storage symptom and defined as the complaint of any involuntary loss of urine. This definition is suitable for epidemiological studies, but when the prevalence of bothersome incontinence is sought, the previous ICS definition of an "involuntary loss of urine that is a social or hygienic problem "can be useful.

Urinary incontinence may be further defined according to the patient's symptoms

a) **Stress (urinary) incontinence:** Complaint of involuntary loss of urine on effort or physical exertion e.g., sporting activities), or on sneezing or coughing. (Sporting activities)

b) **Urgency (urinary) incontinence:** Complaint of involuntary loss of urine associated with urgency.

c) **Postural (urinary) incontinence:** Complaint of involuntary loss of urine associated with change of body position, for example, rising from a seated or lying position.

d) **Mixed (urinary) incontinence:** Complaint of involuntary loss of urine associated with urgency and with effort or physical exertion or on sneezing or coughing.

e) **Incontinence associated with chronic retention of urine:** Complaint of involuntary loss of urine which occurs in conditions where the bladder does not empty completely as indicated by a significantly high residual urine volume and/or a non-painful bladder which remains palpable after the individual has passed urine. (Note: The ICS no longer recommends the term overflow incontinence. A significant residual urine volume denotes a minimum volume of 300 ml, although this figure has not been well established.)

f) **Nocturnal enuresis:** Complaint of involuntary loss of urine which occurs during sleep.

g) **Continuous (urinary) incontinence:** Complaint of continuous involuntary loss of urine.

h) **Insensible (urinary) incontinence:** Complaint of urinary incontinence where the individual is unaware of how it occurred

i) **Coital incontinence (for women only):** Complaint of involuntary loss of urine with coitus. This symptom can be further divided into that occurring with penetration and that occurring at orgasm.

j) **Functional (disability associated) incontinence:** Complaint of involuntary loss of urine that results from an inability to reach the toilet due to cognitive, functional or mobility impairments in the presence of an intact lower urinary tract system.

k) **Multifactorial incontinence:** Complaint of involuntary loss of urine related to multiple interacting risk factors, including factors both within and outside the lower urinary tract such as comorbidity, medication, age-related physiological changes and environmental factors.

Urinary incontinence can exist in isolation or may be associated with other lower urinary tract symptoms. The ICS classifies lower urinary tract symptoms (LUTS) into bladder storage, voiding and post-micturition, and pelvic organ prolapse symptoms. The following section summarises the definitions of LUTS described by the ICS-SSC.

Overactive bladder is characterised by the storage symptoms of urinary urgency, usually accompanied by increased urinary frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.

Urodynamic Diagnosis

- **Detrusor Overactivity** is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked.

Detrusor overactivity is divided into:

  - **Idiopathic Detrusor Overactivity**, defined as overactivity when there is no clear cause
  - **Neurogenic Detrusor Overactivity** is defined as overactivity due to a relevant neurological condition.

- **Urodynamic stress incontinence** is noted during filling cystometry and is defined as the involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS) AND HUNNER LESION DISEASE (HLD)*

- **IC/BPS** is defined as chronic pelvic pain, pressure, or discomfort of greater than 6 months duration perceived to be related to the urinary bladder accompanied by at least one other urinary

symptom such as persistent desire to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded.

- **Hunner Lesion Disease** refers to patients who meet the IC/BPS definition with cystoscopic findings of discrete inflammatory areas in the bladder consistent with the histologic criteria for Hunner lesion.

PELVIC ORGAN PROLAPSE

- **Urogenital prolapse** is defined as the symptomatic descent of one or more of: the anterior vaginal wall, the posterior vaginal wall, and the apex of the vagina (cervix/uterus) or vault (cuff) after hysterectomy. Urogenital prolapse is measured using the POP-Q system.

- **Rectal prolapse** is defined as circumferential full thickness rectal protrusion beyond the anal margin.

ANAL INCONTINENCE

Anal incontinence defined as “any involuntary loss of faecal material and/or flatus and/or mucus” and may be divided into:

- **Faecal incontinence**, any involuntary loss of faecal material

- **Flatus incontinence**, any involuntary loss of gas (flatus)

- **Mucus incontinence**, any involuntary loss of mucus only (not faeces)

* At the time of this consultation, these definitions are not included in the current ICS terminology.

2. EVALUATION

The following phrases are used to classify diagnostic tests and studies:

- **A highly recommended** test is a test of proven value that should be done on every patient.
- **A recommended test** is a test of proven value in the evaluation of most patients and its use is strongly encouraged during evaluation.
- **An optional test** is a test of proven value in the evaluation of selected patients; its use is left to the clinical judgement of the physician
- **A not recommended test** is a test of no proven value.

This section primarily discusses the Evaluation of Urinary Incontinence with or without Pelvic Organ Prolapse (POP) and Faecal Incontinence.

The recommendations are intended to apply to children and adults, including adults over the age of sixtyfive.

These conditions are highly prevalent but often not reported by patients. Therefore, the Consultation strongly recommends case finding, particularly in high-risk groups.

A. HIGHLY RECOMMENDED TESTS DURING INITIAL EVALUATION

The **main recommendations** for this consultation have been abstracted from the extensive work of the twenty-three committees of the 7th International Consultation on Incontinence (ICI, 2021).

Each committee has authored a report that reviews and evaluates the published scientific work in each field of interest to give Evidence Based recommendations. Each report ends with detailed recommendations and suggestions for a programme of research.

The main recommendations should be read in conjunction with the management algorithms for children, men, women, the frail older adult, neurogenic patients, as well as patients with bladder pain, pelvic organ prolapse, and faecal incontinence

The initial evaluation, by a clinician, should be undertaken in patients presenting with symptoms/ signs suggestive of these conditions.

1. HISTORY AND GENERAL ASSESSMENT

Management of a disease such as incontinence requires caregivers to assess the sufferer in a holistic manner. Many factors may influence a particular individual's symptoms, some may cause incontinence, and may influence the choice and the success of treatment. The following components of the medical history are particularly emphasised:

1.1. Review of Systems:

- Presence, severity, duration and bother of any urinary, bowel or prolapse symptoms. Identifying symptoms in the related organ systems is critical to effective treatment planning. The use of validated questionnaires to assess symptoms are recommended. It is also helpful to determine the impact that the leakage has on the patient's daily life and activities if incontinence limits the individual's activity and if the patient made lifestyle changes because of the risk of leakage.
- Effect of any symptoms on sexual function: validated questionnaires including impact on quality of life are a useful part of a full assessment.
- Presence and severity of symptoms suggesting neurological disease

1.2. Medical History:

- Previous conservative, medical and surgical treatment as these affect the genitourinary tract and lower bowel. The effectiveness and side effects of treatments should be noted.
- Coexisting diseases may have a profound effect on patients with incontinence and prolapse, for example, asthma patients with stress incontinence will suffer greatly during attacks. Diseases may also precipitate incontinence or make it more likely than not, particularly in frail older adults.
- Patient medication: it is always important to review every patient's list of medications and to make an assessment as to whether current treatment may be contributing to the patient's condition.
- Obstetric and menstrual history.
- Physical impairment: individuals who have compromised mobility, dexterity, or visual acuity may need to be managed differently

1.3. Social History:

- Environmental issues: these may include the social, cultural, and physical environment.
- Lifestyle: including exercise, smoking and the amount and type of fluid and food intake.

1.4. Other Treatment Planning Issues:

- ***Desire for treatment*** and the extent of treatment that is acceptable
- ***Patient goals*** and expectations of treatment
- ***Patient support*** systems (including caregivers).
- ***Cognitive function***: all individuals need to be assessed for their ability to fully describe their symptoms, symptom bother and quality of life impact, and their preferences and goals for care. They must be able to understand proposed management plans and to discuss, where appropriate, alternative treatment options. In some groups of patients, formal testing is essential e.g., cognitive function testing for individuals for whom the clini-

cian has concerns regarding memory deficits and/or inattention or confusion, and depression screening for individuals for whom the clinician has concerns about abnormal affect. Proxy respondents, such as family and caregivers, may be used to discuss the patient's history, goals of care, and treatment for individuals with dementia, but only if the individual is incapable of accurate reporting or weighing treatment decisions.

- Finally, it is important to emphasize the importance of establishing patient expectation of treatment and an understanding of the balance between the benefits and risks/burden/costs of available treatment options

2. PHYSICAL EXAMINATION

The more complicated the history and the more extensive and/or invasive the proposed therapy, the more complete the examination needs to be. Depending on the patient's symptoms and their severity, there are a number of components in the examination of patients with incontinence and/or pelvic organ prolapse.

Physical examination should be performed regardless of whether the patient is a child, a woman, a man, someone with neurological disease or a frail older adult with respect to the following domains

- General status:
- Mental status
- Obesity (BMI)
- Physical dexterity and mobility

2.1. External genitalia: for genitourinary syndrome of the menopause, incontinence associated dermatitis, hygiene, location of the urethral meatus and phimosis/paraphimosis.

2.2. Abdominal/flank examination: for masses, bladder distention, relevant surgical scars

2.3. Pelvic examination:

- Examination of the perineum and external genitalia including tissue quality and sensation.
- Vaginal (half-bivalve speculum/Sims) examination for pelvic organ prolapse (POP), which should ideally be done in the lithotomy as well as in the vertical position, as dictated by practicality. Ideally, the POPQ staging system should be used
- Bimanual pelvic and anorectal examination for pelvic mass and tenderness
- Digital rectal examination to assess pelvic floor muscle function, reflexes, urethral mobility, and the function of internal and external anal sphincter as well as puborectalis muscle. Assess for prostate size, texture, palpable masses, faecal loading, or impaction. An assessment for pelvic pain should be performed in appropriate patients.
- Stress test (supine /standing) for urinary incontinence in the presence of a comfortably full bladder

2.4. Neurological testing (see chapter on assessment)

3. URINALYSIS

A screening urinalysis is recommended as part of the testing for urinary incontinence. A positive dipstick urinalysis will prompt formal urine microscopy and culture to detect UTI and/or the use of additional tests such as endoscopy and urinary tract imaging. Detection of haemoglobin or glycosuria should, likewise, prompt further testing.

Conclusion

For many, a diagnosis can be made based upon relevant history, directed physical examination and urinalysis and treatment, particularly involving non- invasive and inexpensive therapies, may start without the need for the further investigations listed below.

B. RECOMMENDED FURTHER ASSESSMENT PRIOR TO, OR DURING, SPECIALIST ASSESSMENT

The tests below are recommended when the **appropriate indication(s) is present.** Some recommended tests become highly recommended in specific situations.

This section should also be read in conjunction with the relevant committee reports.

1. FURTHER SYMPTOM AND HEALTH-RELATED QOL ASSESSMENT

1.1. Bladder Diary

In patients with **urinary symptoms** the use of a **bladder diary** (examples in Annex 1) is highly recommended to document the frequency of micturition, the volumes of urine voided, incontinence episodes and the use of incontinence pads. Although never completely diagnostic, diary patterns may characterise normal and abnormal states (Level 2, Grade A).

1.2. Questionnaires

The use of the **highest quality questionnaires** (GoR A, where available) is recommended for the assessment of the patient's perspective of symptoms of incontinence and their impact on quality of life.

The ICIQ is highly recommended (GoR A) for the basic evaluation of the patient's perspective of urinary incontinence, with other GoR A questionnaires recommended for more detailed assessment.

2. RENAL FUNCTION & PROSTATE SPECIFIC ANTIGEN ASSESSMENT

Standard biochemical tests for renal function are recommended ONLY in patients with urinary incontinence when there is suspected renal impairment as a consequence. PSA testing is recommended only in selected males with LUTS, particularly when a diagnosis of prostate cancer could potentially affect the management or in patients receiving 5-alpha-reductase inhibitors.

3. UROFLOWMETRY

Uroflowmetry with the measurement of post void residual urine is recommended as a screening test for symptoms suggestive of urinary voiding dysfunction or physical signs of POP or bladder distension. Uroflowmetry should be part of the initial assessment if the result is likely to influence management e.g., in all children and older men with possible prostatic obstruction.

4. ESTIMATION OF POST VOID RESIDUAL URINE (PVR)

In all adults, PVR should be part of the initial assessment if the result is likely to influence management. Where possible this should, by preference be performed non-invasively.

5. IMAGING

Although routine imaging is not recommended, imaging of the lower urinary tract and pelvis is highly recommended in those with urinary symptoms whose initial evaluation indicates a possible co- existing lower tract or pelvic pathology. Initial imaging may be by ultrasound, or plain X-ray.

Imaging of the upper urinary tract is highly recommended in specific situations. These include:

- Haematuria,
- Neurogenic urinary incontinence e.g., myelodysplasia, spinal cord trauma,
- Incontinence associated with significant post-void residual,
- Co-existing renal disease such as pyelonephritis or reflux, or loin/kidney pain,
- Patients with chronic urinary retention
- In women with severe urogenital prolapse
- Suspected extra-urethral urinary incontinence,
- Children with incontinence and UTIs, where indicated
- Children with extraurethral incontinence
- Urodynamic studies which show evidence of poor bladder compliance or high-pressure detrusor overactivity.

6. INVESTIGATIONS IN FAECAL INCONTINENCE AND RECTAL PROLAPSE

- Endoanal US or MRI prior to anal sphincter surgery is highly recommended, even when obvious anatomic defects are not evident.
- Defaecating proctography or dynamic MRI is recommended in suspected rectal prolapse which cannot be adequately confirmed by physical examination.
- MRI offers no advantage over other imaging modalities except for the lack of ionising radiation and global view of the pelvis
- Evacuation defecography is indicated in patients with constipation, and in patients with obstructive defaecation associated with anal incontinence caused by overflow incontinence or post defaecation leakage
- Anorectal manometry is useful to assess resting and squeeze anal pressures. The resting and squeeze pressures represent the function of the internal and external anal sphincter, respectively.

7. ENDOSCOPY

Although routine cysto-urethroscopy is not recom- mended, LUT endoscopy is **highly recommended** when:

- initial testing is abnormal, e.g., haematuria and suggests other pathologies,
- pain or discomfort feature in the patient's LUTS, these may suggest an intravesical lesion
- appropriate in the evaluation of vesicovaginal fistula and extra-urethral urinary incontinence (in childbirth fistulae, endoscopy is often unnecessary).

In anorectal conditions, Referral for proctosigmoidoscopy and/or colonoscopy may be made at the time of initial assessment to assess for evaluation of specific conditions. Anoscopy and proctoscopy with a rigid instrument or flexible sigmoidoscopy are examinations of value in excluding potentially treatable causes of faecal incontinence

8. URODYNAMIC TESTING

8.1. Urodynamic (multi-channel pressure subtracted cystometry) evaluation is recommended when:

- the results may change management, such as prior to most invasive treatments for UI and POP,
- treatment fails, if more information is needed to plan further therapy,
- used as a prognostic tool, such as part of both initial and long-term surveillance programmes in some types of neurogenic lower urinary tract dysfunction,

- Indicated in “complicated incontinence” (for details please see relevant subcommittee reports).

8.2. The aims of urodynamic evaluation are often diagnostic, but may also relate to prognostic factors, direct management or assess response to prior therapy, and also to:
- reproduce the patient’s symptoms and correlate these with urodynamic findings
- assess bladder sensation
- detect filling pressures (e.g., detrusor overactivity) and bladder capacity
- assess urethral competence during filling
- determine detrusor function during voiding
- assess outlet function during voiding
- assess residual urine

9. SMALL BOWEL FOLLOW-THROUGH, CT ENTOGRAPHY OR CAPSULE ENDOSCOPY

These tests are recommended in those with faecal incontinence and the presence of unexplained diarrhoea or when Crohn’s disease is suspected.

C. FURTHER DIAGNOSTIC TESTS TO BE USED AS APPROPRIATE

1. ADDITIONAL URODYNAMIC TESTING

Video-urodynamics is an optional recommendation and may be useful in the assessment of UI in some children, in patients who fail surgery or who have known or suspected anatomical abnormalities of the lower urinary tract (e.g., diverticula, fistula, vesico-ureteric reflux) and in some neurogenic patients, to obtain additional anatomical information. Either X-ray or US imaging can be used depending on the needs of the individual patient and available resources.

If a more **detailed estimate of urethral function** is required, then the following optional tests may give useful information, in addition to standard multi-channel pressure subtracted cystometry
- Urethral pressure profilometry
- Abdominal leak point pressures
- Video-urodynamics
- Electromyography of pelvic floor or urethral sphincter

If initial urodynamics have failed to demonstrate the cause for the patient’s incontinence, then the following tests are optional:
- Repeated routine urodynamics or video-urodynamics
- The role of ambulatory urodynamics remains unclear in this setting

2. PAD TESTING

Pad testing is an optional test for the evaluation of urinary incontinence and, if carried out, either a 20 min-1 h ward/office test with fixed bladder volume or a 24 h home pad test during usual daily activity is recommended.

3. NEUROPHYSIOLOGICAL TESTING AND IMAGING

The information gained by clinical examination and urodynamic testing may be enhanced by uroneurophysiological tests in selected patient groups with suspected neurogenic urinary incontinence with lesions within the nervous reflex arcs of sacral segments 2 – 5. Concentric needle EMG to diagnose denervation and reinnervation of pelvic floor and perineal muscles, and sacral reflex testing to assess the continuity of the sacral reflex arc, are recommended tests in these circumstances

Appropriately trained personnel should perform these tests. The following neuro-physiological tests can be considered in patients to detect a neurological lesion in case of a urinary or anorectal disorder, to specify the importance, the lesion level and sometimes the prognosis. They may also be of utility in the investigation of idiopathic urinary retention in women and idiopathic faecal incontinence
- Concentric needle EMG
- Sacral reflex responses to electrical stimulation of penile or clitoral nerves.

Imaging of the nervous system (and neighbouring structures, including spine, the abdominal cavity and pelvis) by MRI or CT, may confirm suspected involvement of the nervous system, and the nature of the cause.

4. FURTHER IMAGING

Cysto-urethrography, US, CT and MRI may have an indication in:
- suspected pelvic floor dysfunction
- failed surgery, such as recurrent posterior vaginal wall prolapse or failed sling surgery
- suspected fixed urethra

5. CYSTO-URETHROSCOPY

This is an optional test in patients with complicated, persistent or recurrent UI (e.g., after failed SUI surgery)

3. MANAGEMENT CONSENSUS STATEMENTS

The consensus statements are derived from the **detailed work of the committees** on the management of incontinence in children, men, women, the frail older adult and neurological patients, as well as those with obstetric fistula, pelvic organ prolapse, bladder pain syndrome, and faecal incontinence. The management of incontinence is presented in **algorithm form** with **accompanying notes**.

The chapters analyse the evidence and give it a level of evidence (LoE), and this generates a grade of recommendation (GoR)

The Consultation recognises that no algorithm can be applied to every patient and each patient's management must be individualised.

There are algorithms for

I. Urinary Incontinence in Children

II. Urinary Incontinence in Men

III. Urinary Incontinence in Women

IV. Fistulae

V. Pelvic Organ Prolapse

VI. Urinary Incontinence in Patients with Neurological Disease

VII. Interstitial Cystitis/Bladder Pain Syndrome and Hunner Lesion Disease

VIII. Faecal Incontinence in Adults

IX. Urinary and Faecal Incontinence in frail Older Men and Women

These algorithms are divided into two for groups I to III, VII and X. The two parts, initial **management** and **specialised management** require a little further explanation.

Although the management algorithms are designed for patients whose predominant problem is incontinence, there are many other patients in whom the algorithms may be useful such as those patients with urgency and frequency, so-called "**OAB dry**

Management definitions

Management may be divided into

- Conservative, all methods that are non-medical and non-surgical, some of which do not target the disease process

- Conservative therapy includes

  - Lifestyle interventions e.g., weight loss, fluid management
  - Bladder training and behavioural toileting programmes
  - Pelvic floor muscle training (PFMT)
  - Containment products & appliances, e.g., pads, urinals
  - Dependent continence strategies e.g., regular toileting

Consensus does not exist as to the use of the term "behavioural therapy" as some state that this term only includes techniques where a behavioural change is promoted because of the management technique. Others consider that all conservative management contains a behavioural element, for example wearing and changing pads constitutes a change in behaviour. Hence the consultations recommendations list the elements of conservative management as relevant are intended for use by all clinicians

The algorithms for initial management

These algorithms are intended for use by **all healthcare providers**. The consultation has attempted to phrase the recommendations in the basic algorithms in such a way that they may be readily used by clinicians in all countries of the world, both in the developing and the developed world. For this consultation, conservative management has been incorporated into the algorithms, other than that for urogenital prolapse, where a specific algorithm has been constructed.

The specialised algorithms

The specialised algorithms are intended for use by **specialists**. The specialised algorithms, as well as the initial management algorithms are **based on evidence where possible**, and on the **expert opinion** of the expert clinicians who took part in the Consultation. In this consultation, committees ascribed levels of evidence to the published work on the subject and devised Grades of Recommendation (GoR) to inform patient management.

It should be noted that these algorithms, dated **November 2021**, represent the Consultation **consensus at that time**. There will undoubtedly be changes both in the short term and in the long term as research evidence evolves and continues to guide practice.

ESSENTIAL COMPONENTS OF BASIC ASSESSMENT

Each algorithm contains a core of recommendations in addition to several essential components of basic assessment listed in sections I to III.

- General assessment
- Symptom assessment
- Assessment of impact on quality of life
- Assessment of the desire for treatment
- Physical examination
- Urinalysis & initial investigations where relevant

JOINT DECISION MAKING

The patient's desires and goals for treatment: Treatment is a matter for discussion and joint decision making between the patient and the health care provider. This process of consultation includes the need to assess whether the patient wishes to receive treatment and, if so, what treatments he or she would favour. Implicit in this statement is the assumption that the health care provider will give an **appropriate explanation of the patient's problem**, the **alternative lines of management**, and the potential **benefits** and **risks of treatment**. The assumption that patients almost always wish to have treatment is flawed, and the need to incorporate patient values and preferences is paramount. Clinicians should also consider the **potential treatment burden** associated with their plans and incorporate this into their assessment.

In each algorithm, treatments are listed in **order of simplicity**, the least invasive being listed first. This order does not imply a scale of efficacy or cost, two factors which need to be considered in choosing the sequence of therapy. The order is likewise not meant to imply a suggested sequence of therapy, which should be determined jointly by the treating health care provider and the patient, considering all the relevant factors listed above. This stepwise approach may not be appropriate in all circumstances.

In the **initial management algorithms**, treatment is **empirically based**, whilst the **specialised management** algorithms usually rely on diagnostic information from urodynamics and other testing.

The assumption is made that patients will be reassessed at an appropriate time to evaluate their progress and to readjust management accordingly.

USE OF CONTINENCE PRODUCTS

The possible role of **continence products** to prevent, contain and/or manage bladder and/or bowel leakage should be considered at each stage of patient assessment and treatment, to maintain dignity and social functioning, and/or to support self-management or care by others.

Consider use of continence products:
- while treatment is awaited.
- when treatment is not chosen or not suitable for the individual
- when treatment does not achieve adequate improvement or resolution of symptoms
- for **intermittent use**, for example when the patient has a cough, exercise, or needs to travel without reliable toilet access
- for **continuous use** if incontinence is unpredictable and/or frequent or if complications related to incontinence (e.g., skin breakdown) are imminent or present
- where “check and change” regimens are the only means to achieve social continence

Most patients will benefit from using a **mixture** of continence products to optimise effectiveness and to reduce costs, e.g., assorted products for day and night; or for staying at home and for going out/travel/specific activities.

Further guidance on management with continence products is given in Chapter 19 and at the ICI/ICS supported website:

www.continenceproductadvisor.org

At the foot of each of the treatment algorithms below, the phrase “Consider appropriate use of CONTINENCE PRODUCTS,” emphasizes the importance of continence products for many sufferers of incontinence

I. URINARY INCONTINENCE IN CHILDREN

A INITIAL MANAGEMENT

Children present specific management problems for a variety of reasons: assessment requires help from their parents and caregivers; consent to treatment may be problematic; and cooperation in both assessment and treatment may be difficult.

Initial assessment should involve a detailed investigation of voiding and bowel habits using bladder/bowel diaries and structured and validated questionnaires.

The child's social environment and general and behavioural development should also be formally assessed and recorded. Physical examination should be done to detect a palpable bladder, faecal loading and exclude anatomical and neurological causes (e.g., sacral dimple). Urine analysis and culture is sufficient to exclude the presence of infection. If possible, the child should be observed voiding.

- Referrals for specialist treatment are recommended for children who have complicated incontinence associated with:
  - Recurrent and febrile urinary infection
  - Voiding symptoms or evidence of poor bladder emptying
  - Urinary tract anomalies
  - Previous pelvic surgery
  - Neuropathy or neuropathic origin
  - Bowel dysfunction not responsive to treatment
  - Comorbid behavioural (e.g., ADHD and ODD) and emotional disorders.

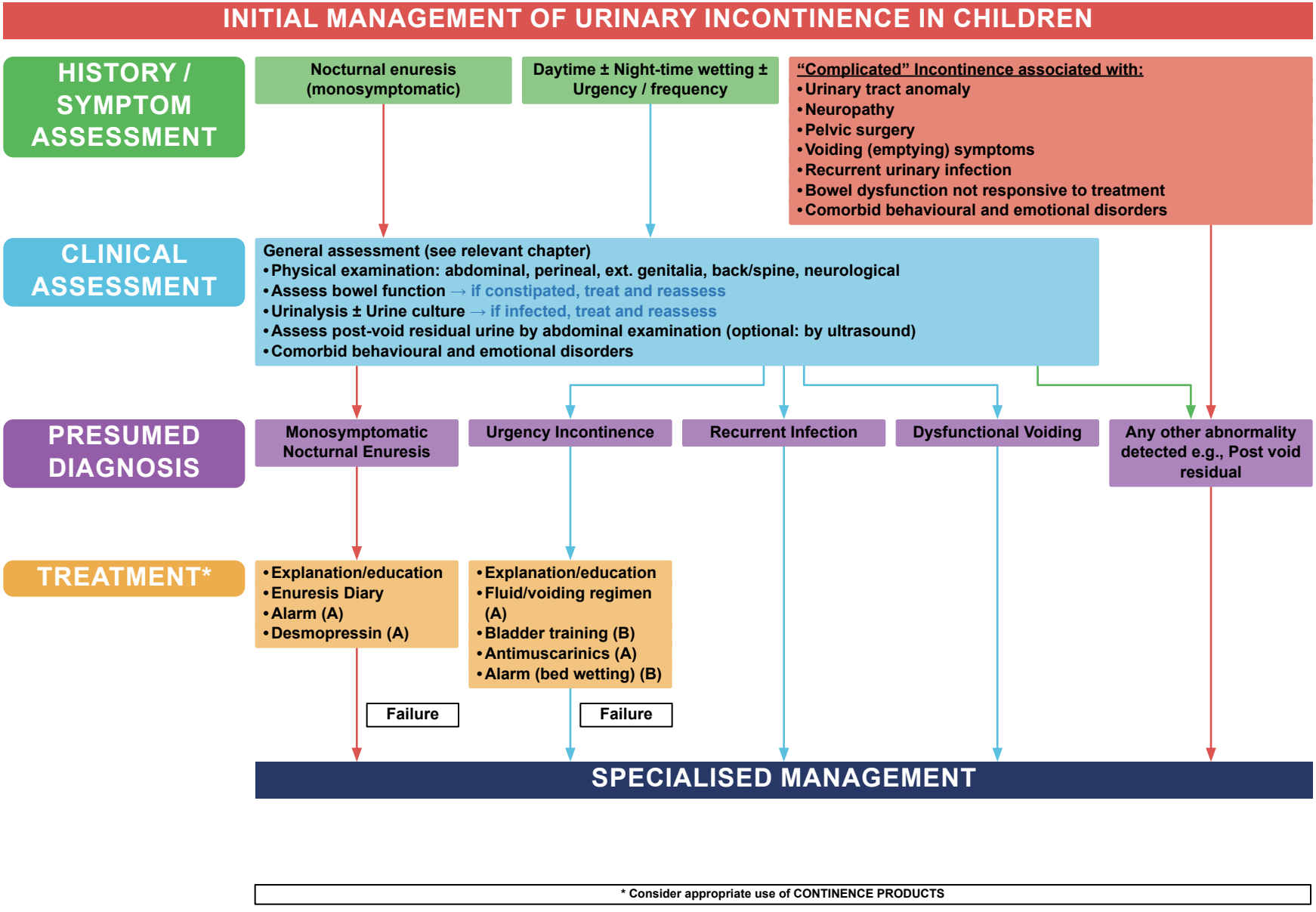
- **Initial treatment is recommended for the remaining patients who have:**
  - Nocturnal enuresis without other symptoms (monosymptomatic enuresis).
  - Daytime symptoms of frequency, urgency, voiding postponement, straining, interrupted voiding, urgency incontinence with or without nighttime wetting.

TREATMENT

- Initial treatment for **mono-symptomatic nocturnal** enuresis should include:
  - Parental and child counselling and motivation
  - Review of bladder diary with attention to night-time polyuria
  - Age-appropriate education and demystification or explanation

- A choice between either bed wetting alarm (GoR A) or anti-diuretic hormone analogues of desmopressin (GoR A). It may be a parental and child choice if advantages and disadvantages are well explained.

- Daytime incontinence should be managed holistically including:
  - Counselling, timed voiding, behaviour modification and bowel management when necessary (GoR B).
  - Antimuscarinics may be used if the child has OAB symptoms (GoR A)


INITIAL MANAGEMENT OF URINARY INCONTINENCE IN CHILDREN
HISTORY / SYMPTOM ASSESSMENT
Nocturnal enuresis (monosymptomatic)
Daytime ± Night-time wetting ± Urgency / frequency
"Complicated" Incontinence associated with:
• Urinary tract anomaly
• Neuropathy
• Pelvic surgery
• Voiding (emptying) symptoms
• Recurrent urinary infection
• Bowel dysfunction not responsive to treatment
• Comorbid behavioural and emotional disorders
CLINICAL ASSESSMENT
General assessment (see relevant chapter)
• Physical examination: abdominal, perineal, ext. genitalia, back/spine, neurological
• Assess bowel function → if constipated, treat and reassess
• Urinalysis ± Urine culture → if infected, treat and reassess
• Assess post-void residual urine by abdominal examination (optional: by ultrasound)
• Comorbid behavioural and emotional disorders
PRESUMED DIAGNOSIS
Monosymptomatic Nocturnal Enuresis
Urgency Incontinence
Recurrent Infection
Dysfunctional Voiding
Any other abnormality detected e.g., Post void residual
TREATMENT*
• Explanation/education
• Enuresis Diary
• Alarm (A)
• Desmopressin (A)
• Explanation/education
• Fluid/voiding regimen (A)
• Bladder training (B)
• Antimuscarinics (A)
• Alarm (bed wetting) (B)
Failure
Failure
SPECIALISED MANAGEMENT
* Consider appropriate use of CONTINENCE PRODUCTS

I. URINARY INCONTINENCE IN CHILDREN

B SPECIALISED MANAGEMENT

- Two groups of children with ‘‘complicated’’ incontinence should have spe- cialist management from the outset (Fig. 2).

- Children whose incontinence is due to, or associated with, **urinary tract anomalies** and **neuropathy**.

- **Children** without urinary tract anomalies, but with **recurrent febrile infection** and, proven or suspected, **lower urinary tract dysfunction**.

- Children who **fail the basic treatment**, but who have neither neurogenic nor anatomical problems, should also receive specialist management.

Children with comorbid behavioural and emotional disorders require referral to mental health services, as compliance and treatment outcomes are lower.

Assessment and treatment should follow evidence-based practice guidelines

ASSESSMENT

- As part of further assessment, the measurement of **urine flow** (in children old enough), together with the **ultrasound estimate of residual urine** and appearance of the bladder wall and rectum are highly recommended. An evaluation of the **upper urinary tracts with ultrasound is also highly recommended**.

Those who do not improve **with treatment** and have neither neurogenic nor anatomical problems **should be reassessed** using bladder diaries, symptom questionnaires, urinalysis, uroflowmetry and residual urine determination.

If there are recurrent and febrile infections, upper tract imaging and a VCUG should be considered. However, endoscopy is rarely indicated.

- **Urodynamics should be considered:**

- If the type and severity of lower tract dysfunction **cannot be explained by clinical findings** or in the presence of possible relevant neuropathy or urinary tract anomalies. (GoR B)

- If **invasive treatment** is under consideration, for example, stress incontinence surgery if there is sphincteric incompetence, or bladder augmentation if there is detrusor overactivity. (GoR B)

- **If upper tract dilation exists** and is thought to be due to bladder dysfunction. (Gor A)

- **Invasive urodynamic studies are generally not recommended** if the child has normal upper tract imaging and is to be treated by noninvasive means. (Gor B)

- **Spinal Imaging** (US/X-ray/MRI) may be needed if a bony abnormality or neuro-logical condition is suspected. (GoR A)

TREATMENT

The treatment of incontinence associated with **urinary tract anomalies** is complex and cannot easily be dealt with in an algorithm. In many children **more than one pathology** demands treatment. If there are **complex congenital abnormalities present**, the treatment is often surgical, and it should be individualised according to the type and severity of the problem (please see Children’s Committee Report).

Specialist children’s nurses and therapists should give care.

- **Initial treatment should be non-surgical.**

- **For stress urinary incontinence** (SUI): pelvic floor muscle training (GoR C).

- **For** OAB symptoms: fluid/voiding regimens and antimuscarinics (GoR A).

- **For voiding dysfunction:** timed voiding, voiding re-education, pelvic floor muscle relaxation (+/- biofeedback), alpha-blocker therapy, and intermittent catheterisation (when PVR >30% of bladder capacity) (GoR A/B).

- **For bowel dysfunction:** high fibre diet and laxatives as appropriate, and. transanal irrigation in severe cases (GoR A).

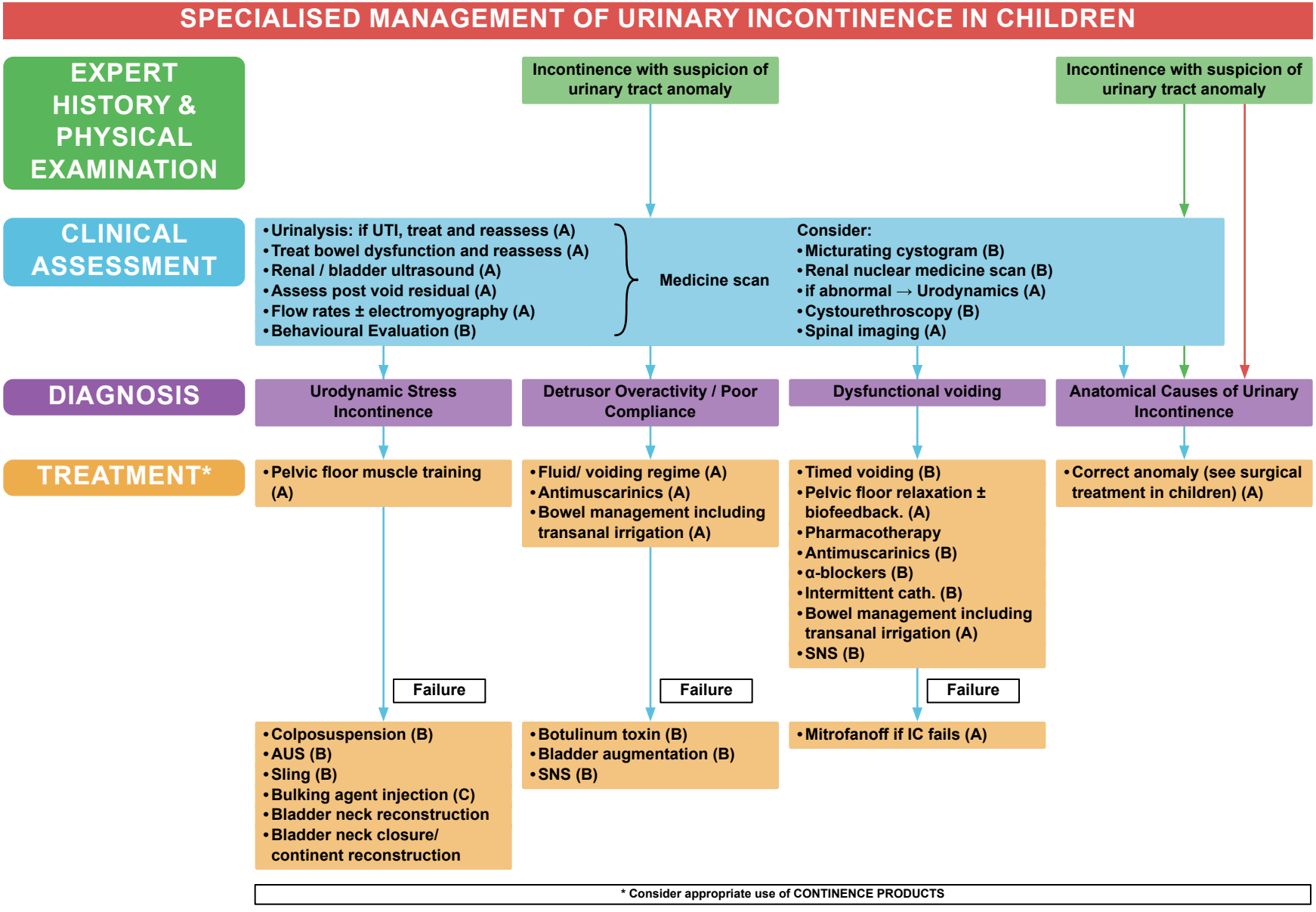
The child's progress should be assessed and, if quality of life is still significantly impaired, or if the upper urinary tracts are at risk, **surgical treatment** is likely to be necessary.

- **If surgical treatment is required**, then urodynamic studies are recommended to confirm the diagnosis.

- **For USI**, bladder neck reconstruction,colposuspension, sling surgery, bulking agent injection,AUS, and rarely, bladder neck closure and continent reconstruction may be considered (GoR B).

- **For DO/poor compliance**, botulinum toxin (for DO, and off-label) and bladder augmentation may be performed (GoR B).

- **If the child cannot do IC,** then a Mitrofanoff channel may be needed (GoR A).


SPECIALISED MANAGEMENT OF URINARY INCONTINENCE IN CHILDREN
EXPERT HISTORY & PHYSICAL EXAMINATION
Incontinence with suspicion of urinary tract anomaly
Incontinence with suspicion of urinary tract anomaly
CLINICAL ASSESSMENT
•Urinalysis: if UTI, treat and reassess (A)
•Treat bowel dysfunction and reassess (A)
•Renal / bladder ultrasound (A)
•Assess post void residual (A)
•Flow rates ± electromyography (A)
•Behavioural Evaluation (B)
Medicine scan
Consider:
•Micturating cystogram (B)
•Renal nuclear medicine scan (B)
•if abnormal → Urodynamics (A)
•Cystourethroscopy (B)
•Spinal imaging (A)
DIAGNOSIS
Urodynamic Stress Incontinence
Detrusor Overactivity / Poor Compliance
Dysfunctional voiding
Anatomical Causes of Urinary Incontinence
TREATMENT*
•Pelvic floor muscle training (A)
•Fluid/ voiding regime (A)
•Antimuscarinics (A)
•Bowel management including transanal irrigation (A)
•Timed voiding (B)
•Pelvic floor relaxation ± biofeedback. (A)
•Pharmacotherapy
•Antimuscarinics (B)
•α-blockers (B)
•Intermittent cath. (B)
•Bowel management including transanal irrigation (A)
•SNS (B)
•Correct anomaly (see surgical treatment in children) (A)
Failure
Failure
Failure
•Colposuspension (B)
•AUS (B)
•Sling (B)
•Bulking agent injection (C)
•Bladder neck reconstruction
•Bladder neck closure/ continent reconstruction
•Botulinum toxin (B)
•Bladder augmentation (B)
•SNS (B)
•Mitrofanoff if IC fails (A)
* Consider appropriate use of CONTINENCE PRODUCTS

II. URINARY INCONTINENCE IN MEN

A INITIAL MANAGEMENT

INITIAL ASSESSEMENT SHOULD IDENTIFY:

- **"Complicated" incontinence group**

Those with pain or with haematuria, recurrent infection, suspected or proven poor bladder emptying (for example due to bladder outlet obstruction), or incontinence following pelvic irradiation or radical surgery, are recommended for **specialised management**.

Poor bladder emptying may be suspected from symptoms, physical examination or if imaging has been performed by X-ray or ultrasound after voiding.

- **Four other main groups** of men should be identified by initial assessment as being suitable for **initial management**.

- Those with post-micturition dribble alone,
- Those with overactive bladder (OAB) symptoms: urgency with or without urgency incontinence, together with frequency and nocturia
- Those with stress urinary incontinence (most often post-prostatectomy),
- Those with mixed urinary urgency and stress incontinence (most often post- prostatectomy)

MANAGEMENT

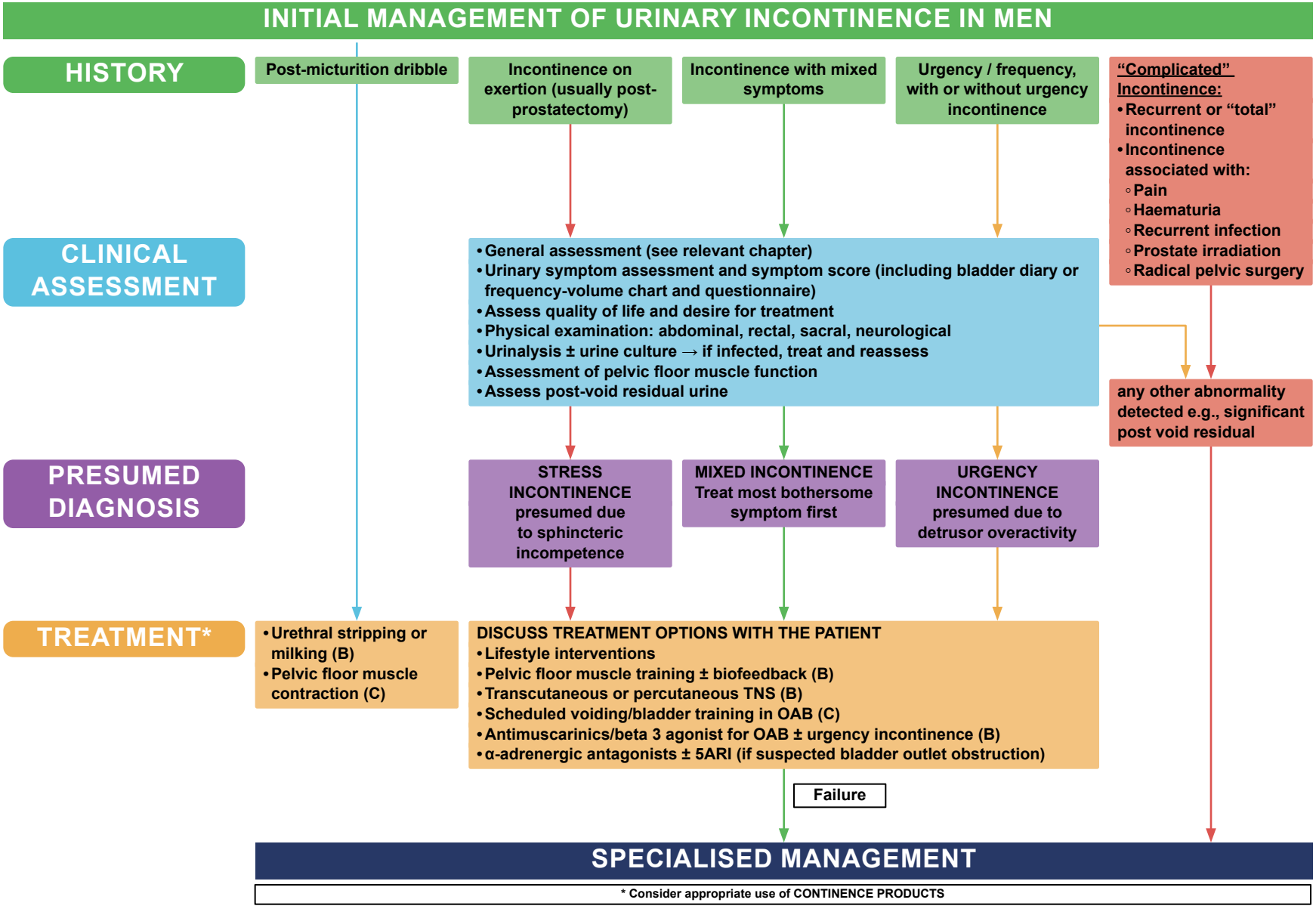
- For men with **post-micturition dribble**, this requires no assessment and can usually be treated by teaching the man how to do a strong pelvic floor muscle contraction after voiding, or manual compression of the bulbous urethra directly after micturition (urethral "stripping" or "milking". (GoR C (for strong PFM contraction))

- For men with **stress**, **urgency** or **mixed** urgency / stress incontinence, initial treatment should include appropriate lifestyle advice, pelvic floor muscle training, scheduled voiding regimens, behavioural therapies, and medication. In particular:

- Lifestyle interventions (e.g., weight loss GoR B)
- Supervised pelvic floor muscle training either pre-operatively or early post operatively for men with post radical prostatectomy SUI accelerates recovery time (GoR B)
- Scheduled voiding regimen for OAB (GoR C)
- Transcutaneous or percutaneous posterior tibial nerve stimulation for men who do not achieve satisfactory results from lifetsylt and behavioural management (GoR B)
- Antimuscarinic/beta 3 agonist drugs for OAB symptoms with or without urgency incontinence (GoR B) if the patient has no evidence of significant post-void residual urine
- α-adrenergic antagonists (a-blockers), alone or in combination with 5-alpha-reductase inhibitors (5ARI), can be added if it is thought that there may also be benign prostatic obstruction. (GoR C)

- **Should initial treatment be unsuccessful** after a reasonable time (for example, 8-12 weeks), **specialist advice** is highly recommended.

Clinicians are likely to wish to treat the **most bothersome symptom** first in men with symptoms of **mixed** incontinence.


INITIAL MANAGEMENT OF URINARY INCONTINENCE IN MEN
HISTORY
Post-micturition dribble
Incontinence on exertion (usually post-prostatectomy)
Incontinence with mixed symptoms
Urgency / frequency, with or without urgency incontinence
"Complicated" Incontinence:
• Recurrent or "total" incontinence
• Incontinence associated with:
◦ Pain
◦ Haematuria
◦ Recurrent infection
◦ Prostate irradiation
◦ Radical pelvic surgery
CLINICAL ASSESSMENT
• General assessment (see relevant chapter)
• Urinary symptom assessment and symptom score (including bladder diary or frequency-volume chart and questionnaire)
• Assess quality of life and desire for treatment
• Physical examination: abdominal, rectal, sacral, neurological
• Urinalysis ± urine culture → if infected, treat and reassess
• Assessment of pelvic floor muscle function
• Assess post-void residual urine
any other abnormality detected e.g., significant post void residual
PRESUMED DIAGNOSIS
STRESS INCONTINENCE presumed due to sphincteric incompetence
MIXED INCONTINENCE Treat most bothersome symptom first
URGENCY INCONTINENCE presumed due to detrusor overactivity
TREATMENT*
• Urethral stripping or milking (B)
• Pelvic floor muscle contraction (C)
DISCUSS TREATMENT OPTIONS WITH THE PATIENT
• Lifestyle interventions
• Pelvic floor muscle training ± biofeedback (B)
• Transcutaneous or percutaneous TNS (B)
• Scheduled voiding/bladder training in OAB (C)
• Antimuscarinics/beta 3 agonist for OAB ± urgency incontinence (B)
• α-adrenergic antagonists ± 5ARI (if suspected bladder outlet obstruction)
Failure
SPECIALISED MANAGEMENT
* Consider appropriate use of CONTINENCE PRODUCTS

II. URINARY INCONTINENCE IN MEN

B SPECIALISED MANAGEMENT

The specialist may first **reinstitute initial management** if it is felt that previous therapy had been inadequate.

ASSESSMENT

- Patients with **"complicated" incontinence** referred directly to specialised management, are likely to require **additional testing**, such as cytology, cystourethroscopy, and urinary tract imaging.

If additional testing is normal, then those individuals can be treated for incontinence by the initial or specialised management options as appropriate.

If symptoms suggestive of detrusor overactivity, or of sphincter incompetence **persist**, then **urodynamic** studies are optional to arrive at a precise diagnosis, prior to invasive treatment.

TREATMENT

When basic management has been unsuccessful and if the patient's incontinence markedly disrupts his quality of life, then **invasive therapies** should be considered.

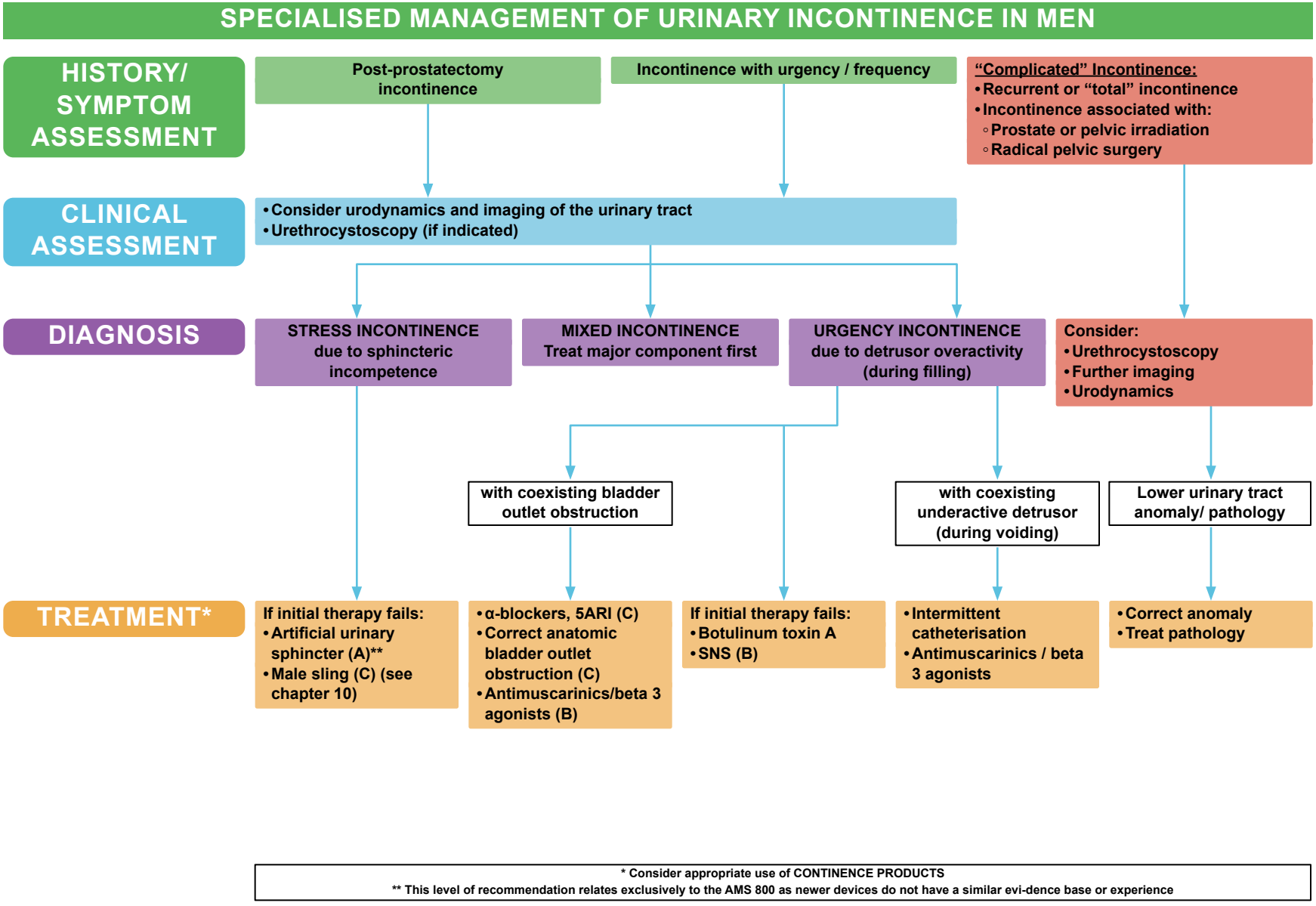
- **For sphincter incompetence** the recommended option is the artificial urinary sphincter (GoR B). Other options, such as a male sling, may be considered (GoR C).

- **For refractory idiopathic detrusor overactivity**, (with intractable overactive bladder symptoms) the recommended therapies are Botulinum toxin A (GoR B), and SNS (GoR C),

- When incontinence has been shown to be associated with **poor bladder emptying** due to **detrusor underactivity**, it is recommended that effective means are used to ensure bladder emptying, for example, intermittent catheterisation (GoR B/C).

- If incontinence is associated with bladder outlet obstruction, then consideration should be given to surgical treatment to relieve obstruction (GoR B). α-blockers and/or 5α-reductase inhibitors would be an optional treatment (GoR C).

- There is increased evidence for the safety of antimuscarinics for overactive bladder symptoms in men, chiefly in combination with an α-blocker. (Men presenting with a Qmax below 5 ml/seg and/or increased PVR (e.g., > 150 or 200 ml) were excluded from trials) (GoR B).


SPECIALISED MANAGEMENT OF URINARY INCONTINENCE IN MEN
HISTORY/ SYMPTOM ASSESSMENT
Post-prostatectomy incontinence
Incontinence with urgency / frequency
"Complicated" Incontinence:
• Recurrent or "total" incontinence
• Incontinence associated with:
◦ Prostate or pelvic irradiation
◦ Radical pelvic surgery
CLINICAL ASSESSMENT
• Consider urodynamics and imaging of the urinary tract
• Urethrocystoscopy (if indicated)
DIAGNOSIS
STRESS INCONTINENCE due to sphincteric incompetence
MIXED INCONTINENCE Treat major component first
URGENCY INCONTINENCE due to detrusor overactivity (during filling)
Consider:
• Urethrocystoscopy
• Further imaging
• Urodynamics
with coexisting bladder outlet obstruction
with coexisting underactive detrusor (during voiding)
Lower urinary tract anomaly/ pathology
TREATMENT*
If initial therapy fails:
• Artificial urinary sphincter (A)**
• Male sling (C) (see chapter 10)
• α-blockers, 5ARI (C)
• Correct anatomic bladder outlet obstruction (C)
• Antimuscarinics/beta 3 agonists (B)
If initial therapy fails:
• Botulinum toxin A
• SNS (B)
• Intermittent catheterisation
• Antimuscarinics / beta 3 agonists
• Correct anomaly
• Treat pathology
* Consider appropriate use of CONTINENCE PRODUCTS
** This level of recommendation relates exclusively to the AMS 800 as newer devices do not have a similar evi-dence base or experience

III. URINARY INCONTINENCE IN WOMEN

A INITIAL MANAGEMENT

INITIAL ASSESSMENT SHOULD IDENTIFY:

- **"Complicated" incontinence group.**

Those with pain or haematuria, recurrent infections, suspected or proven voiding problems, significant pelvic organ prolapse or who have persistent incontinence or recurrent incontinence after pelvic irradiation, radical pelvic surgery, previous incontinence surgery, or who have a suspected fistula, should be referred to a specialist.

- **Three other main groups** of patients should be identified by initial assessment.

- Women with **stress incontinence** on physical activity
- Women with **urgency, frequency** with or without urgency incontinence: overactive bladder (OAB)
- Those women with **mixed** urgency and stress incontinence

Abdominal, pelvic and perineal examinations should be a routine part of physical examination. Women should be asked to perform a "stress test" (cough and strain to detect leakage likely to be due to sphincter incompetence). Any pelvic organ prolapse, or urogenital atrophy should be assessed. Vaginal or rectal examination allows the assessment of voluntary pelvic floor muscle function, a key step prior to the teaching of pelvic floor muscle training.

TREATMENT

- For women with **stress, urgency or mixed** urinary incontinence, initial treatment should include appropriate lifestyle advice, pelvic floor muscle training, PFMT), scheduled voiding regimes, behavioural therapies, and medication. In particular:

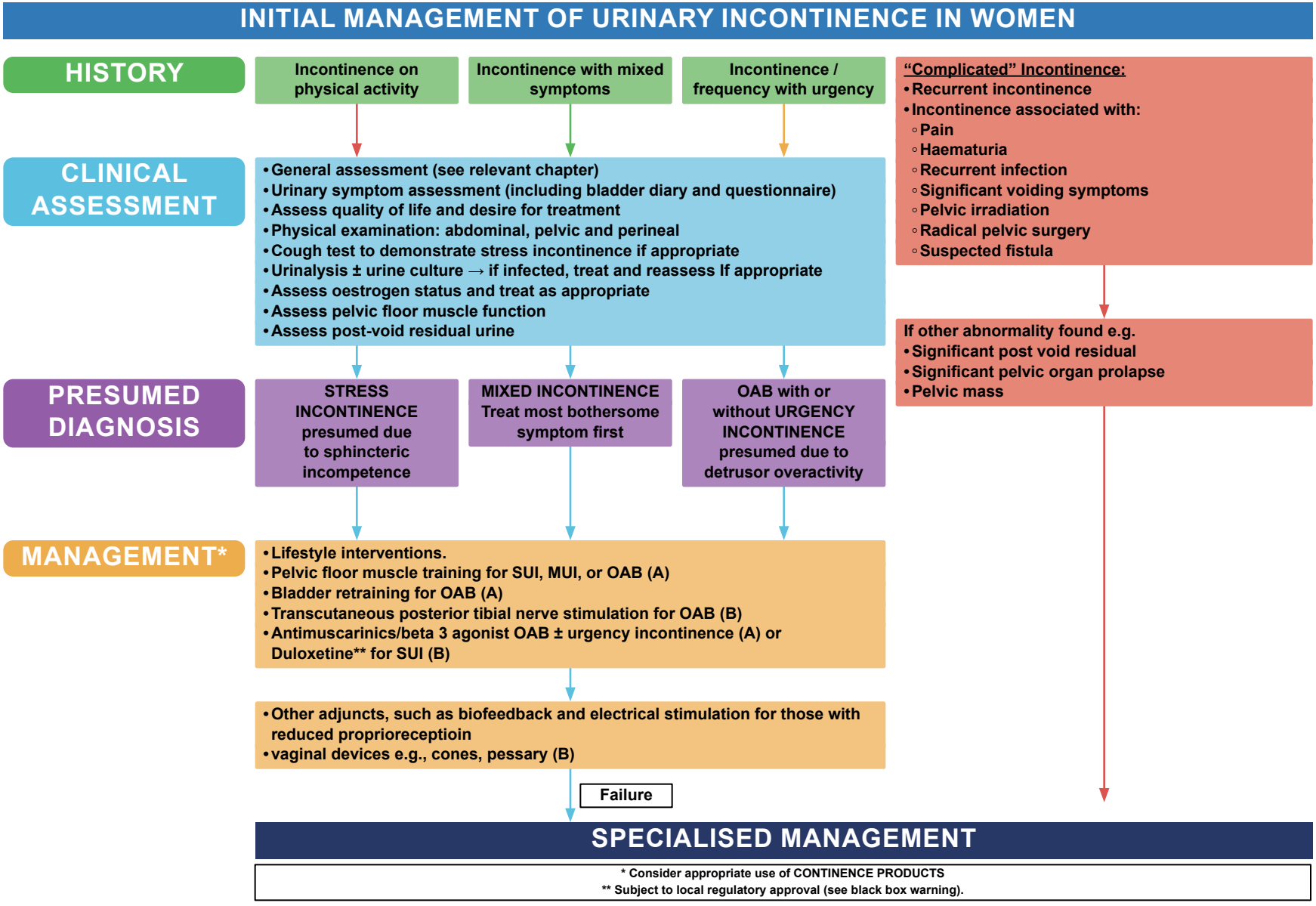
- **Advice** on caffeine reduction for OAB (GoR B) and weight reduction (GoR A). Fluid balance & regular physical activity should be maintained / encouraged.
- Supervised pelvic floor muscle training (GoR A), supervised vaginal cones training for women with stress incontinence (GoR B).
- Supervised bladder training (GoR A) for OAB.
- Transcutaneous or percutaneous posterior tibial nerve stimulation can be offered to adults who do not achieve satisfactory results from fist-line lifestyle and behavioral intervention (B)
- **If oestrogen deficiency** and/or **UTI** is found, the patient should be treated at initial assessment and then reassessed after using vaginal oestrogens for a suitable period (GoR B). Topical oestrogen may alleviate OAB symptoms in post menopausal women (GoR C)
- **Antimuscarinics/beta 3 agonist** for OAB symptoms with or without urgency incontinence (GoR A); duloxetine* may be considered for stress urinary incontinence (GoR B)

PFMT should be based on sound muscle training principles such as specificity, overload progression, correct contraction confirmed prior to training and use of "the Knack" for 12 weeks before reassessment and specialist referral.

Clinicians are likely to wish to treat the **most bothersome symptom first** in women with symptoms of mixed incontinence. (GoR C).

- Some women with significant pelvic organ prolapse can be treated by vaginal devices that treat both incontinence and prolapse (incontinence rings and dishes).

*Duloxetine is not approved for use in United States. In Europe it is approved for use in severe stress incontinence (see committee report on pharmacological management for information regarding efficacy, adverse events, and 'black box' warning by the Food and Drug Administration of the United States).


INITIAL MANAGEMENT OF URINARY INCONTINENCE IN WOMEN
HISTORY
Incontinence on physical activity
Incontinence with mixed symptoms
Incontinence / frequency with urgency
"Complicated" Incontinence:
• Recurrent incontinence
• Incontinence associated with:
◦ Pain
◦ Haematuria
◦ Recurrent infection
◦ Significant voiding symptoms
◦ Pelvic irradiation
◦ Radical pelvic surgery
◦ Suspected fistula
CLINICAL ASSESSMENT
• General assessment (see relevant chapter)
• Urinary symptom assessment (including bladder diary and questionnaire)
• Assess quality of life and desire for treatment
• Physical examination: abdominal, pelvic and perineal
• Cough test to demonstrate stress incontinence if appropriate
• Urinalysis ± urine culture → if infected, treat and reassess If appropriate
• Assess oestrogen status and treat as appropriate
• Assess pelvic floor muscle function
• Assess post-void residual urine
If other abnormality found e.g.
• Significant post void residual
• Significant pelvic organ prolapse
• Pelvic mass
PRESUMED DIAGNOSIS
STRESS INCONTINENCE presumed due to sphincteric incompetence
MIXED INCONTINENCE Treat most bothersome symptom first
OAB with or without URGENCY INCONTINENCE presumed due to detrusor overactivity
MANAGEMENT*
• Lifestyle interventions.
• Pelvic floor muscle training for SUI, MUI, or OAB (A)
• Bladder retraining for OAB (A)
• Transcutaneous posterior tibial nerve stimulation for OAB (B)
• Antimuscarinics/beta 3 agonist OAB ± urgency incontinence (A) or Duloxetine** for SUI (B)
• Other adjuncts, such as biofeedback and electrical stimulation for those with reduced proprioreceptioin
• vaginal devices e.g., cones, pessary (B)
Failure
SPECIALISED MANAGEMENT
* Consider appropriate use of CONTINENCE PRODUCTS
** Subject to local regulatory approval (see black box warning).

III. URINARY INCONTINENCE IN WOMEN

B SPECIALISED MANAGEMENT

ASSESSMENT

Women who have **"complicated" incontinence** (see initial algorithm) may need to have additional tests such as cytology, urodynamics, cystourethroscopy or urinary tract imaging. If these tests are normal, then they should be treated for incontinence by the initial or specialised management options as appropriate.

- Those women with persistent symptoms despite **initial management** and whose quality of life is impaired are likely to request further treatment. If initial management has been given an adequate trial, then **interventional therapy may be desired**. When the results of urodynamic testing may change management, we highly recommend testing prior to intervention to diagnose the incontinence type and, therefore, inform the management plan. Urethral function testing by urethral pressure profile or leak point pressure is optional.

- Systematic assessment for **pelvic organ prolapse** is highly recommended and the POP-Q method should be used in research studies. Women with co-existing pelvic organ prolapse should have their prolapse treated as appropriate.

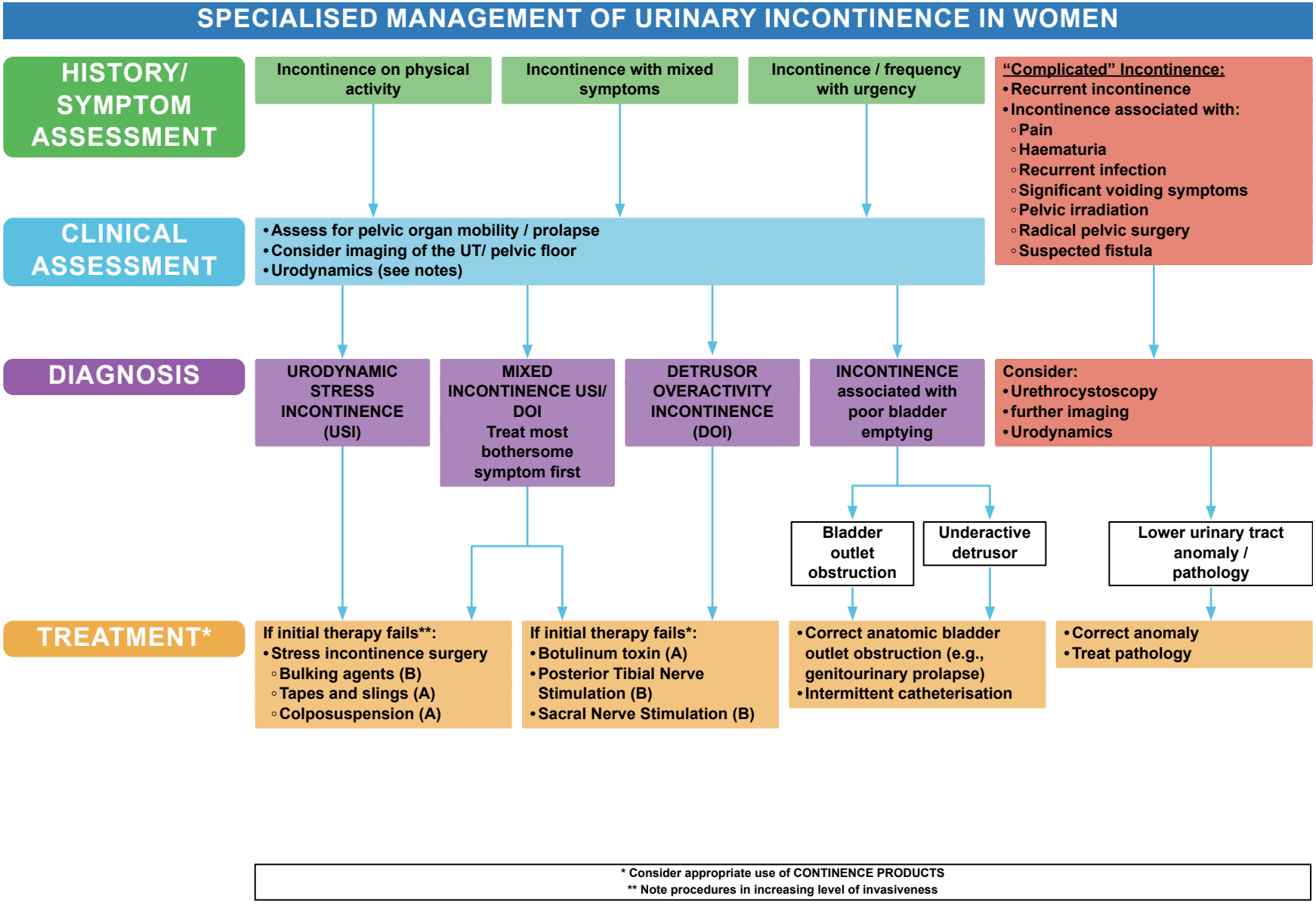
TREATMENT

- **If stress incontinence is confirmed** then the treatment options that are recommended for patients include the full range of non-surgical treatments, as well as colposuspension procedures, (GoR A) and bladder neck/sub-urethral sling operations (GoR A). All these procedures have potential risks and associated complications which should be discussed with the individual. **The correction of symptomatic** pelvic organ prolapse may be desirable at the same time. For selected patients injectable bulking agents (GoR B) and the artificial urinary sphincter (GoR C) can be considered.

- **Refractory urgency incontinence** (overactive bladder) secondary to idiopathic detrusor overactivity may be treated by botulinum toxin A (GoR A), posterior tibial nerve stimulation or sacral nerve stimulation (GoR B). Bladder augmentation/intestinal cystoplasty is recommended only for women with severely reduced bladder capacity who are willing to consider the complication rate and need for long term surveillance (GoR D).

- Those patients with **voiding dysfunction** leading to significant post-void residual urine (for example, >30% of total bladder capacity) may have bladder outlet obstruction or detrusor underactivity. Prolapse is a common reversible cause, of voiding dysfunction.

- For women with intractable incontinence or voiding dysfunction, long term urethral or suprapubic catheterisation may be offered if clean intermittent catheterisation is impractical


SPECIALISED MANAGEMENT OF URINARY INCONTINENCE IN WOMEN
HISTORY/ SYMPTOM ASSESSMENT
Incontinence on physical activity
Incontinence with mixed symptoms
Incontinence / frequency with urgency
"Complicated" Incontinence:
• Recurrent incontinence
• Incontinence associated with:
◦ Pain
◦ Haematuria
◦ Recurrent infection
◦ Significant voiding symptoms
◦ Pelvic irradiation
◦ Radical pelvic surgery
◦ Suspected fistula
CLINICAL ASSESSMENT
• Assess for pelvic organ mobility / prolapse
• Consider imaging of the UT/ pelvic floor
• Urodynamics (see notes)
DIAGNOSIS
URODYNAMIC STRESS INCONTINENCE (USI)
MIXED INCONTINENCE USI/ DOI
Treat most bothersome symptom first
DETRUSOR OVERACTIVITY INCONTINENCE (DOI)
INCONTINENCE associated with poor bladder emptying
Consider:
• Urethrocystoscopy
• further imaging
• Urodynamics
Bladder outlet obstruction
Underactive detrusor
Lower urinary tract anomaly / pathology
TREATMENT*
If initial therapy fails**:
• Stress incontinence surgery
◦ Bulking agents (B)
◦ Tapes and slings (A)
◦ Colposuspension (A)
If initial therapy fails*:
• Botulinum toxin (A)
• Posterior Tibial Nerve Stimulation (B)
• Sacral Nerve Stimulation (B)
• Correct anatomic bladder outlet obstruction (e.g., genitourinary prolapse)
• Intermittent catheterisation
• Correct anomaly
• Treat pathology
* Consider appropriate use of CONTINENCE PRODUCTS
** Note procedures in increasing level of invasiveness

IV. FISTULAE

In the developing world fistulae most often occur because of poor perinatal care. Despite vast surgical experience in some centres, published research is of low quality.

In the developed world, iatrogenic urogenital fistulae are known complications of pelvic surgery and oncological treatments such as radiotherapy, chemotherapy or a combination of both. In the oncological context, fistulae may also occur because of primary or recurrent malignancy. The development of fistula following radiotherapy for primary treatment should trigger a search for evidence of tumour recurrence (GoR D). The use of neoadjuvant or adjuvant therapies is likely to be associated with a greater risk of fistula development than the primary treatment alone.

The most common non-obstetric causes of fistulae involving the gastro-intestinal tract are diverticular disease, Crohn's disease, malignancy and radiotherapy.

Surgical fistulae

Immediate management

- If a vesico-vaginal fistula is diagnosed within (*three to*) six weeks of surgery, indwelling catheterisation should be considered for a period of up to (*six to*) 9 weeks (*i.e.* up to 12 weeks after the causative event
- Retrograde, ureteroscopically-assisted or antegrade ureteric stenting should be considered for immediate management for all uretero-vaginal fistulae

Timing of surgery

The timing of VVF repair should be tailored to the individual patient requirements, and can be undertaken as soon as any local oedema, inflammation, necrosis & infection resolved

Bowel preparation

No benefit from mechanical or laxative bowel preparation prior to colonic surgery; this can be extrapolated to include fistula surgery

Antibiotic prophylaxis

Perioperative antibiotic prophylaxis should follow local policies

Counselling & support

- Realistic counselling by the surgeon, nursing staff and/ or counsellors with experience of fistula patients is highly desirable
- Support from previously treated patients is appreciated and very valuable

Surgical approach

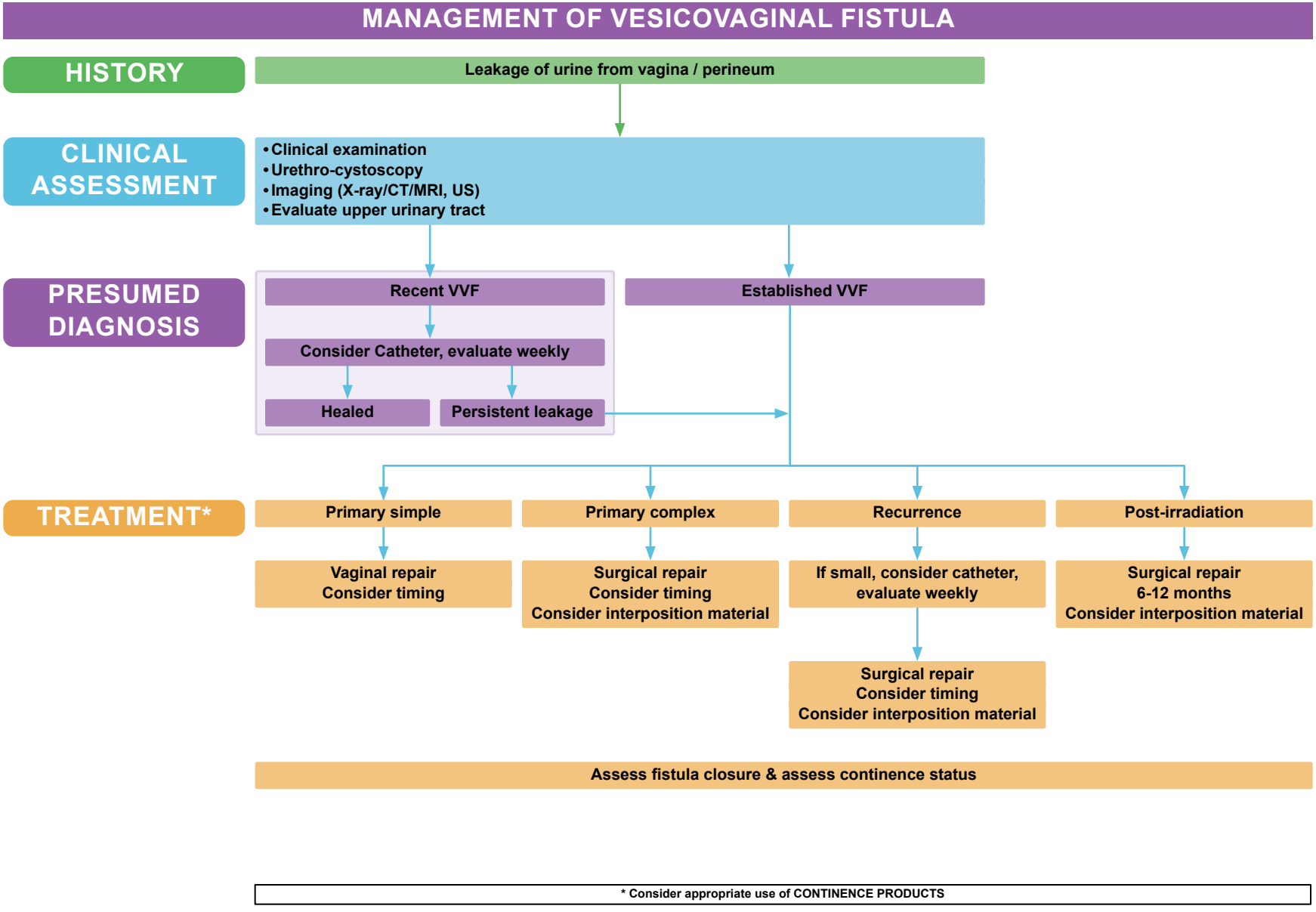
- Surgeons involved in fistula surgery should have appropriate training, skills, experience and versatility to select an appropriate procedure for any patient
- Both vaginal and abdominal approaches have an established role in fistula repair
- The majority of VVFs and all urethro-vaginal fistulae can be repaired vaginally, regardless of aetiology
- Where concurrent ureteric re-implantation or augmentation cystoplasty are required, and abdominal approach is essential
- A variety of interposition grafts are described for use in either abdominal or vaginal procedures, although there is no high level evidence to support their use
- Conventional and robotically-assisted laparoscopic approaches have both been shown to be feasible in selected cases; the place of these techniques is not yet clear

Postoperative drainage

A period of continuous bladder drainage is crucial to successful fistula repair

- 10-14 days for simple and/or surgical
- 14-21 days for complex and/or radiation

Treatment recommendations for surgical fistulae


MANAGEMENT OF VESICOVAGINAL FISTULA
HISTORY
Leakage of urine from vagina / perineum
CLINICAL ASSESSMENT
•Clinical examination
•Urethro-cystoscopy
•Imaging (X-ray/CT/MRI, US)
•Evaluate upper urinary tract
PRESUMED DIAGNOSIS
Recent VVF
Established VVF
Consider Catheter, evaluate weekly
Healed
Persistent leakage
TREATMENT*
Primary simple
Primary complex
Recurrence
Post-irradiation
Vaginal repair
Consider timing
Surgical repair
Consider timing
Consider interposition material
If small, consider catheter, evaluate weekly
Surgical repair
6-12 months
Consider interposition material
Surgical repair
Consider timing
Consider interposition material
Assess fistula closure & assess continence status
* Consider appropriate use of CONTINENCE PRODUCTS

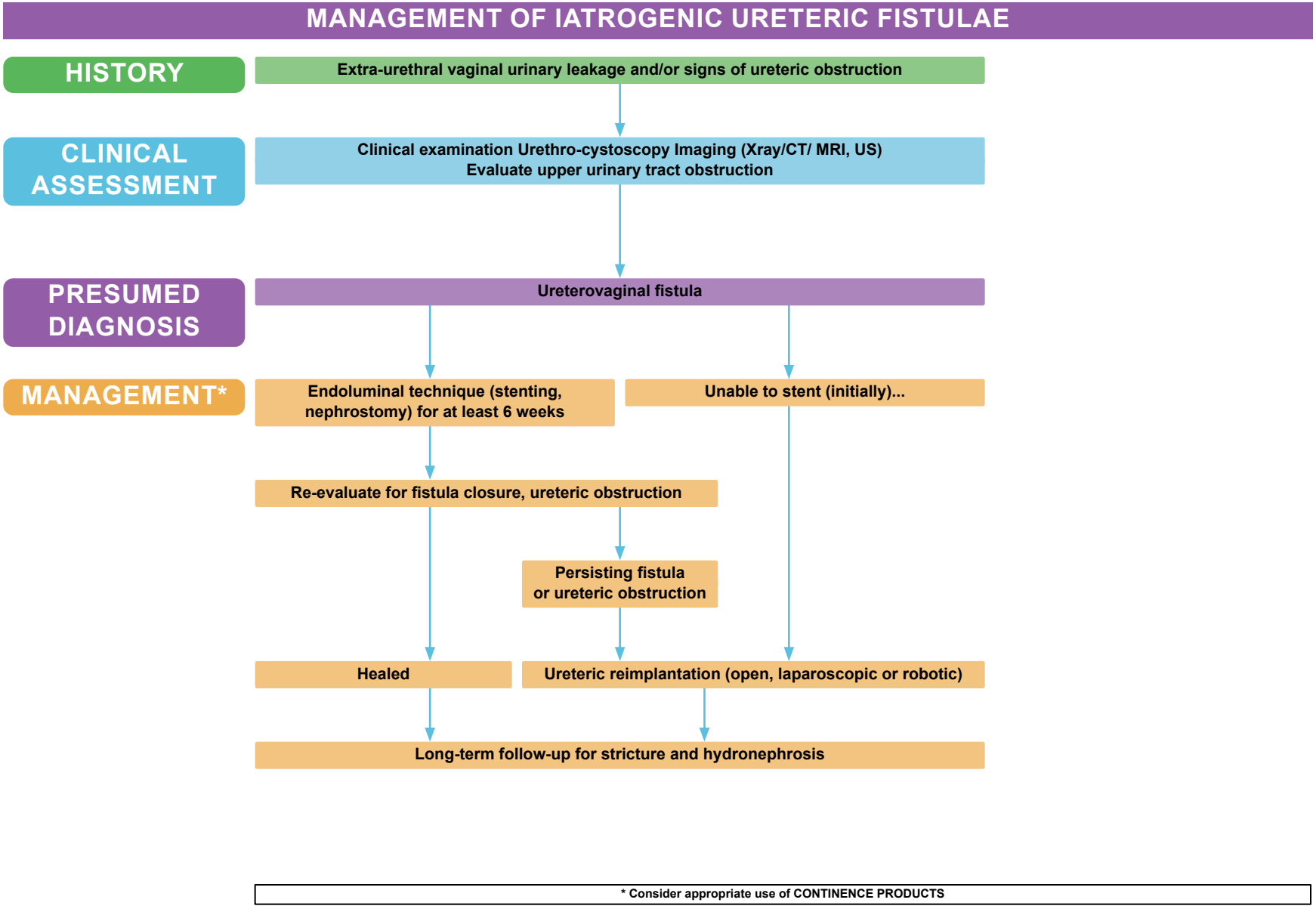
Radiotherapy fistulae

Spontaneous healing	Rare, if ever
Repair procedures	• Careful selection necessary as results poorer than in non-irradiated cases • Colpocleisis preferable to 'flap-splitting' • Consider interposition graft
Urinary/faecal diversion	• Required more often than in non-irradiated cases, but ONLY after careful consideration of alternatives • Avoid irradiated bowel if possible
Intractable incontinence, life expectancy poor	Consider nephrostomy or ureteric occlusion

Fistulae involving GIT

Investigations	May require several approaches especially CT & cystoscopy
Diverticular (colo-vesical) fistulae • Frail elderly, limited symptoms of urinary infection or diarrhoea	Consider trial of conservative management
Crohn's fistulae	Consider trial of *infliximab*, esp. for any external fistulae
Simple fistulae • Nutritional state good • No additional intra-abdominal pathology (*e.g.* severe inflammation, radiation injury, advanced malignancy, intestinal obstruction) • No major co-morbidity	One-stage surgery
Complex fistulae • Nutritional state poor • Severe inflammation • Radiation injury • Advanced malignancy • Intestinal obstruction • Major co-morbidity • Multiple organ involvement	Specialist referral centre for phased management • Proximal defunctioning and distal drainage • TPN, organ support, radiological planning • Joint urological and gastrointestinal surgery

Treatment recommendations for radiation fistula and fistula involving the gastro-intestinal tract


MANAGEMENT OF IATROGENIC URETERIC FISTULAE
HISTORY
Extra-urethral vaginal urinary leakage and/or signs of ureteric obstruction
CLINICAL ASSESSMENT
Clinical examination Urethro-cystoscopy Imaging (Xray/CT/ MRI, US)
Evaluate upper urinary tract obstruction
PRESUMED DIAGNOSIS
Ureterovaginal fistula
MANAGEMENT*
Endoluminal technique (stenting, nephrostomy) for at least 6 weeks
Unable to stent (initially)...
Re-evaluate for fistula closure, ureteric obstruction
Persisting fistula or ureteric obstruction
Healed
Ureteric reimplantation (open, laparoscopic or robotic)
Long-term follow-up for stricture and hydronephrosis
* Consider appropriate use of CONTINENCE PRODUCTS

V. PELVIC ORGAN PROLAPSE

INTRODUCTION

Pelvic organ prolapse includes vaginal and rectal prolapse. Treatment of pelvic organ prolapse is generally reserved for symptomatic prolapse. Clinicians should recognise that coexistent pelvic floor symptoms are frequently present and that these symptoms may or may not be related to the prolapse. Women with prolapse require a careful and detailed initial assessment not only of the prolapse but associated bladder, bowel and sexual function.

ASSESSMENT

Symptom assessment preferably with a validated pelvic floor questionnaire that assesses bladder, bowel, vaginal and sexual function and bothersomeness is required. (Grade C).

Physical examination should:

- Report the most distal site of vaginal descent in relation to a fixed point such as the hymen and include an assessment of the anterior posterior and apical vagina. While standardised reporting utilising tools such as the Pelvic Organ Prolapse Quantification (POP-Q) are encouraged. The system used to measure the extent of the prolapse should be documented.
- Be undertaken in the standing position to evaluate the full extent of the prolapse.
- Determine if coexistent pelvic pathology is present on careful bimanual examination. Cytological screening of the cervix should be undertaken if indicated.
- The prolapse should be reduced to document the presence of occult stress urinary incontinence (see chapter for prolapse and urinary incontinence pathway).
- Assess pelvic floor muscle function (see chapter for full review).
- Determine if epithelial/ mucosal ulceration is present.
- Evaluate anal sphincter tone and or the presence of rectal prolapse in those with bowel symptoms (refer to chapter for pelvic organ prolapse and bowel symptom pathway).

When examination findings of the extent of the prolapse are not consistent with the history the examination can be repeated in a few weeks' time. (GoR C).

Post void residual should be measured; while most elevated post-void residual urines (150mls) resolve with treatment of the prolapse, a specialist consultation is required.

CONSERVATIVE MANAGEMENT

Observation is appropriate when medically safe and the patient is not bothered (GoR C).

Lifestyle interventions include weight loss, treating constipation, avoiding straining at stool and heavy lifting (GoR C).

Pelvic floor muscle training:

- Reduces associated pelvic floor symptoms (GoR A).
- May reduce the symptom of vaginal bulge (GoR C).
- Does not reduce extent of prolapse on examination based on POP-Q stage (GoR B).

Vaginal Pessary: when successfully fitted

- May reduce prolapse symptoms (GoR B)
- Need to be regularly reviewed (GoR C)
- May be associated with high rates of discontinuation (GoR C)

Local Oestrogens are recommended in those with hypo-oestrogenic symptoms and in those with urethral prolapse or vaginal ulceration (GoR B)

Reconstructive surgery is reserved for those with symptomatic prolapse and is aimed at correcting the vaginal topography and functional pathology. Please see text for full recommendations.

Obliterative surgery is an important and effective treatment option in those who are willing to forgo future coital activity. (GoR C)

PATHWAY FOR THE MANAGEMENT OF PELVIC ORGAN PROLAPSE

CONSERVATIVE MANAGEMENT

- Lifestyle interventions (GoR B and C).
  - Educational intervention
  - weight loss
  - Treatment of constipation

- Pelvic floor muscle training (GoR A and B), either alone or with biofeedback or electrical stimulation in those with reduced proprioception
- Pessary GoR B).
- Pessary plus PFMT (GoR B)
  - Women should be informed about the advantages and disadvantages of different interventions.

SURGICAL MANAGEMENT

The pelvic organ prolapse (POP) surgery pathway was designed to provide an evidence-based guide for both clinicians and women for the surgical management of pelvic organ prolapse. Within the pathway green lines highlight the preferred option and yellow lines indicate reasonable options.

An early option in the treatment pathway for women not wanting to preserve sexual function is obliterative surgery (colpocleisis) which is an efficacious intervention that has low morbidity (LoE 3).

Most women will enter the reconstructive pathway. Apical suspension procedures should be considered in all cases with 10-year re-operation rates for prolapse being significantly reduced if apical suspensions are performed concomitantly with both anterior and posterior colporrhaphy as compared to those performed without apical support.

In those undergoing anterior and posterior colporrhaphy the evidence is supportive of traditional native tissue suture plications (LoE 1). In the anterior compartment permanent mesh could be considered for recurrent cases when the patient understands the risk benefit profile for these interventions and that the data for their use is scant. Evidence is not supportive of biological grafts in the anterior compartment (LoE 2).

In the posterior compartment, fascial plication is superior to site specific native tissue repair (LoE 2) and levatorplasty should be avoided due to higher rates of dyspareunia (LoE3). Data are not supportive of biological or permanent mesh grafts. Posterior colporrhaphy is superior to transanal repair of rectocele (LoE 1) and there is no data to support ventral rectopexy with or without vaginal graft for rectocele.

With recognition of the importance of apical vaginal support in minimising the risk of subsequent recurrence, the pathway separates those with post-hysterectomy (vault) prolapse from those with uterine prolapse.

Data are supportive of sacral colpopexy as the preferred intervention for vault prolapse with superior anatomical and functional outcomes when compared to a variety of vaginal based interventions with and without transvaginal mesh (LoE1). This preference is highlighted by a green preferred option arrow in the management pathway. In recognition that not all patients are suitable for sacral colpopexy, a yellow reasonable option is included for vaginal based apical support (uterosacral or sacrospinous colpopexy). Both uterosacral and sacrospinous colpopexy are equally effective vaginal options (LoE 1) and utilisation of transvaginal permanent mesh apical support is not supported by the data (LoE1).

When performing sacral colpopexy the laparoscopic approach is preferred with reduced peri-operative morbidity and cost when compared to both the open and robotic approach (LoE 2). The yellow reasonable option pathway exists for both open and robotic options in recognition of the longer learning curve associated with the laparoscopic approach (LoE3).

Apical support in those with uterine prolapse can be performed abdominally or vaginally and includes options for both uterine preservation (hysteropexy) and hysterectomy, with not insignificant relative contraindications for uterine preservation listed in Table 6. In post-menopausal women undergoing hysterectomy, bilateral salpngo-oopherectomy (BSO) significantly reduces the rate of ovarian cancer without increased morbidity. In those retaining ovaries at hysterectomy, bilateral salpingectomy also reduces rate of subsequent ovarian cancer.

Vaginal hysteropexy is equally effective as vaginal hysterectomy with apical suspension and is associated with reduced blood loss and operating time as compared to hysterectomy (LoE 1). Vaginal hysterectomy with apical support has a lower re-operation for prolapse than abdominal sacrohysteropexy (LoE1). Sacrohysteropexy has a higher re-operation for prolapse than sacral colpopexy with hysterectomy however sacral colpopexy with hysterectomy is not recommended due to the high rate of mesh exposure (LoE2). Supra-cervical hysterectomy at sacral colpopexy reduces the rate of mesh exposure associated with hysterectomy and sacral colpopexy however in a single retrospective study, recurrent prolapse was more common in the supracervical hysterectomy group. Although those data are not complete, vaginal based hysterectomy and hysteropexy with apical support should generally be considered as preferred options for uterine prolapse with sacral colpopexy reserved for vault prolapse.

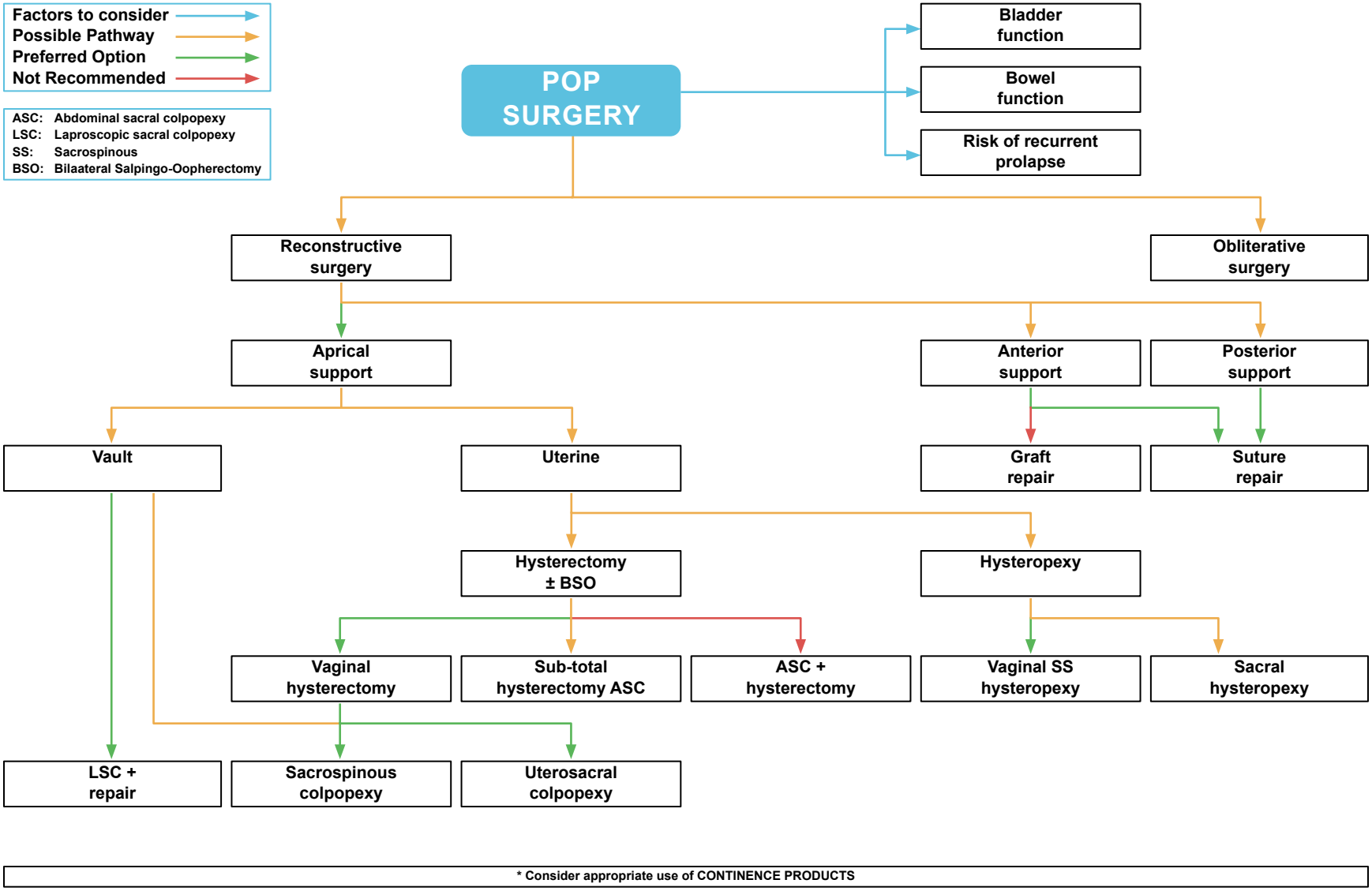
Those undergoing prolapse surgery with stress urinary incontinence (SUI) and occult SUI should generally have continence surgery performed at the time of prolapse surgery

(LoE1). Those with prolapse without SUI or occult SUI should not undergo continence surgery at time of prolapse surgery (LoE1).

Based largely upon expert opinion (LoE3) those with prolapse without bowel symptoms and those with impaired defaecation with rectocele should undergo prolapse surgery as per the above pathway. Those with POP and impaired defaecation without rectocele, and those with faecal incontinence require colorectal assessment. If rectal prolapse exists, these patients may benefit from combined colorectal and gynaecological interventions. Those with significant constipation and prolapse should be approached cautiously and may benefit from gastroenterology assessment prior to entering the POP surgery pathway.

Those undergoing POP surgery generally have improved sexual function post-operatively but a small number undergoing any POP surgery will experience painful intercourse post-operatively that may require subsequent intervention (LoE 1).

ICI 2021 SURGICAL TREATMENT OF PELVIC ORGAN PROLAPSE



VI. URINARY INCONTINENCE IN PATIENTS WITH NEUROLOGICAL DISEASE

A INITIAL MANAGEMENT

STRONG GENERAL RECOMMENDATIONS

- Patients with known neurological disease often need evaluation to exclude lower urinary tract dysfunction (LUTD), not only if symptoms occur, but as a standard assessment as neurogenic LUTD has a high prevalence in the disease.
- A possible neurological cause of “idiopathic” incontinence should always be considered. Diagnostic steps to evaluate this include basic assessments, such as history and physical examination, urodynamics and specialised tests.
- Incontinence in neurological patients does not necessarily relate to the neurologic pathology. Other diseases such as prostate pathology, pelvic organ prolapse, might have an influence. These factors should be evaluated as potential primary or contributory causes.
- Extensive diagnostic evaluation is often useful and necessary to tailor an individual treatment based on complete neurofunctional data. This may not be needed in every patient e.g., patients with suprapontine lesions or in patients where treatment will consist merely of bladder drainage when the person is frail or has limited life expectancy.
- There is often a need to manage lower urinary tract, sexual and bowel dysfunction simultaneously

INITIAL ASSESSMENT

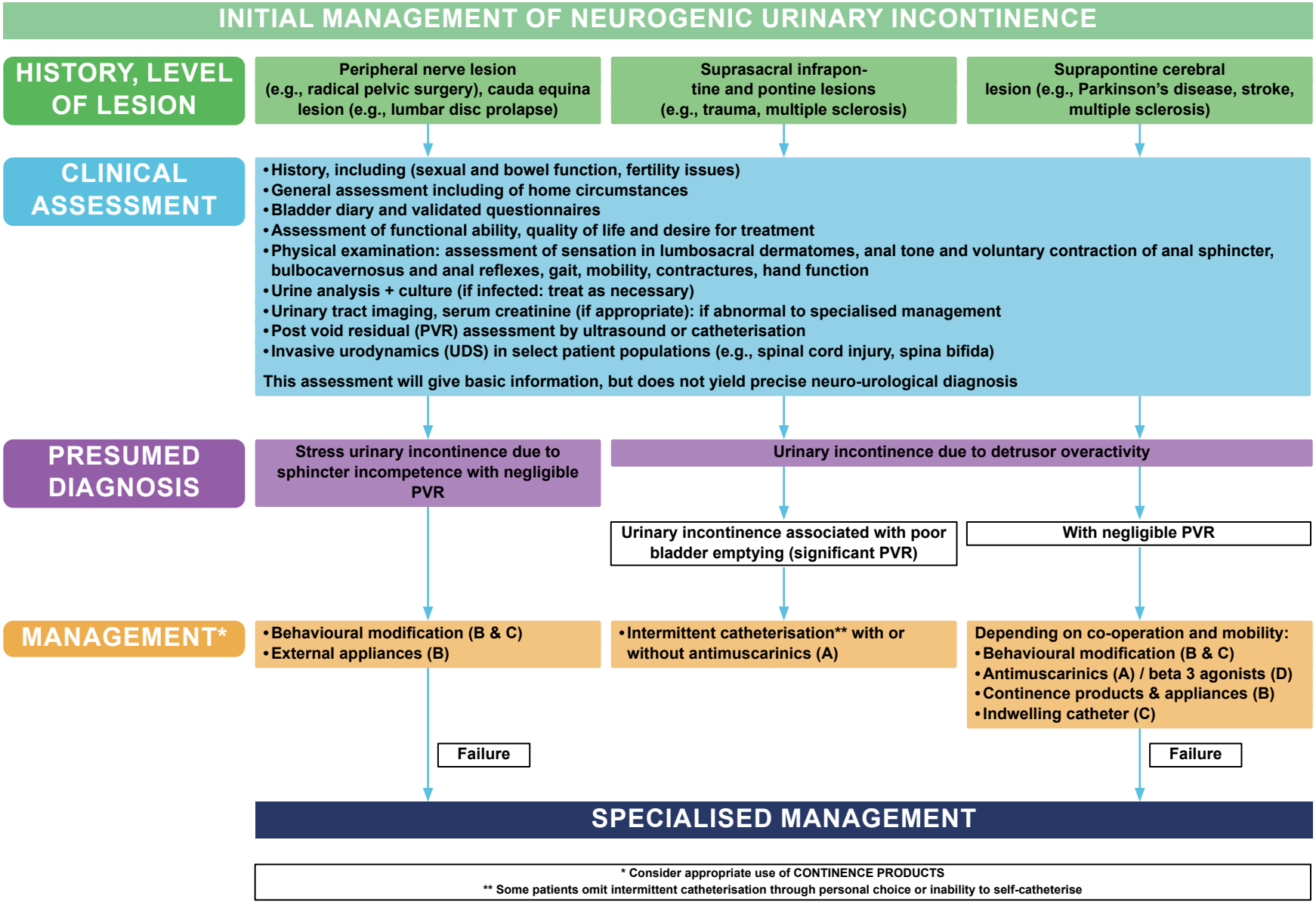
- The management of neurological urinary incontinence depends on an understanding of the likely mechanisms producing incontinence. This can in turn depend on the site and extent of the nervous system abnormality.
- Under current classifications, neurogenic incontinence patients can be divided into four groups. History and physical examination are important in helping distinguish these groups:
- peripheral lesions (as after major pelvic surgery) including those with lesions of the cauda equina (e.g., lumbar disc prolapse).
- sacral spinal cord lesions involving the sacral micturition centre
- suprasacral spinal cord lesions (suprasacral infrapontine spinal cord lesions).
- central lesions of the brain or brain stem (stroke, Parkinson’s disease).
- Assessment should be made using standardized questionnaires, urinalysis, bladder diary, uroflowmetry with assessment of PVR, and optional imaging of the urinary tract (ultrasonography); all provide basic data for the initial assessment of the NLUTD.
- Invasive urodynamics should be used as part of the initial assessment in select patient populations (SCI, spina bifida)
- Due to increasing data on organ cross-sensitisation and the debilitating effect of sexual and bowel dysfunction on QOL, a history of sexual and bowel function should be also included

INITIAL TREATMENT

- Patients with peripheral nerve lesions (e.g., denervation after pelvic surgery) and patients with spinal cord lesions (e.g., traumatic spinal cord lesions) should receive specialised urological management
- Initial treatment for patients with incontinence due to suprapontine pathology, such as stroke, need to be assessed for degree of mobility and ability to cooperate. Initial recommended treatments are behavioural therapy (GoR B & C) and anti-muscarinic drugs for presumed detrusor overactivity (GoR A). If incontinence persists and if operative procedures are not indicated, then continence products (GoR B) or catheters (GoR C) may be necessary on a long-term basis. These can also be necessary in non-cooperative or less mobile patients.

Pharmacological detrusor relaxation and/or antibiotics may be useful in cases of persistent bypass leakage and/or recurrent UTI (patients with continuous drainage)

In all cases, bowel management should complement management of NLUTD


INITIAL MANAGEMENT OF NEUROGENIC URINARY INCONTINENCE
HISTORY, LEVEL OF LESION
Peripheral nerve lesion (e.g., radical pelvic surgery), cauda equina lesion (e.g., lumbar disc prolapse)
Suprasacral infrapontine and pontine lesions (e.g., trauma, multiple sclerosis)
Suprapontine cerebral lesion (e.g., Parkinson's disease, stroke, multiple sclerosis)
CLINICAL ASSESSMENT
•History, including (sexual and bowel function, fertility issues)
•General assessment including of home circumstances
•Bladder diary and validated questionnaires
•Assessment of functional ability, quality of life and desire for treatment
•Physical examination: assessment of sensation in lumbosacral dermatomes, anal tone and voluntary contraction of anal sphincter, bulbocavernosus and anal reflexes, gait, mobility, contractures, hand function
•Urine analysis + culture (if infected: treat as necessary)
•Urinary tract imaging, serum creatinine (if appropriate): if abnormal to specialised management
•Post void residual (PVR) assessment by ultrasound or catheterisation
•Invasive urodynamics (UDS) in select patient populations (e.g., spinal cord injury, spina bifida)
This assessment will give basic information, but does not yield precise neuro-urological diagnosis
PRESUMED DIAGNOSIS
Stress urinary incontinence due to sphincter incompetence with negligible PVR
Urinary incontinence due to detrusor overactivity
Urinary incontinence associated with poor bladder emptying (significant PVR)
With negligible PVR
MANAGEMENT*
•Behavioural modification (B & C)
•External appliances (B)
•Intermittent catheterisation** with or without antimuscarinics (A)
Depending on co-operation and mobility:
•Behavioural modification (B & C)
•Antimuscarinics (A) / beta 3 agonists (D)
•Continence products & appliances (B)
•Indwelling catheter (C)
Failure
Failure
SPECIALISED MANAGEMENT
* Consider appropriate use of CONTINENCE PRODUCTS
** Some patients omit intermittent catheterisation through personal choice or inability to self-catheterise

VI. URINARY INCONTINENCE IN PATIENTS WITH NEUROLOGICAL DISEASE

B SPECIALISED MANAGEMENT

ASSESSMENT

- Most patients with neurogenic urinary incontinence require specialised assessment: Invasive urodynamic studies should be used with video urodynamics if available when surgical interventions are planned or when the “bladder may be unsafe”.
- Upper tract imaging is needed in some patients and more detailed renal function studies will be desirable if the upper tract is considered in danger: high bladder pressure, upper urinary tract dilation, recurrent or chronic upper tract infection, (major) stones, (major) reflux.
- In patients with peripheral lesions, clinical neurophysiological testing may be helpful for better definition of the lesion

TREATMENT

For specialised management, conservative treatment is the mainstay (GoR A). Management of neurogenic urinary incontinence has several options. The algorithm details the recommended options for different types of neurogenic LUTD. The dysfunction does not necessarily correspond to one type/level of neurological lesion and is defined best by urodynamic studies. One should always ascertain that the management ensures a safe lower and upper urinary tract (storage at low pressure and complete emptying)

Urinary, sexual and bowel function should be assessed together as symptoms and treatment of one system can influence the other, and *vice versa*.

As therapeutic approaches can differ in various neurological diseases, the most prevalent diseases are discussed separately in the chapter

TREATMENT MODALITIES (OFTEN IN COMBINATION)

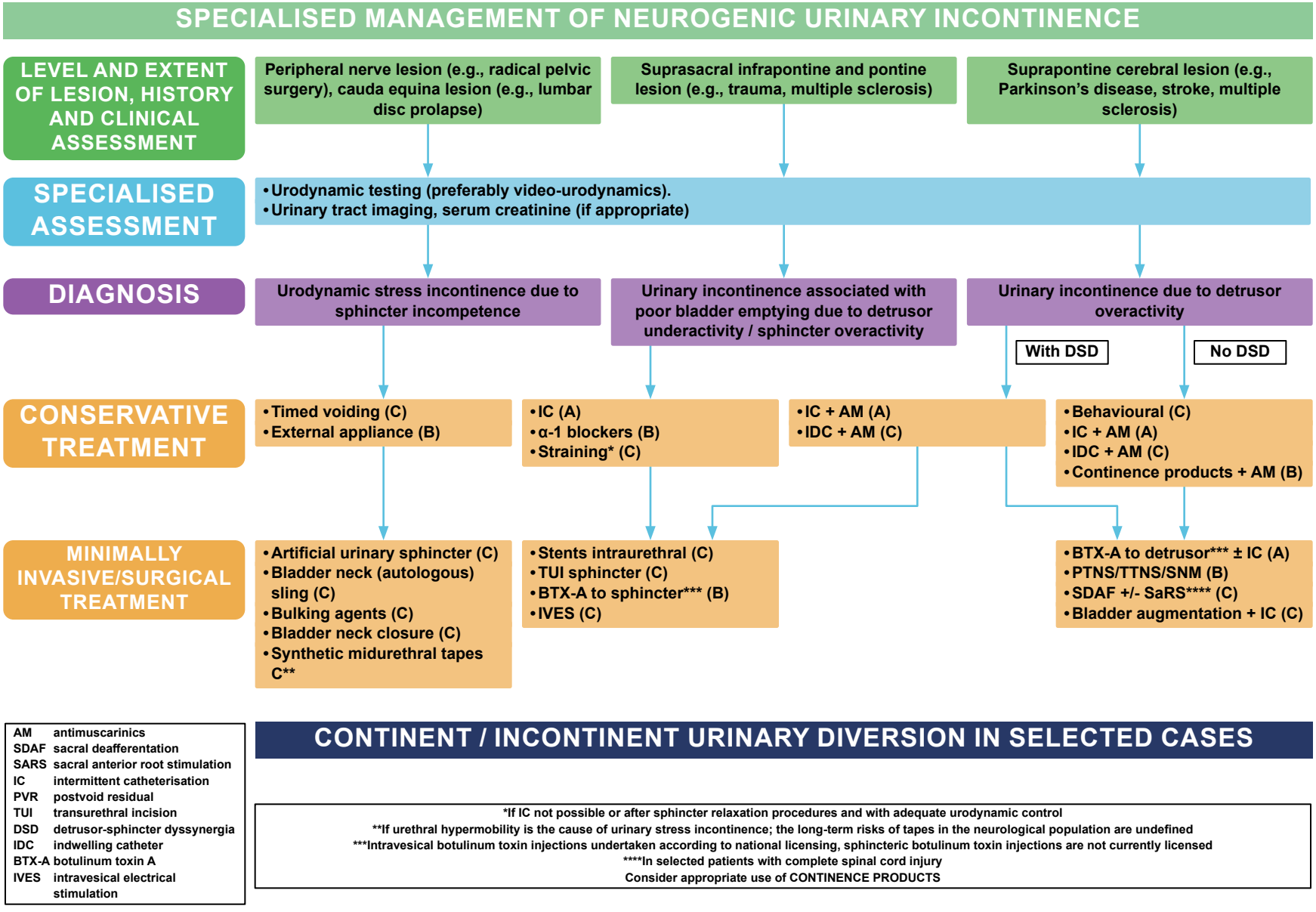
- **Conservative**
- Intermittent catheterisation (GoR A)
- PFMT for patients with MS & PD (GoR B)
- PTNS for OAB symptoms in patients with MS, PD, incomplete SCI & post- stroke (GoR C)
- TENS for post stroke patients with OAB (GoR B)
- Timed voiding (GoR C)
- Continence products (GoR B)
- Antimuscarinics (GoR A)
- Alpha-1-adrenergic blockers (GoR B)
- Oral cannabinoid agonists (MS) (GoR C)
- Beta-3-agonist alone or as an add-on to AM (GoR D)
- Bladder expression (GoR C)
- Triggered voiding (GoR C)
- Indwelling catheter (GoR C)

Minimally invasive treatments

- Botulinum toxin for: detrusor (A), sphincter (B)
- Intravesical electrical stimulation (C)
- PTNS / TTNS (B)
- SNM (stable disease only) (B)

Surgical treatment

- Artificial urinary sphincter (C)
- Bladder neck sling (C)
- Sub-urethral tapes (C)
- Bulking agents (C)
- Bladder neck closure (C)
- Stents intraurethral (C)
- TUI sphincter (C)
- Sacral deafferentation (C)
- Sacral anterior root stimulator (C)
- Bladder augmentation (C)


SPECIALISED MANAGEMENT OF NEUROGENIC URINARY INCONTINENCE
LEVEL AND EXTENT OF LESION, HISTORY AND CLINICAL ASSESSMENT
Peripheral nerve lesion (e.g., radical pelvic surgery), cauda equina lesion (e.g., lumbar disc prolapse)
Suprasacral infrapontine and pontine lesion (e.g., trauma, multiple sclerosis)
Suprapontine cerebral lesion (e.g., Parkinson's disease, stroke, multiple sclerosis)
SPECIALISED ASSESSMENT
•Urodynamic testing (preferably video-urodynamics).
•Urinary tract imaging, serum creatinine (if appropriate)
DIAGNOSIS
Urodynamic stress incontinence due to sphincter incompetence
Urinary incontinence associated with poor bladder emptying due to detrusor underactivity / sphincter overactivity
Urinary incontinence due to detrusor overactivity
With DSD
No DSD
CONSERVATIVE TREATMENT
•Timed voiding (C)
•External appliance (B)
•IC (A)
•α-1 blockers (B)
•Straining* (C)
•IC + AM (A)
•IDC + AM (C)
•Behavioural (C)
•IC + AM (A)
•IDC + AM (C)
•Continence products + AM (B)
MINIMALLY INVASIVE/SURGICAL TREATMENT
•Artificial urinary sphincter (C)
•Bladder neck (autologous) sling (C)
•Bulking agents (C)
•Bladder neck closure (C)
•Synthetic midurethral tapes C**
•Stents intraurethral (C)
•TUI sphincter (C)
•BTX-A to sphincter*** (B)
•IVES (C)
•BTX-A to detrusor*** ± IC (A)
•PTNS/TTNS/SNM (B)
•SDAF +/- SaRS**** (C)
•Bladder augmentation + IC (C)
AM antimuscarinics
SDAF sacral deafferentation
SARS sacral anterior root stimulation
IC intermittent catheterisation
PVR postvoid residual
TUI transurethral incision
DSD detrusor-sphincter dyssynergia
IDC indwelling catheter
BTX-A botulinum toxin A
IVES intravesical electrical stimulation
CONTINENT / INCONTINENT URINARY DIVERSION IN SELECTED CASES
*If IC not possible or after sphincter relaxation procedures and with adequate urodynamic control
**If urethral hypermobility is the cause of urinary stress incontinence; the long-term risks of tapes in the neurological population are undefined
***Intravesical botulinum toxin injections undertaken according to national licensing, sphincteric botulinum toxin injections are not currently licensed
****In selected patients with complete spinal cord injury
Consider appropriate use of CONTINENCE PRODUCTS

VII. INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME, HUNNER LESION DISEASE

ASSESSMENT

Males or females whose symptoms meet the requirements of the definition of interstitial cystitis/bladder pain syndrome (IC/BPS) should be evaluated. The presence of commonly associated disorders including irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia in the presence of the cardinal symptoms of interstitial cystitis/bladder pain syndrome also suggests the diagnosis. Abnormal gynaecological findings in women and well-characterised, confusable diseases that may explain the symptoms must be ruled out.

All patients should be evaluated with cystoscopy to determine if they have a Hunner lesion. While presentation is similar, Hunner lesion disease (HLD) differs markedly from IC/BPS. Cystoscopy is the method of choice to identify Hunner lesions and histopathology the method to confirm it. HLD cannot be distinguished from IC/BPS by means of symptoms, physical examination, or laboratory testing. HLD is less common overall but commonly identified in older onset populations. They are not a continuum of conditions and IC/BPS does not progress to HLD in the vast majority of patients. IC/BPS is a symptom-based syndrome without specific objective finding. HLD has a typical pathology, typical findings on endoscopy, is not associated with other chronic pain syndromes (unlike IC/BPS), and uniquely responds to fulguration, excision, intralesional steroid injection, and oral cysclosporin. It should be considered a confounding disease rather than a phenotype of IC/BPS. Cystoscopy is recommended early in the evaluation of patients who meet the IC/BPS definition and can be done with flexible endoscopy without sedation in most patients.

The initial assessment consists of a bladder diary or frequency/volume chart, focused physical examination, urinalysis, and urine culture. In the absence of confusable disorders, a diagnosis can be made, and treatment instituted. Urine cytology and urodynamic evaluation are recommended if clinically indicated and/or the diagnosis is in doubt. Patients with urinary infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and microscopic or gross haematuria are evaluated with appropriate imaging and endoscopic procedures, and only if the findings are unable to explain the symptoms, are they diagnosed with BPS. GoR C

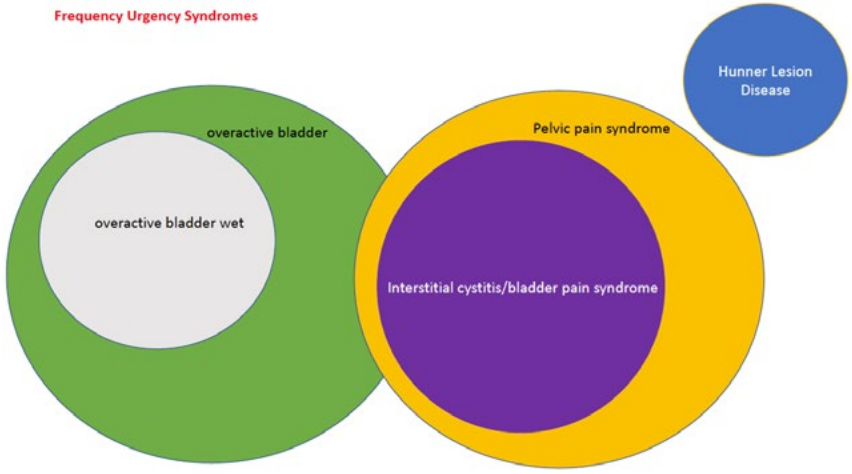


Figure 1

TREATMENT: IC/BPS

- Patient education, behavioral modification (GoR B)
- Dietary manipulation, (GoR B)
- Nonprescription analgesics, (GoR C)
- Stress reduction, (GoR C)
- Physical therapy, employing pelvic floor relaxation techniques, comprises the initial treatment of IC/BPS. In the patient with findings suggesting pelvic floor dysfunction, pelvic floor physical therapy with myofascial trigger point release and intravaginal Thiele massage is often an effective therapeutic intervention. The treatment of pain needs to be addressed directly, and in some instances referral to an anesthesia/pain centre can be an appropriate early step in conjunction with ongoing treatment of the syndrome. (GoR A)

When conservative therapy fails or symptoms are severe and conservative management is unlikely to succeed,

- Oral medication (GoR B) or
- Intravesical treatment can be prescribed. It is recommended to initiate a single form of therapy and observe results, adding other modalities or substituting other modalities as indicated by the degree of response or lack of response to treatment. (GoR B)

SECONDARY ASSESSMENT

If initial oral or intravesical therapy fails, or before beginning such therapy based on clinician judgment, it is reasonable to consider further evaluation which can include urodynamics, pelvic imaging, and cystoscopy with bladder distention and possible bladder biopsy under anaesthesia.

- Findings of detrusor overactivity suggest a trial of antimuscarinic or beta-3-agonist therapy.
- The presence of a Hunner lesion (10% may be missed on the initial office cystoscopy) suggests therapy with transurethral resection, fulguration of the lesion, or direct steroid injection into the lesion. (GoR B)
- Bladder distention itself can have therapeutic benefit in 30-50% of patients, though benefits rarely persist for longer than a few months. (GoR C)

REFRACTORY IC/BPS

Those patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive treatment modalities. Many of these are best administered within the context of a clinical trial if possible. These may include

- Sacral nerve stimulation, (GoR)
- Intradetrusor botulinum toxin, (GoR B)
- Clinical trials of newly described pharmacological management techniques.
- By this point and often before, most patients will benefit from the expertise of an anaesthesia pain clinic.

The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urinary stream.

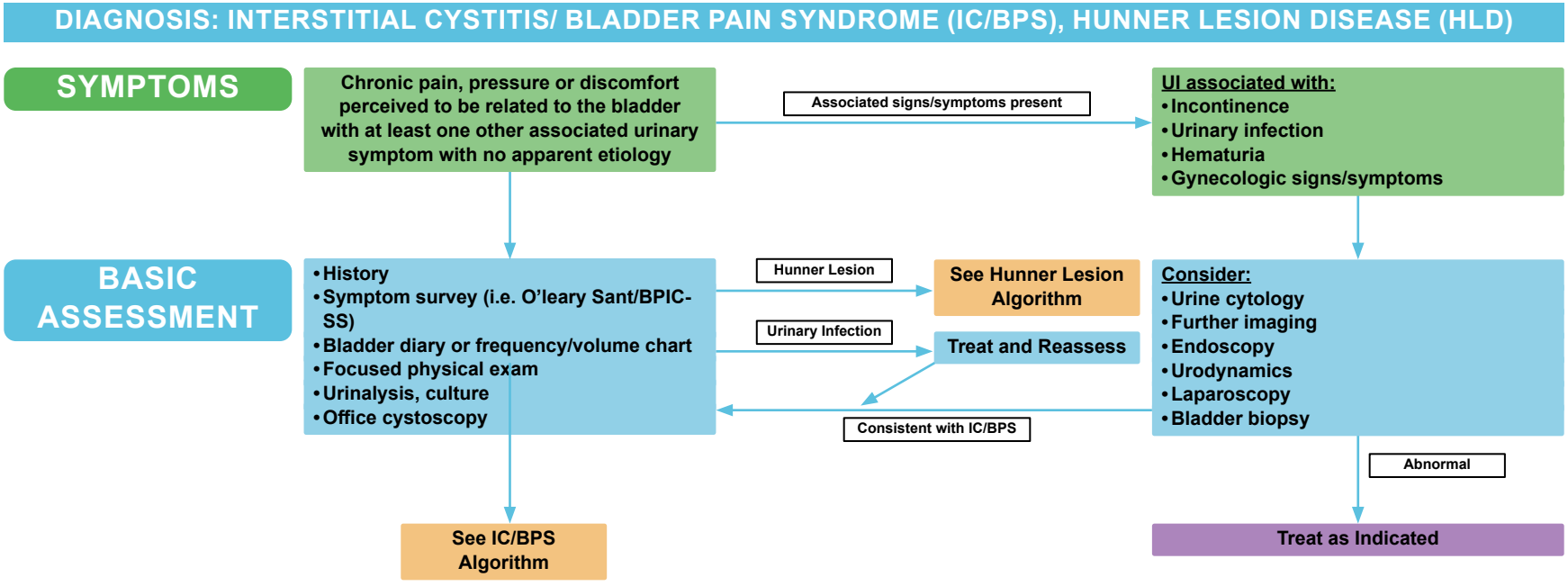
- Urinary diversion with or without cystectomy has been used as a last resort with good results in selected patients. Cystectomy and urethrectomy do not appear to add any additional efficacy to diversion alone. (GoR B)
- Augmentation or substitution cystoplasty seems less effective and more prone to recurrence of chronic pain in small reported series (GoR C)

HUNNER LESION DISEASE

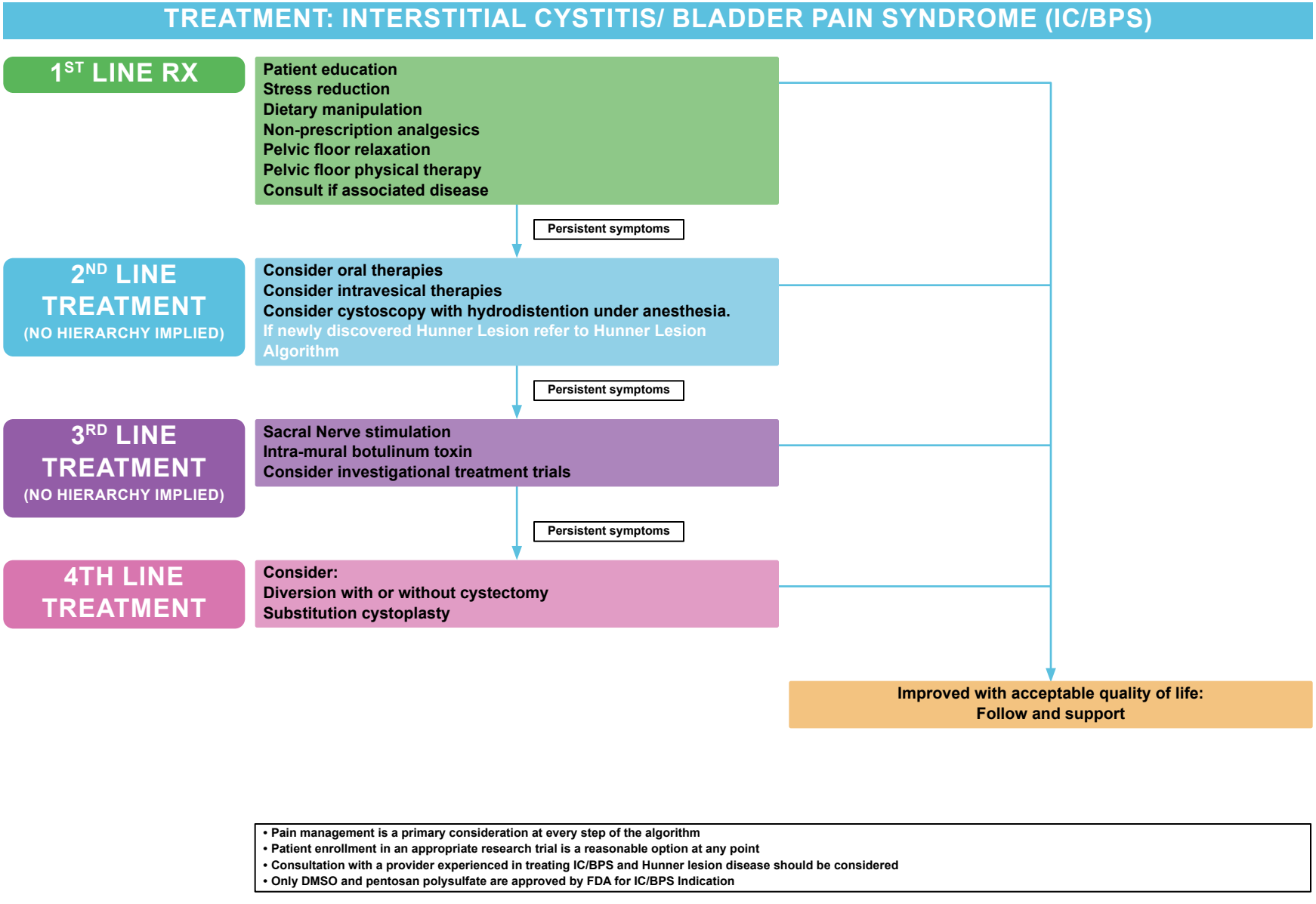
- Hunner lesion disease is treated initially with bladder distention under sedation to 60-80cm water pressure for 2-5 minutes followed by extensive fulguration or resection of Hunner lesion(s). (GoR A)
- Biopsy with a partially distended bladder is recommended if definitive diagnosis has not been previously made as required to rule out a malignant process or other treatable condition.

Symptoms often respond for periods up to 12 months or longer.

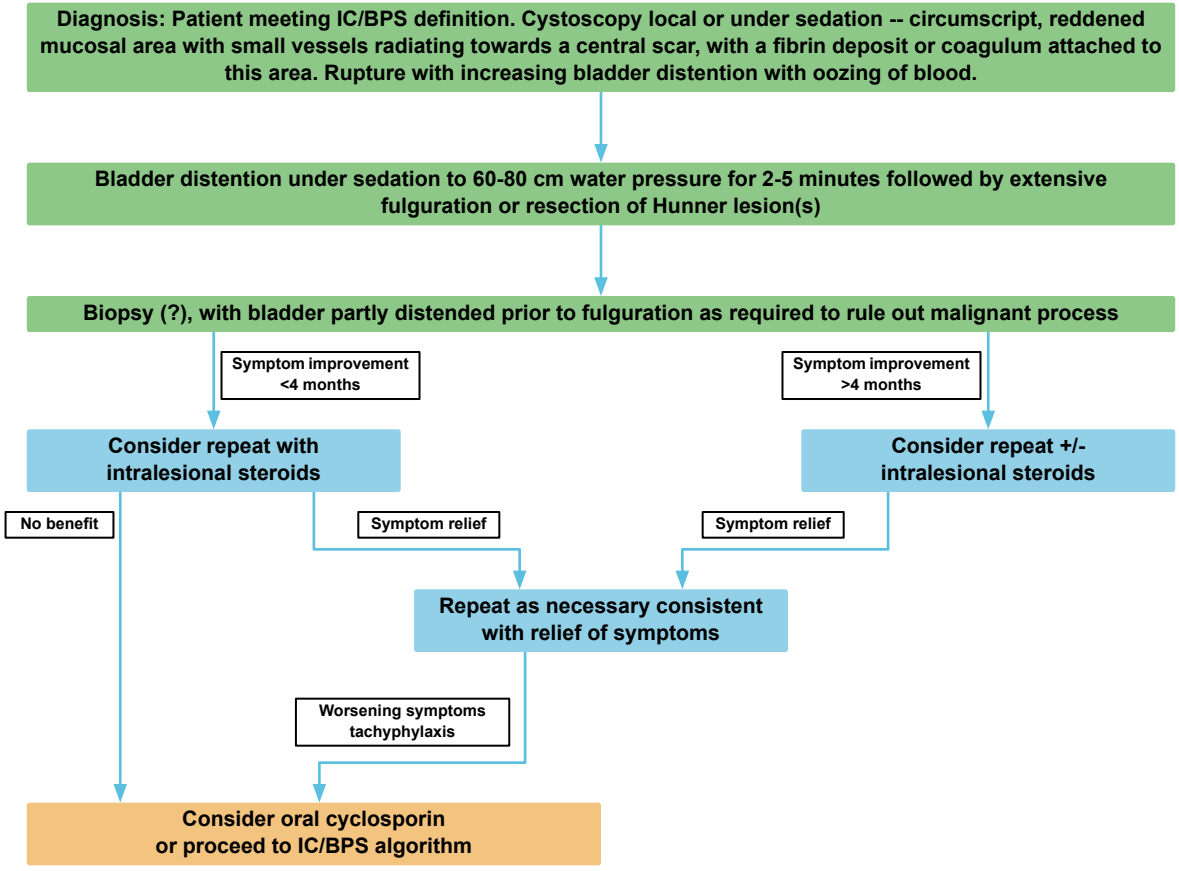
- Recurrence suggests the need to repeat the procedure and consider intralesional steroid Injection as an adjunct to fulguration or in addition to it.
- With tachyphylaxis or failure of the treatment to result in improvement consider
- Oral cyclosporin (GoR C)
- proceed to the IC/BPS treatment algorithm.



Algorithm for Diagnosis/C/BPS and HLD symptom complex: 2023 International Consultation an Incontinence.
Early cystoscopy is recommended to differentiate IC/BPS syndrome from MLD.


TREATMENT: INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME (IC/BPS)
1ST LINE RX
Patient education
Stress reduction
Dietary manipulation
Non-prescription analgesics
Pelvic floor relaxation
Pelvic floor physical therapy
Consult if associated disease
Persistent symptoms
2ND LINE TREATMENT
(NO HIERARCHY IMPLIED)
Consider oral therapies
Consider intravesical therapies
Consider cystoscopy with hydrodistention under anesthesia.
If newly discovered Hunner Lesion refer to Hunner Lesion Algorithm
Persistent symptoms
3RD LINE TREATMENT
(NO HIERARCHY IMPLIED)
Sacral Nerve stimulation
Intra-mural botulinum toxin
Consider investigational treatment trials
Persistent symptoms
4TH LINE TREATMENT
Consider:
Diversion with or without cystectomy
Substitution cystoplasty
Improved with acceptable quality of life:
Follow and support
• Pain management is a primary consideration at every step of the algorithm
• Patient enrollment in an appropriate research trial is a reasonable option at any point
• Consultation with a provider experienced in treating IC/BPS and Hunner lesion disease should be considered
• Only DMSO and pentosan polysulfate are approved by FDA for IC/BPS Indication

HUNNER LESION DISEASE



VIII. FAECAL INCONTINENCE IN ADULT PATIENTS

CLINICAL ASSESSMENT AND MANAGEMENT

INITIAL CLINICAL ASSESSMENT

- History will include review of daily bowel habit and the type and severity of bowel incontinence (optimally reported using a bowel diary), neurological diseases, other comorbidities and systemic disorders, and anorectal surgeries (e.g., haemorrhoidectomy), obstetric history for women, medications, diet, constipation and chronic straining, toileting ability, cognitive function, and effects of symptoms on quality of life. **(GoR C)**

- Assessing the type of bowel incontinence may help identify an aetiology. Types of bowel incontinence: Anal incontinence is the involuntary loss of faeces and/or flatus and/or mucus). Faecal incontinence is the involuntary loss of faeces. Flatus incontinence is the involuntary loss of rectal gas, which may indicate rectal sensory impairment and/or anal sphincter dysfunction. Mucus incontinence is the involuntary loss of mucus only. **(GoR C)**

- A subtype of faecal incontinence is urge faecal incontinence, which is the involuntary loss of faeces due to an inability to defer defaecation once the urge is perceived for long enough to reach a toilet. Passive faecal incontinence refers to incontinence without forewarning, which is typically related to internal anal sphincter dysfunction or poor closure of the external sphincter due to rectal prolapse or stage III/IV haemorrhoids. It also could occur as overflow faecal incontinence due to rectal faecal impaction. Functional (disability associated) faecal incontinence is due to limitations in mobility, toileting ability or delayed assistance.

- Physical examination should include a general health examination, anal and peri-anal inspection, abdominal palpation, a brief neurological examination, digital rectal examination and usually proctosigmoidoscopy or colonoscopy. **(GoR C)**

- Further diagnostic testing needs to be considered if there is an unexplained change in bowel habit, weight loss, anaemia, rectal bleeding, severe or nocturnal diarrhoea, or an abdominal or pelvic mass and bowel pathology or when organic conditions such as cancer, inflammatory bowel disease (IBD), a recto-vaginal fistula, full thickness rectal prolapse, or cloacal deformity are suspected. Condition specific management is indicated for these patients. **(GoR C)**

INITIAL CONSERVATIVE INTERVENTIONS

Initial conservative interventions include:

- Discussion with the patient of options and goals of management **(GoR B)**

- Education about faecal incontinence and conservative and self-management support **(GoR B)**

- Modification of diet, fluid, and eating pattern advice **(GoR B/C)**

- Supplementation with dietary fibre **(GoR A)**

- Anti-motility medication, especially if stools are loose **(GoR B)**

- Establishing a regular bowel habit **(GoR C)** and urgency training if relevant **(GoR C)**

- Pelvic floor muscle training (PFMT) **(GoR B)**

- Transanal irrigation to empty the rectum **(GoR B)**

- Use of absorbent products including various types and sizes of absorbent pads, briefs, etc., to contain leaked faeces and prevent skin damage **(GoR B)**

- Provide advice on practical coping skills when incontinence occurs **(GoR C)**

- Provide emotional support and empathy (Grade of Recommendation C)

- For individuals with faecal incontinence due to neurological diseases and conditions, prevention and management of constipation and rectal impaction are additional treatments that may be needed (Grade of Recommendation B)

SECONDARY INTERVENTIONS

If initial interventions fail to improve symptoms secondary interventions include:

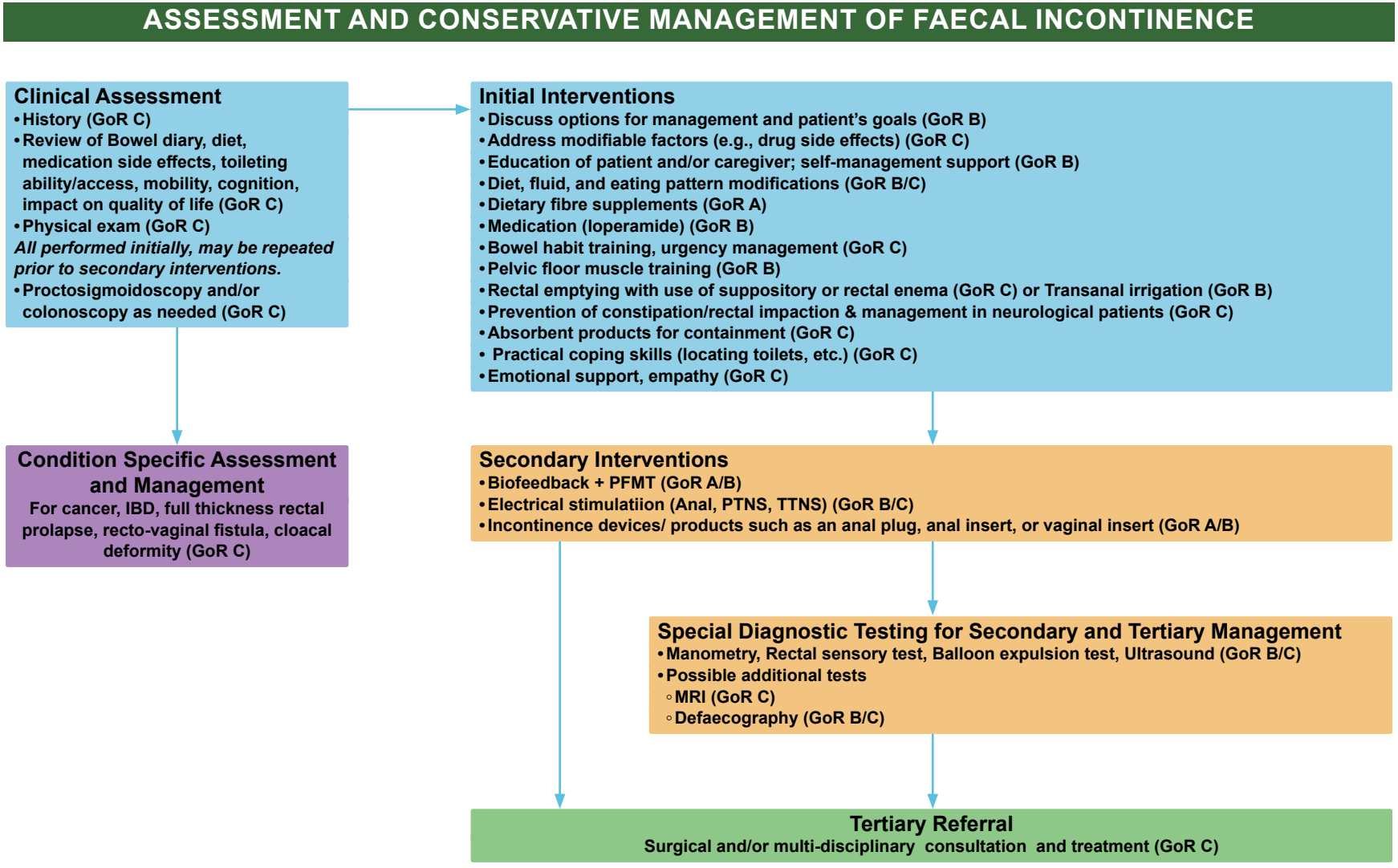
- Biofeedback therapy or biofeedback therapy combined with PFMT. **(GoR A/B)**
- Electrical simulation (can be combined with biofeedback). **(GoR B)**
- anal plug, or anal or vaginal insert, as temporary barriers blocking leakage from the rectum. **(GoR A/B)**

SPECIAL DIAGNOSIC TESTING FOR SECONARY AND TERTIARY MANAGEMENT OF FAECAL INCONTINENCE

- A variety of anorectal diagnostic investigations, including the rectal sensory test, balloon expulsion test, manometry, anal ultrasound, MRI, and defaecagraphy can help to define structural or functional abnormalities of anorectal function, determine whether surgery is indicated, and guide management if initial and/or secondary interventions are ineffective.

TERTIARY REFERRAL FOR SURGICAL OR MULTI-DISCIPLINARY CONSULTATION AND INTERVENTION

- Faecal incontinence that fails to respond to initial and secondary management requires specialised consultation from a colorectal surgeon, gastroenterologist, urogynecologist, and/or a multi-disciplinary team. **(GoR C)**


ASSESSMENT AND CONSERVATIVE MANAGEMENT OF FAECAL INCONTINENCE
Clinical Assessment
• History (GoR C)
• Review of Bowel diary, diet, medication side effects, toileting ability/access, mobility, cognition, impact on quality of life (GoR C)
• Physical exam (GoR C)
All performed initially, may be repeated prior to secondary interventions.
• Proctosigmoidoscopy and/or colonoscopy as needed (GoR C)
Initial Interventions
• Discuss options for management and patient's goals (GoR B)
• Address modifiable factors (e.g., drug side effects) (GoR C)
• Education of patient and/or caregiver; self-management support (GoR B)
• Diet, fluid, and eating pattern modifications (GoR B/C)
• Dietary fibre supplements (GoR A)
• Medication (loperamide) (GoR B)
• Bowel habit training, urgency management (GoR C)
• Pelvic floor muscle training (GoR B)
• Rectal emptying with use of suppository or rectal enema (GoR C) or Transanal irrigation (GoR B)
• Prevention of constipation/rectal impaction & management in neurological patients (GoR C)
• Absorbent products for containment (GoR C)
• Practical coping skills (locating toilets, etc.) (GoR C)
• Emotional support, empathy (GoR C)
Condition Specific Assessment and Management
For cancer, IBD, full thickness rectal prolapse, recto-vaginal fistula, cloacal deformity (GoR C)
Secondary Interventions
• Biofeedback + PFMT (GoR A/B)
• Electrical stimulatiion (Anal, PTNS, TTNS) (GoR B/C)
• Incontinence devices/ products such as an anal plug, anal insert, or vaginal insert (GoR A/B)
Special Diagnostic Testing for Secondary and Tertiary Management
• Manometry, Rectal sensory test, Balloon expulsion test, Ultrasound (GoR B/C)
• Possible additional tests
◦ MRI (GoR C)
◦ Defaecography (GoR B/C)
Tertiary Referral
Surgical and/or multi-disciplinary consultation and treatment (GoR C)

VIII. FAECAL INCONTINENCE IN ADULT PATIENTS

SURGERY FOR FAECAL INCONTINENCE

PATIENT ASSESSMENT

- The reader is referred to the relevant chapter sections in “Dynamic Testing” and “Conservative Treatment for Faecal Incontinence.” In general, patients referred for surgical management of faecal incontinence must either have failed conservative therapy or not be candidates for conservative therapy due to severe anatomic abnormality.
- Prior to surgical management of faecal incontinence, the integrity of the anal sphincter complex should be assessed. This assessment is best performed with clinical examination and endoanal ultrasound. Ancillary tests include anal manometry and defaecography.
- If the patient has persisting faecal incontinence, he or she should undergo repeat assessment, including endoanal ultrasound.

MANAGEMENT

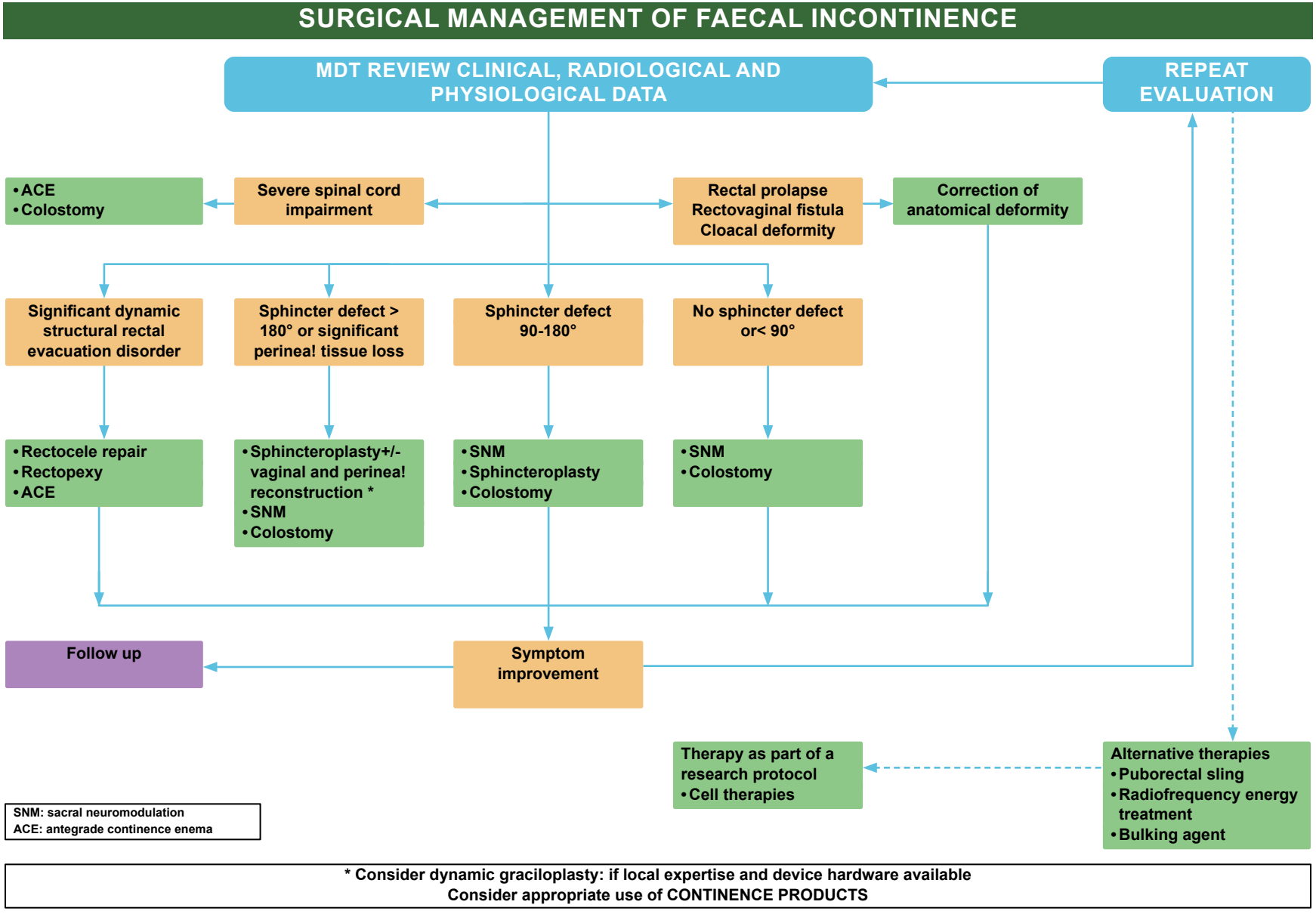
- The surgical approach is influenced by the presence and magnitude of an anatomical anal sphincter defect. If no defect is present, or if the sphincter defect is small, options include SNM (GoR B) and colostomy.
- Acute anal sphincter repair is usually required following obstetric or direct trauma. End to end or overlapping repair may be performed. When possible, the internal anal sphincter should be separately repaired. (GoR B)
- Patients with rectal prolapse, rectovaginal fistula or cloacal deformity often have associated faecal incontinence. Initial therapy should be directed at correction of the anatomical abnormality. (GoR D)
- Patients with concomitant symptoms of obstructed defaecation may have a dynamic structural abnormality leading to evacuatory impairment e.g., rectocele, intussusception, or both. These patients may benefit from primary treatment of this problem even if there is also sphincter dysfunction. (GoR C)
- For patients with moderate sphincter defects (90-180 degrees), sphincteroplasty, SNS or colostomy can be considered. For patients with large clinically overt defects, sphincteroplasty is likely to be the best option, though SNM can be considered. (GoR C)
- Patients with sphincter defects of greater than 180° or major perineal tissue loss require individualised treatment. Reconstruction may require major reconstructive surgery. Should incontinence persist, SNM can be used as an adjunct. Stimulated muscle transposition (usually gracilloplasty) is now rarely practiced. (GoR C)

ALTERNATIVE MANAGEMENT

- For patients who remain incontinent following sphincteroplasty, repeat endoanal ultrasound can reassess the status of the repair. If no defect is present, or if the defect is minimal, options include SNM. If there is a large persisting sphincter defect, repeat sphincteroplasty can be considered. (GoR C)
- Patients who fail reconstructive approaches and/or SNM or who do not wish to undergo extensive pelvic reconstruction, should consider end sigmoid colostomy. (GoR C) While this does not restore continence, it does restore substantial bowel control and appears to improve social function and quality of life.
- Injection of a biomaterial to bulk the sphincter remains an option but evidence to support use (and choice of agent to use) is poor. (GoR C)
- Novel therapies can also be considered under protocol: puborectal sling, radiofrequency ablation and cell therapies. (GoR C)

SPECIAL SITUATIONS

- Individuals with congenital abnormalities may be amenable to specialist abdominal and perineal surgical repair. Poor functional outcomes may be treated by an Antegrade Continence Enema (ACE) procedure or colostomy. Patients with cauda equina type neurological disorders, either congenital or acquired, should be considered for an ACE procedure or colostomy. (GoR C)


SURGICAL MANAGEMENT OF FAECAL INCONTINENCE
MDT REVIEW CLINICAL, RADIOLOGICAL AND PHYSIOLOGICAL DATA
REPEAT EVALUATION
•ACE
•Colostomy
Severe spinal cord impairment
Rectal prolapse
Rectovaginal fistula
Cloacal deformity
Correction of anatomical deformity
Significant dynamic structural rectal evacuation disorder
Sphincter defect > 180° or significant perinea! tissue loss
Sphincter defect 90-180°
No sphincter defect or< 90°
•Rectocele repair
•Rectopexy
•ACE
•Sphincteroplasty+/- vaginal and perinea! reconstruction *
•SNM
•Colostomy
•SNM
•Sphincteroplasty
•Colostomy
•SNM
•Colostomy
Follow up
Symptom improvement
Therapy as part of a research protocol
•Cell therapies
Alternative therapies
•Puborectal sling
•Radiofrequency energy treatment
•Bulking agent
SNM: sacral neuromodulation
ACE: antegrade continence enema
* Consider dynamic graciloplasty: if local expertise and device hardware available
Consider appropriate use of CONTINENCE PRODUCTS

IX. FAECAL INCONTINENCE IN NEUROLOGICAL PATIENTS

INITIAL MANAGEMENT

Patients with known neurological disease may present with symptoms related to neurological bowel dysfunction, such as difficulty in defaecation, constipation and faecal incontinence which disturb their activities of daily living and impair quality of life. Many have permanent impairments and functional limitations and disabilities, which are due to neurological deficits and complications

INITIAL ASSESSMENT

- The history should include:
  - Neurological diagnosis and functional level
  - Previous and present lower gastrointestinal (LGIT) function and disorders
  - Severity of neurogenic bowel dysfunction
  - Current bowel care and management including diet, fluid intake, medications affecting bowel functions
  - Co-morbidity / complication e.g., urinary incontinence, autonomic dysreflexia, pressure ulcers, sexual dysfunction
  - Patient's satisfaction, needs, restrictions and quality of life
  - Environmental factors and barriers and facilitators to independent bowel management.
- Physical examination:
- Cognitive function; motor, sensory and sacral reflexes – voluntary anal sphincter contraction, deep perianal sensation, anal tone, anal and bulbo- cavernosus reflexes
- Spasticity of the lower limbs
- Abdominal palpation for faecal loading and rectal examination
- Functional assessment:
  - Hand and arm use, fine hand use, mobility – maintaining body position, transfer, and walking ability.
- Environmental factors assessment:
  - toilet accessibility; devices for bowel care and mobility; caregiver support and attitude.

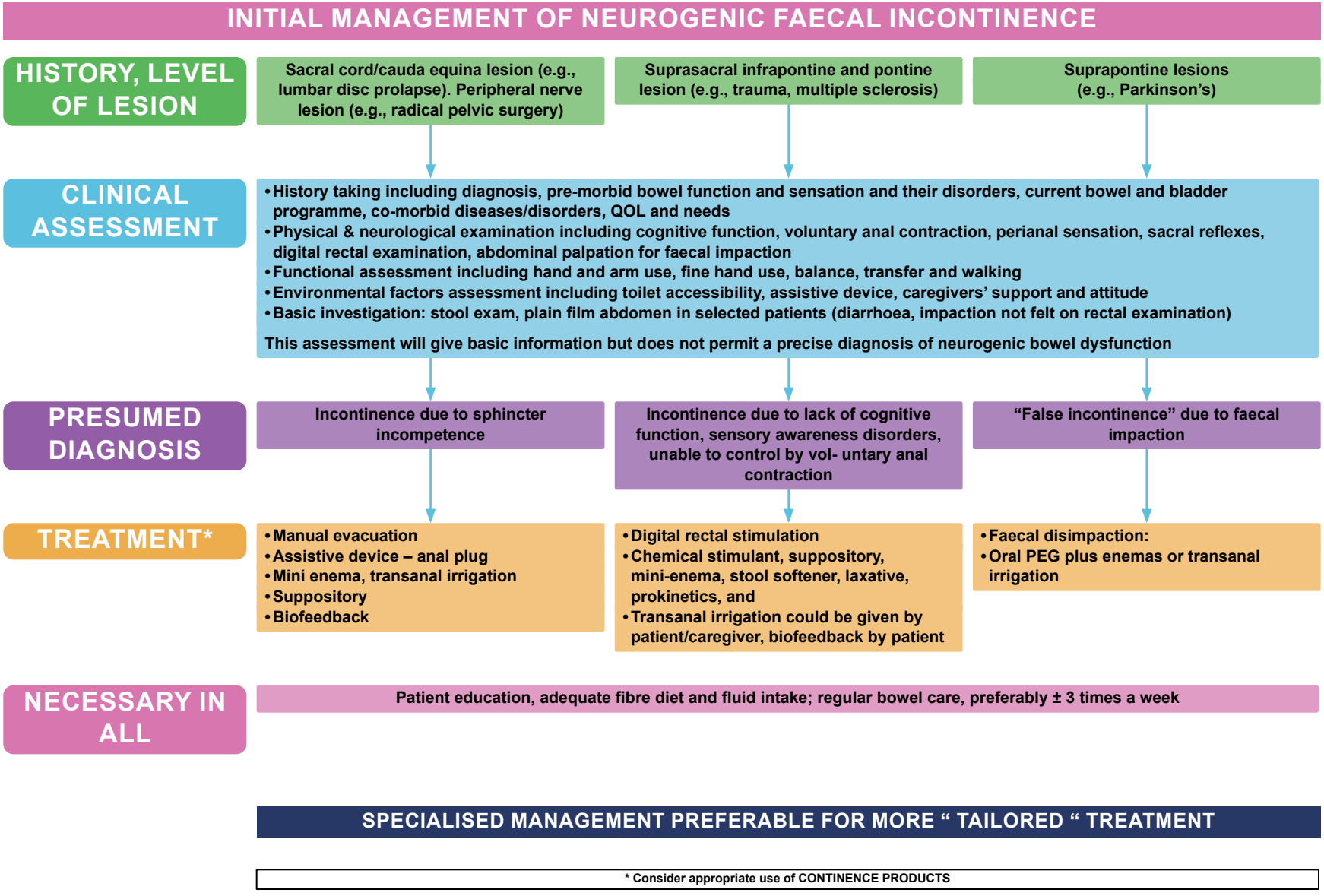
BASIC INVESTIGATIONS

Stool examination, plain abdominal X-Ray

INITIAL TREATMENTS

- Patient education and goals-setting to achieve complete defaecation on a regular basis and faecal continence based on right time, right place, right trigger, and right consistency
- Adequate fibre diet and fluid intake; appropriate trigger according to preservation of sacral (anorectal) reflex – digital rectal stimulation (GoR C); suppository and enema (GoR B); if no anorectal reflex, manual evacuation (GoR B); abdominal massage (GoR C) can also be helpful
- Prescribe medications – stool softener, laxative, prokinetic agents, anti-diarrhoeal drugs as necessary
- Assistive techniques may be necessary for
  - Defaecation – transanal irrigation (GoR A)
  - For incontinence – anal plug (GoR C)

The algorithm does not apply to management in acute neurological patients that need regular bowel emptying.


INITIAL MANAGEMENT OF NEUROGENIC FAECAL INCONTINENCE
HISTORY, LEVEL OF LESION
Sacral cord/cauda equina lesion (e.g., lumbar disc prolapse). Peripheral nerve lesion (e.g., radical pelvic surgery)
Suprasacral infrapontine and pontine lesion (e.g., trauma, multiple sclerosis)
Suprapontine lesions (e.g., Parkinson's)
CLINICAL ASSESSMENT
•History taking including diagnosis, pre-morbid bowel function and sensation and their disorders, current bowel and bladder programme, co-morbid diseases/disorders, QOL and needs
•Physical & neurological examination including cognitive function, voluntary anal contraction, perianal sensation, sacral reflexes, digital rectal examination, abdominal palpation for faecal impaction
•Functional assessment including hand and arm use, fine hand use, balance, transfer and walking
•Environmental factors assessment including toilet accessibility, assistive device, caregivers' support and attitude
•Basic investigation: stool exam, plain film abdomen in selected patients (diarrhoea, impaction not felt on rectal examination)
This assessment will give basic information but does not permit a precise diagnosis of neurogenic bowel dysfunction
PRESUMED DIAGNOSIS
Incontinence due to sphincter incompetence
Incontinence due to lack of cognitive function, sensory awareness disorders, unable to control by vol- untary anal contraction
"False incontinence" due to faecal impaction
TREATMENT*
•Manual evacuation
•Assistive device – anal plug
•Mini enema, transanal irrigation
•Suppository
•Biofeedback
•Digital rectal stimulation
•Chemical stimulant, suppository, mini-enema, stool softener, laxative, prokinetics, and
•Transanal irrigation could be given by patient/caregiver, biofeedback by patient
•Faecal disimpaction:
•Oral PEG plus enemas or transanal irrigation
NECESSARY IN ALL
Patient education, adequate fibre diet and fluid intake; regular bowel care, preferably ± 3 times a week
SPECIALISED MANAGEMENT PREFERABLE FOR MORE " TAILORED " TREATMENT
* Consider appropriate use of CONTINENCE PRODUCTS

IX. FAECAL INCONTINENCE IN NEUROLOGICAL PATIENTS

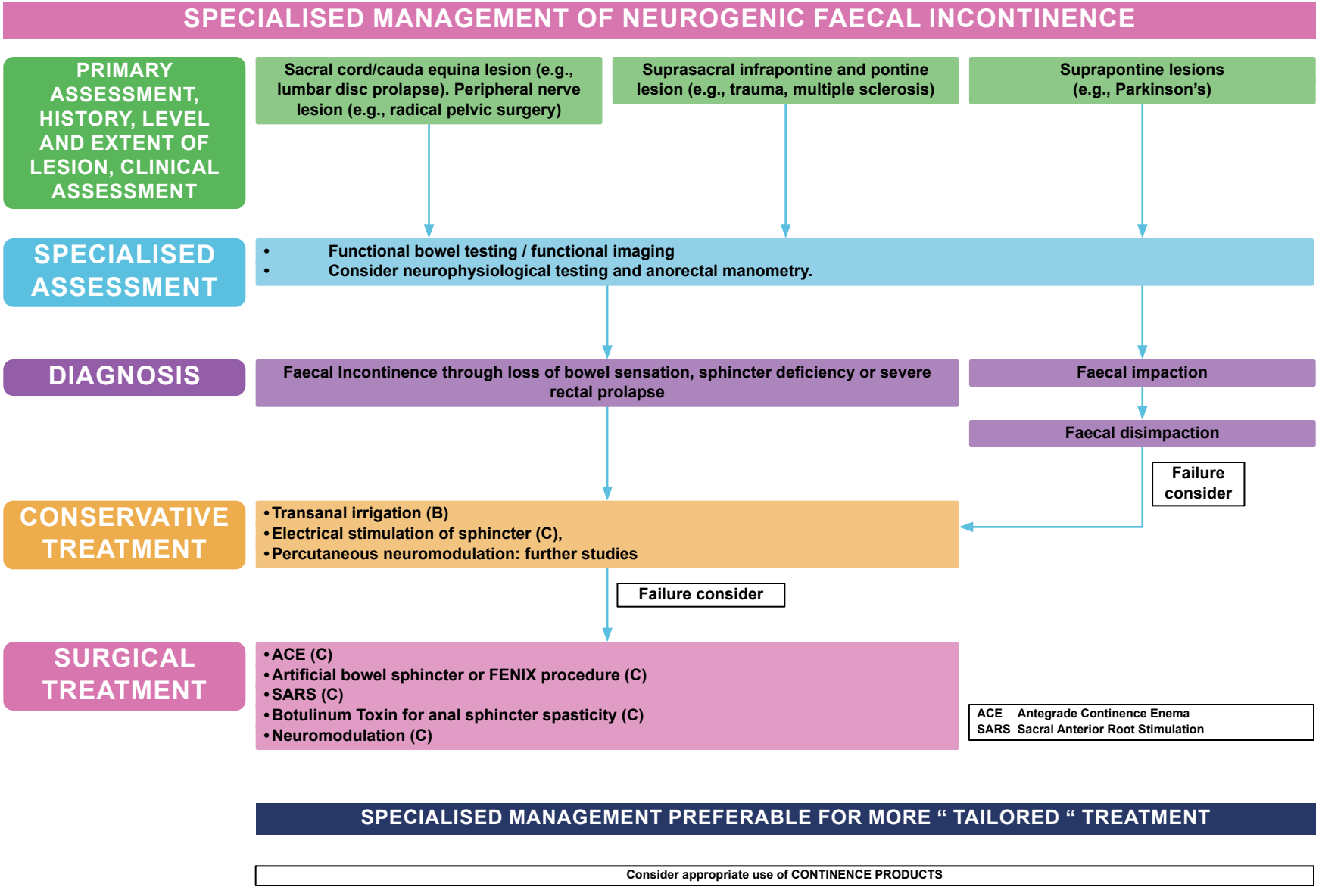
B SPECIALISED MANAGEMENT

ASSESSMENT

- Some patients with neurogenic faecal incontinence will need specialised assessment, especially if initial management is unsuccessful to look for comorbidity and certainly before performing invasive treatment
- Do not assume that all symptoms are due to neuropathy, e.g., women with neurological pathology might have had childbirth injury to the sphincter
- Special investigations: manometry, endoanal ultrasound, (dynamic) MRI, (needle) EMG. These specific bowel functional tests and electro-diagnostic tests must be considered optional, as their value in neurological pathology is not sufficiently demonstrated so far.

TREATMENTS

- Conservative treatment for neurological faecal incontinence is also the mainstay for specialised management, (GoR C).
- Management of neurological incontinence does not include very extensive treatment modalities and many conservative interventions are still empirical.
- Transanal irrigation (GoR B).
- Electrical stimulation sphincter, (GoR C).
- Percutaneous neuromodulation and sacral nerve stimulation: further research is required (GoR D).
- Surgical management of neurogenic faecal incontinence has different options which need a very strict patient selection
- Antegrade Continence Enema ACE (GoR C).
- Artificial bowel sphincter or FENIX procedure (GoR C).
- Sacral Anterior Root Stimulation SARS (GoR C).
- Botulinum Toxin (GoR C).
- Neuromodulation (GoR C).
- It is recommended that urinary and bowel function are assessed simultaneously if both systems are affected, as symptoms and treatment of one system can influence the other and vice versa (GoR A).
- As the therapeutic approach can differ in different neurological diseases, the most prevalent diseases are discussed separately in the chapter.


SPECIALISED MANAGEMENT OF NEUROGENIC FAECAL INCONTINENCE
PRIMARY ASSESSMENT, HISTORY, LEVEL AND EXTENT OF LESION, CLINICAL ASSESSMENT
Sacral cord/cauda equina lesion (e.g., lumbar disc prolapse). Peripheral nerve lesion (e.g., radical pelvic surgery)
Suprasacral infrapontine and pontine lesion (e.g., trauma, multiple sclerosis)
Suprapontine lesions (e.g., Parkinson's)
SPECIALISED ASSESSMENT
• Functional bowel testing / functional imaging
• Consider neurophysiological testing and anorectal manometry.
DIAGNOSIS
Faecal Incontinence through loss of bowel sensation, sphincter deficiency or severe rectal prolapse
Faecal impaction
Faecal disimpaction
Failure consider
CONSERVATIVE TREATMENT
• Transanal irrigation (B)
• Electrical stimulation of sphincter (C),
• Percutaneous neuromodulation: further studies
Failure consider
SURGICAL TREATMENT
• ACE (C)
• Artificial bowel sphincter or FENIX procedure (C)
• SARS (C)
• Botulinum Toxin for anal sphincter spasticity (C)
• Neuromodulation (C)
ACE Antegrade Continence Enema
SARS Sacral Anterior Root Stimulation
SPECIALISED MANAGEMENT PREFERABLE FOR MORE " TAILORED " TREATMENT
Consider appropriate use of CONTINENCE PRODUCTS

X. URINARY AND FAECAL INCONTINENCE IN FRAIL OLDER MEN AND WOMEN

- There is no reason to suspect why interventions which have proven efficacy in community dwelling older adults should not also be effective in frail older adults. Clinicians should, however, take due regard of the practicality, potential benefits, and risks of employing any single intervention in this population.
- Frail older adults do require a different approach which addresses the potential role of co-morbid disease, current medications (prescribed, over the counter and/or naturopathic), physical and cognitive impairment in urinary and faecal incontinence.
- The extent of the investigation and management should consider the degree of bother to the older adult and/or caregiver, the goals for care, the degree that the older person is able to undertake any intervention, considering treatment burden and the overall prognosis and life expectancy.
- Effective management to meet the goals of care should be possible for most frail older adults.

HISTORY AND SYMPTOM ASSESSMENT

- Active case finding for urinary and faecal incontinence should be done in all frail older adults (GoR A).
- History should include comorbid conditions and medications that could cause or worsen incontinence.
- Physical examination should include a rectal examination for faecal loading or impaction (GoR C), functional assessment (mobility, transfers, manual dexterity, dressing and undressing ability, ability to toilet) (GoR A), a screening test for depression (GoR B), and cognitive assessment (to assist in planning and management, (GoR C)).
- The mnemonic DIPPERS (see urinary and faecal incontinence algorithms) cover some of these comorbid conditions. Note that genitourinary syndrome of the menopause does not cause urinary incontinence and should not be treated for this purpose (GoR B).
- The patient and / or caregiver should be asked about the degree of bother of urinary incontinence and/or faecal incontinence (GoR B); goals for urinary and faecal incontinence care (dryness, decrease in specific symptoms, quality of life, reduction of comorbidity, lesser care burden) (GoR B); and ability to undertake management, given the burden of care for any associated comorbid conditions (GoR C).
- Evaluation for bowel “red flag” symptoms (rectal bleeding, positive blood screening from stool studies, obstructive symptoms, recent onset of constipation, weight loss, and a change in stool calibre) will need more extensive evaluation (GoR A)
- Urinalysis is recommended for all patients (GoR C).
- Treatment of otherwise asymptomatic bacteriuria/pyuria is not beneficial (GoR C), except in the setting of planned GU surgery, and it may cause harm by increasing the risk of antibiotic resistance and severe adverse effects. e.g., Clostridium difficile colitis (GoR C).
- Stool studies may not be needed in all patients with faecal incontinence. Patients with diarrhoea, especially those with more acute onset diarrhoea, may need to be tested for infectious causes of their diarrhoea. Other stool studies could involve testing for malabsorption syndromes.
- The utility of the Clinical Stress test in this population is uncertain (GoR D).
- Wet checks can assess urinary incontinence frequency in long-term care residents (GoR C).
- A post voiding residual volume (PVR) test is impractical in many care settings and there is no consensus for the definition of what constitutes a “high” PVR in any population. A PVR measurement is not recommended in the routine initial assessment of frail older people with urinary incontinence.
- However, there is compelling clinical experiential evidence for PVR testing in selected frail older people with: diabetes mellitus (especially long standing); prior urinary retention or high PVR; recurrent UTIs; medications that impair bladder emptying (e.g., opiates); severe constipation; persistent or worsening urgency urinary incontinence despite antimuscarinic/beta-3-agonist treatment; prior urodynamics showing detrusor underactivity and/or bladder outlet obstruction or prior to antimuscarinic therapy (GoR C). Treatment of contributing comorbidity may reduce PVR. Trial with catheter may be considered for PVR > 200-500 ml if the PVR is felt to contribute to UI or urinary frequency (GoR C).
- Nocturia Assessment of frail older adults with bothersome nocturia should identify potential underlying causes including nocturnal polyuria (by bladder diary/frequency-volume chart or wet checks; oedema on examination) (GoR C), primary sleep problems (e.g., sleep apnoea); and low voided volumes (e.g., from high PVR).

- Stool impaction/loading. If suspected on digital rectal examination, an abdominal x-ray may be necessary to further evaluate the degree and location of impaction/loading in frail older adults.

CLINICAL DIAGNOSIS

The most common types of Urinary Incontinence in frail older people are urgency, stress, and mixed urinary incontinence. Frail older people with urgency urinary incontinence also may have detrusor underactivity during voiding with a high PVR but without outlet obstruction. There is no evidence that antimuscarinics are less effective or cause retention in this situation (GoR D).

The most common types of faecal incontinence in frail older people are related to urgency and passive leakage. Passive leakage can refer to leakage, seepage and staining following bowel movements that are not associated with faecal urgency and may also occur with faecal impaction. Because constipation and impaction often contribute to faecal incontinence in older adults, these are considered separately in the algorithm.

INITIAL MANAGEMENT

- Initial treatment should be individualised and influenced by goals of care, treatment preferences and estimated remaining life expectancy, as well as the most likely clinical diagnosis (GoR C). In some frail older adults, the only possible outcome may be containment for social continence, especially for people with minimal mobility (require assistance of > 2 people to transfer), advanced dementia and /or nocturnal urinary and faecal incontinence.

- Conservative and behavioural therapy for UI includes lifestyle changes (GoR C), bladder training for more fit alert persons (GoR B), and prompted voiding for frailer, more impaired older people (GoR A).

- For the select cognitively intact older person with UI or FI, pelvic floor muscle therapy can be considered, but there are few studies (GoR C). Antimuscarinics or mirabegron may be added to conservative therapy of urgency UI (GoR A-C, depending on agent).

- For the select cognitively intact older with FI, biofeedback may be considered, but few studies exist among frail older adults.

- Alpha-blockers may be cautiously considered in frail men with suspected prostatic obstruction (GoR C). All drugs should be started at the lowest dose and titrated with regular review until either care goals are met, or adverse effects are intolerable.

- DDAVP (vasopressin) has a high risk of severe hyponatraemia in frail older persons and should not be used outside specialist centres. or without very careful monitoring and long term follow up (GoR A).

- Improving stool consistency can be done with dietary fibre and supplementary fibre in older adults (GoR C). In older adults with diarrhoea, loperamide may be considered at low doses to improve stool consistency. However, close monitoring for constipation and impaction is needed.

ONGOING MANAGEMENT AND REASSESSMENT

Optimal urinary and faecal incontinence management is usually possible with the above approaches. If initial management fails to achieve the desired goals, the next steps are reassessment and treatment of contributing comorbidity and/or functional impairment.

In chronic intractable incontinence, in frail and/or physically impaired older adults or those with limited life expectancy or in receipt of palliative care, long term urethral or suprapubic catheterisation may be an acceptable pragmatic solution for containment. (GoR D)

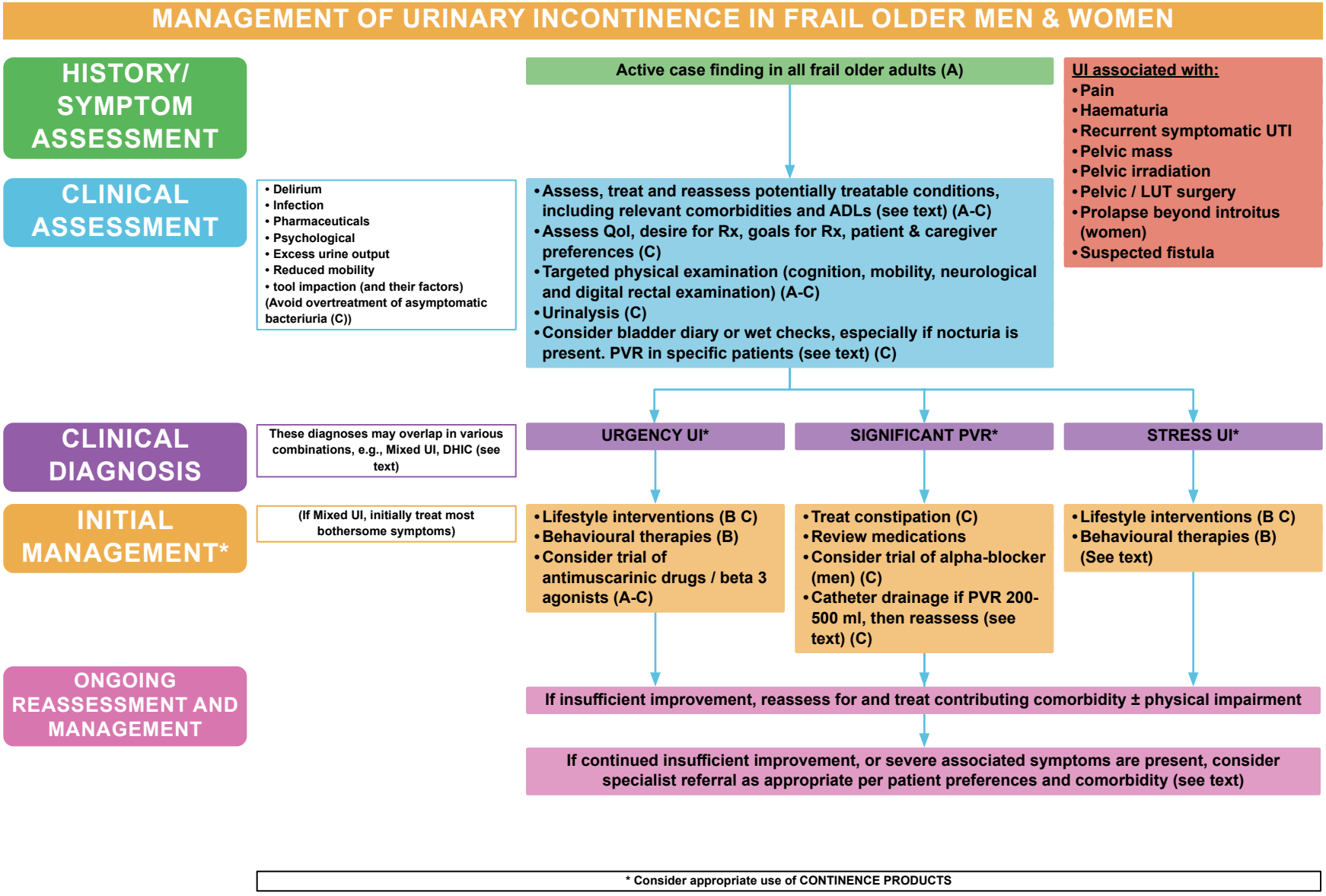
SPECIALISED MANAGEMENT

If frail older people have either other significant factors (e.g., pain, haematuria, bowel “red flag” symptoms), UI or FI symptoms that cannot be classified as urgency, stress, or mixed or overflow or other complicated comorbidity which the primary clinician cannot address (e.g., dementia, disability associated incontinence), then specialist referral should be considered. Referral may also be appropriate when there has been insufficient response to initial management. The type of specialist will depend on local resources and the reason for referral: surgical specialists (urologists, gynaecologists, colorectal surgeons), gastroenterologists, geriatricians or physical therapists (physical and cognitive impairment); or continence nurse specialists. Referral decisions should consider goals of care, patient/caregiver desire for invasive therapy and estimated remaining life expectancy.

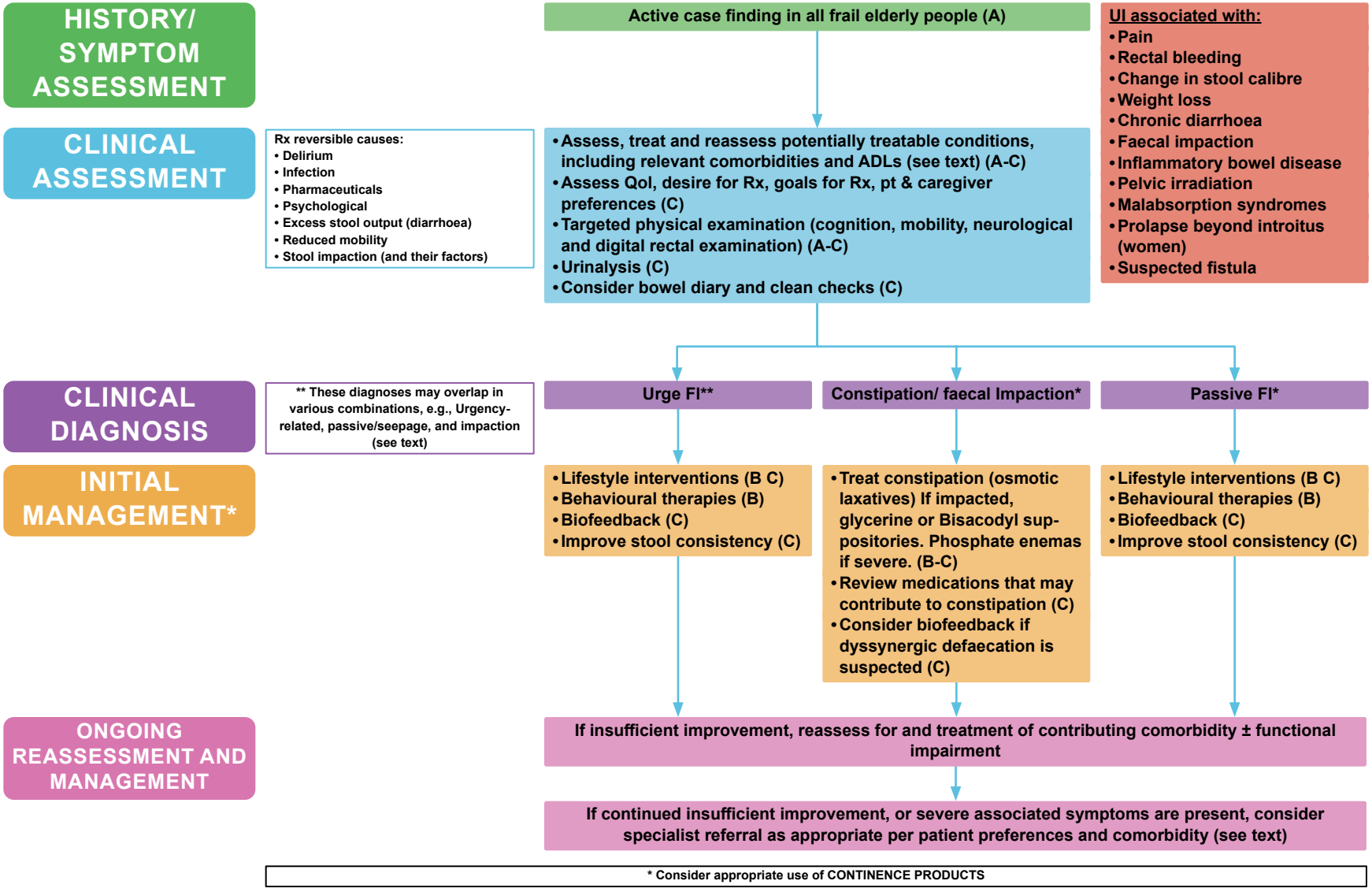
Age *per se* is not a contraindication to UI or FI surgery (GoR C), but before sur- gery is considered, all patients should have:

- Evaluation and treatment for any comorbidity, medications, and cognitive or functional impairments contributing to UI that could compromise surgical outcome (e.g., dementia that precludes patient ability to use artificial sphincter) (GoR C).

- Adequate trial of conservative therapy, including pharmacological therapies where relevant (GoR C).
- Discussion (including the caregiver) to ensure that the anticipated surgical outcome is consistent with goals of care in the context of the patient's life (GoR C).
- Urodynamic testing or imaging for fecal incontinence because clinical diagnosis may be inaccurate and prior to invasive surgery (GoR B).
- Preoperative assessment and perioperative care to establish risk of, and to minimise the risk of common geriatric post-operative complications such as delirium and infection (GoR A), dehydration and falls (GoR C).


MANAGEMENT OF URINARY INCONTINENCE IN FRAIL OLDER MEN & WOMEN
HISTORY/ SYMPTOM ASSESSMENT
Active case finding in all frail older adults (A)
UI associated with:
• Pain
• Haematuria
• Recurrent symptomatic UTI
• Pelvic mass
• Pelvic irradiation
• Pelvic / LUT surgery
• Prolapse beyond introitus (women)
• Suspected fistula
CLINICAL ASSESSMENT
• Delirium
• Infection
• Pharmaceuticals
• Psychological
• Excess urine output
• Reduced mobility
• tool impaction (and their factors)
(Avoid overtreatment of asymptomatic bacteriuria (C))
• Assess, treat and reassess potentially treatable conditions, including relevant comorbidities and ADLs (see text) (A-C)
• Assess QoI, desire for Rx, goals for Rx, patient & caregiver preferences (C)
• Targeted physical examination (cognition, mobility, neurological and digital rectal examination) (A-C)
• Urinalysis (C)
• Consider bladder diary or wet checks, especially if nocturia is present. PVR in specific patients (see text) (C)
CLINICAL DIAGNOSIS
These diagnoses may overlap in various combinations, e.g., Mixed UI, DHIC (see text)
URGENCY UI*
SIGNIFICANT PVR*
STRESS UI*
INITIAL MANAGEMENT*
(If Mixed UI, initially treat most bothersome symptoms)
• Lifestyle interventions (B C)
• Behavioural therapies (B)
• Consider trial of antimuscarinic drugs / beta 3 agonists (A-C)
• Treat constipation (C)
• Review medications
• Consider trial of alpha-blocker (men) (C)
• Catheter drainage if PVR 200-500 ml, then reassess (see text) (C)
• Lifestyle interventions (B C)
• Behavioural therapies (B) (See text)
ONGOING REASSESSMENT AND MANAGEMENT
If insufficient improvement, reassess for and treat contributing comorbidity ± physical impairment
If continued insufficient improvement, or severe associated symptoms are present, consider specialist referral as appropriate per patient preferences and comorbidity (see text)
* Consider appropriate use of CONTINENCE PRODUCTS

MANAGEMENT OF FAECAL INCONTINENCE IN FRAIL OLDER MEN & WOMEN



4. RECOMMENDATIONS FOR FURTHER RESEARCH IN EPIDEMIOLOGY

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

1. URINARY INCONTINENCE

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

There is still little knowledge regarding prevalence, incidence, and other epidemiological data in developing countries. A recent review on the global prevalence of UUI clearly showed that prevalence rates are unknown for many countries in the world. It is recommended that fundamental research regarding prevalence, incidence, and other epidemiological data in developing countries should be encouraged, and tailored to the cultural, economic and social environment of the population under study.

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

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

Primary prevention is the main goal in the management of human disease. An important strategy would thus be to identify the individuals at risk, and then take measures to reduce the risk among those individuals or in certain risk groups. A predictive modelling system based on risk factors identified in population studies has been put forward. Primary prevention studies should be encouraged, but the epidemiological basis for choosing appropriate interventions is weak.

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

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

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

2. FAECAL INCONTINENCE AND PELVIC ORGAN PROLAPSE

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

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

5. RECOMMENDATIONS FOR PRIMARY PREVENTION, CONTINENCE AWARENESS & PROMOTION, MODELS OF CARE AND EDUCATION

Primary prevention, continence promotion and advocacy, models of care and education involves informing and educating the public and health care professionals that UI and FI are not inevitable but are treatable or at least manageable. Other bladder disorders such as BPS/IC and POP can also be treated successfully. The committee found information about recent practice and research initiatives in all these areas but evidence-based research only on primary prevention of UI. Continence promotion and advocacy, and professional and non-professional education, require prioritisation by public health professionals, educationalists, clinicians and researchers to reduce the burden that UI, FI, BPS/IC and POP places on society, healthcare systems, caregivers, and above all, affected adults. As to models of care, the evidence supports nurse-led community services as leading to higher health-related QoL and in some instances, higher cure rates. The multidisciplinary referral settings are also reporting favourable outcomes.

PRIMARY PREVENTION

- Primary prevention of urinary and fecal incontinence remains in its nascent stage, but population aging, preventable obstetric incontinence outcomes, and significant advances in understanding bladder health and UI primary prevention are driving the need to develop effective primary prevention interventions across the human life-course. Foundational evidence has demonstrated that modifiable risk factors exist across multiple levels: intrapersonal, environmental, and societal. High quality RCTs are needed in men, women, and children at different life stages and across the life-course to develop evidence for the effectiveness of population and individual-level primary prevention intervention for UI and FI.
- Pelvic floor muscle exercises can prevent UI and FI in pregnant and postpartum women. (LoE: 1)
- Education designed for community dwelling older women can prevent UI. (LoE 1)
- Pelvic floor muscle exercises should be provided to pregnant women. (GoR A)
- Education to prevent UI for older women should be provided. (GoR : A)

CONTINENCE AWARENESS & PROMOTION

- Continence promotion is required to address broad gaps in knowledge about incontinence. This includes effective communication to and education of both HCPs and the public, through a variety of media, regarding UI and FI potentially affecting all age groups (LoE 3).
- Strategies to promote awareness about incontinence and its treatment can be strengthened using evidence-based theories and methods from the field of health promotion, including the social determinants of health (LoE 4)
- The internet represents an important source of information about incontinence, however the quality of information is variable (LoE 3)
- Evidence for the impact of continence advocacy worldwide was based on opinion (LoE 4) (No recommendation)

MODELS OF CARE

- Service delivery models for Continence Care can be effective. (LoE 4)
- A care delivery model should be based on the principles as described in the Optimum Continence Service Specification. (GoR C)
- Increased emphasis is needed on non-physician models of care (nursing, nurse practitioner, continence advisor, physiotherapy, physician assistants, etc.). (GoR: C)
- Despite the proliferation of guidelines, there is increasing evidence that practicing clinicians and nurses (in the community, acute care, and in long term care) are not consistently following them. Implementation models should be developed on how to translate guidelines into practice. (GoR C)

EDUCATION & CLINICAL GUIDELINES

- Professional and public education of UI, FI and POP is not evidence based on the materials reviewed (LoE: 3-4)
- There is a need for research on both educational content and methodology across all disciplines, particularly as the emphasis on primary care education increases and the opportunities for exposure to targeted content decreases GoR C)
- There is a need for additional research on interdisciplinary and team education, virtual education methods, and hands-on and simulation training related broadly to continence care (GoR C)
- There is a need for additional focused research on methods to enhance patient and public education about UI, FI, and POP, both at an individual and broader public level (GoR C)
- Research is needed to examine methods to improve efficiency of public education including group training, mass marketing, and other techniques (GoR C)
- The role of technology in public education for continence promotion should be examined in more depth (GoR C)
- Future research methodologies should incorporate the standardised methods and definitions as set out in new consensus and standardisation documents (GoR C)

- Guidelines for various aspects of continence evaluation and management have been established (LoE: 3 to 4)

- There is a need to continue to evaluate the quality and relevance of existing clinical guidelines, particularly in the context of updating these materials or creating new guidelines based on emerging evidence (GoR B)

- There is a need for additional research on guideline dissemination, awareness and adoption among clinicians, and the impact on a wide range of outcomes including incidence and prevalence of disease, treatment efficacy, prevention efforts, costs, and health care policies (GoR C)

6. RECOMMENDATIONS FOR PRIORITIES IN RESEARCH

A. PRIORITIES IN FUNDAMENTAL RESEARCH

Integrate data from reductionist experiments to inform the formulation of better systems-based approaches in the investigation of the pathology of the lower urinary tract (LUT), the genital tract (GT) and the lower gastrointestinal tract (LGIT) through:

- the development of animal models that accurately describe human pathological conditions, including the greater use of large-animal models
- the better use of reverse translational approaches for linking animal models to the human disease.

Encourage greater emphasis on basic research to characterise tissues receiving little attention: i.e., the lower gastrointestinal tract; the bladder neck and urethra; the ureter, pelvic floor musculature

Generate research programmes for foetal and neonatal research in LUT and LGIT function.

Use genome-wide bioinformatics and population health surveys to generate testable hypotheses regarding the physiological and pathophysiological functions of the LUT, GT and LGIT.

Generate improved experimental approaches to investigate the pathophysiology of the LUT and LGIT by:

- the use of human tissue from well-characterised patient groups.
- the development of emerging areas such as: tissue engineering; proteomics and metabolomics
- increased collaborations between biological, physical, and mathematical sciences.

Develop centres of excellence or consortia of excellence in LUT, GT and GIT research

integrate expertise from university departments, academic medical units and industry

Encourage translational approaches to research by development of inter-institutional research training programs to allow new researchers the opportunity to better interact and exchange ideas.

Additional emphasis on the importance of research to medical trainees and science graduates through:

- Establishing research training as a core component of postgraduate clinical development
- Increased access to support funds, especially scholarships and personal awards
- organisation of focused multidisciplinary research meetings, either stand-alone or as dedicated sessions during national and international conferences
- greater interaction between medical centres and Higher Education Institutions (HEIs).
- allowing researchers-in-training better access to international meetings through reduced registration charges and improved travel grants.
- inclusion in clinical meetings of point-counterpoint session(s) with both basic science and clinical viewpoints.
- development of research fora for exchange of ideas between active researchers and industry.
- lobbying research funding organisations about the medical and social importance of LUT and LGIT disorders.

Increase emphasis on research into LUT and LGIT in HEIs through greater representation on grant-funding agencies

B. PRIORITIES IN CLINICAL RESEARCH

1. RESEARCH PRIORITIES FOR TRIALS OF CONSERVATIVE TREATMENT

Use correct terminology to describe the intervention.

In trials of pelvic floor muscle exercise, report details of ability to perform correct contraction, dose-response issues and adherence.

Use recommended outcome measures with high responsiveness, reliability and validity.

Compare new methods with the best available intervention.

Use power calculation in planning of the study. Avoid large sample sizes and weak (ineffective dosages) interventions.

For long-term follow-up studies report cross over, co-interventions, recurrent and competing events, adherence in the follow-up period and loss to follow-up

2. RESEARCH PRIORITIES FOR TRIALS OF PHARMACOTHERAPY

As effective drug therapy is available for most forms of incontinence, active drug comparator arms are recommended for most trials.

Long-term follow-up of RCT cohorts in an observational cohort is recommended.

Further studies focused on the anticholinergic load in frail older adults with OAB are recommended.

3. RESEARCH PRIORITIES FOR SURGICAL AND DEVICE TRIALS

An agreed and standardised technique for the surgical procedure or device application should be clearly defined

The safety and serious side effects of new operations or devices, especially implantable devices, and biologic materials, must be completely defined with adequate follow-up so that risks can be weighed against efficacy. At a minimum, this requires more use of large scale, independent, prospective, multicentre cohort studies when RCTs are not practical.

Valid informed research consent is required in all trials of research surgical interventions; this research consent is separate from the main surgical consent.

Whenever possible, randomisation for surgical trials should occur at the time of surgery to minimise dropouts and switch of procedure

Reports of successful treatment should be limited to subjects with a minimum (not mean) of one-year follow-up and should include a patient perspective measure. Specific assumptions about subjects lost to follow-up should be stated.

Long-term follow-up of RCT cohorts in an observational cohort is recommended.

C. RESEARCH PRIORITIES FOR SPECIFIC PATIENT GROUPS

1. MEN AND WOMEN WITH LUTS

1.1. Men

Measurement of prostate size should be performed before and after treatment (at the same time as continence outcome measures where possible) whenever prostate size is a potentially important variable, or to change during the intervention and follow up.

Maximum free flow rate and measurement of post-void residual urine should be recorded pretreatment and the effect of therapy on these parameters should be documented simultaneously with assessment of the primary outcome variables. HIGH

Participants should be stratified by prostate size at randomisation when size is a potentially important determinant of treatment outcome.

Clinical evaluations of different male UI products, including strengths, limitations, and efficacy in clinically relevant subgroups.

1.2. Women

Specific information about menopausal status, hysterectomy, parity/obstetric history, and hormonal status should be included in baseline clinical trial data and controlled for in specified analyses in the research protocol. HIGH

High quality, symptom and bother scores (e.g., ICIQ-FLUTS, KHO, PISQ, ICIQ-FLUTSsex) validated in women should be employed when assessing outcomes HIGH

Standardised assessment of pelvic organ pro lapse (by POP-Q) should be performed before treatment and at the time of other outcome assessments in all research where prolapse and continence outcomes are being assessed. HIGH

Criteria for cure/improvement/failure from incontinence treatment should be defined in the protocol based on patient perception as well as objective and semi-objective instruments such as validated questionnaires, diaries, and pad tests.

Assessment of the impact of treatment on sexual function should be performed with other outcome assessments when appropriate.

2. CHILDREN, ADOLESCENTS & TRANSITIONAL CARE

Long-term follow-up is of critical importance in the paediatric population to ascertain the effect of a treatment on normal growth and development.

improve symptom-based classification to identify the degree of bladder and non-bladder symptoms.

Establish patient databases in different regions and conduct longitudinal follow-up to understand the natural history of the disease and to examine the differences in disease natural history among regions

Develop standardized outcome measures including validated, age specific symptom and disease specific quality of life outcome measures.

Research of problems specific to different age groups is needed. Especially, incontinence in preschool children and in adolescents is needed.

The transition and transfer from pediatric to adult care should be studied and evidence-based recommendations should be formulated.

Develop a practical multi-disciplinary care model and test it in various settings.

Develop an easy-to-use tool for non-specialists to readily identify co-morbid conditions that may impact on the need for additional consultation and suggest specific treatment pathways.

The specific incontinence problems of young adults aged 18-21 years need more attention in research.

Incontinence in children and adults with special needs is a neglected part of research and clinical care. These include individuals with intellectual disability, specific syndromes, autism spectrum and other disorders.

The interaction between brain and bladder and/or gut needs to be studied with new functional and structural imaging techniques of the CNS.

Treatment studies of daytime urinary incontinence, including pharmacotherapy and urotherapy, are needed.

The correlates of sleep in children with nocturnal enuresis needs to be elucidated in more detail.

Life span, longitudinal epidemiological studies from childhood to adulthood in a prospective design are required to procure representative data.

3. NEUROGENIC POPULATIONS

An area of high priority for research is the development of a more directly informative classification system which would include anatomical location and aetiology in association with corresponding urinary, faecal, and neurological symptoms, information from clinical neurophysiological testing and urodynamic abnormalities as well as prognostic biomarkers.

As such, the classification would describe a patient suffering from NLUTD and simultaneously inform about the most appropriate treatment, follow-up regimen, and long-term prognosis.

The thalamus may be a promising target for the development of new therapies for lower urinary tract dysfunction. Further investigation on this matter is needed before its potential role can be elaborated.

3.1. Diagnostics
Additional studies are needed to establish neurological populations and absolute indications for the use of invasive urodynamics as a primary and specialized assessment tool as well as to establish its best application for follow-up of treatment modalities

Research to establish what is 'urodynamic safety' in NLUTD, preferably by population studied

Identify clinical predictors of urodynamic findings in NLUTD

Further development of patient reported outcome measures needed in NLUTD

Further research into neuroimaging and its association with clinical neurourological practice

Further development and standardisation for the use of electrosensation tests to assess their role as a clinical test

Research to produce high level evidence to define UTIs in neurological patients

Need more evidence for the use of prophylactic antibiotics to reduce symptomatic urinary tract infections after invasive UDS

3.2. Management
Research into mechanisms and prognosis of the development of bladder cancer in patients with NLUTD

Further research on whether any CISC method or catheter type is advantageous

3.3. Pharmacotherapy
Further research is needed to establish the efficacy and safety of the newer antimuscarinics in NLUTD, long-term outcomes and safety, the efficacy and safety of mirabegron in NLUTD, as well as combination treatments

Oral and intravesical cannabinoid agonists should be further investigated for optimal balance between efficacy and safety

Further research on pharmacotherapy for detrusor-sphincter dyssynergia, sphincter deficiency and detrusor underactivity

3.4. Minimally Invasive Treatments
a. Botulinum Toxin

Further research is needed on long-term outcomes and safety, administration techniques, the bioequivalence of the various preparations, the concomitant use of anticholinergic drugs or beta-3 agonists, mechanisms of action, and wider effects

Future research should focus on PROs and patient satisfaction, tolerability, alternative techniques of application & ways to minimise posttreatment voiding dysfunction in patients who void freely

Larger studies in select patient populations are required.

b. Electrical Neuromodulation

Further studies on chronic pudendal nerve stimulation must be carried out to identify the best stimulation parameters and to verify the long-term results in patients with inadequate bladder emptying due to DBND, either as a first-line procedure or as a complementary approach to DBND following permanent urethral stenting.

controlled evidence is needed for the use of IVES to induce/improve bladder sensation and to enhance the micturition reflex in patients with incomplete central or peripheral nerve damage.

Research to establish indications for sacral neuromodulation in the care of DSD in neurological urinary dysfunction.

Effectiveness of tibial nerve stimulation (transcutaneous, percutaneous, and implantable)

c. Biomaterials

Preliminary results of bladder augmentation using biomaterials or tissue engineering is promising, but the need to be confirmed by larger studies.

3.5 Specific Neurological Conditions

There is a need for robust epidemiological research, insight into mechanisms, studies on utility of diagnostic tests, assessment of urinary tract risk factors, and randomised trials to assess benefits and harms of therapy for specific neurological diseases.

Urinary incontinence and faecal incontinence, both suffer from limited high-quality research. Priority research Topics include investigations into:

systematic cataloguing of the specific brain centres pertinent to lower urinary tract control, and how they are at risk in given neurological diseases

how medications for LUTS may influence specific neurological diseases or associated dysfunctions (e.g., blood pressure control)

The clinical relevance of functional brain imaging to clinical management

Indicators of neurological presentation or progression that may be first evident in urological clinics

Outcomes for interventions for detrusor sphincter dyssynergia.

4. RESEARCH PRIORITIES IN POPULATIONS AFFECTED BY BLADDER PAIN (INCLUDING INTERSTITIAL CYSTITIS)

Research that focuses identify bladder-specific pathology, a bladder pain syndrome-specific biomarker

Develop a simple, non-invasive diagnostic tools for Hunner Lesion Disease and Bladder Pain Syndromes BPS).

Research that focuses identifying specific pathology (the pathogenesis of a B-cell population abnormality in Hunner lesions) and biomarkers for HIC and NHIC/BPS.

Standardised methods of hydrodistension.

Research to develop a curative treatment for HLD and BPS.

Establish patient databases in different regions and conduct longitudinal follow-up to understand the natural history of the disease and to examine the differences in disease natural history between regions.

Develop a simple, non-invasive diagnostic test for BPS

Research that focuses identify bladder-specific pathology, a bladder pain syndrome-specific biomarker

Broaden the research scope to improve symptom-based classification to identify the degree of bladder and non-bladder symptoms.

Develop a practical multi-disciplinary care model and test it in various settings.

Develop an easy-to-use tool for non-specialists to readily identify co-morbid conditions that may impact on the need for additional consultation and suggest specific treatment pathways.

5. RESEARCH PRIORITIES IN POPULATIONS AFFECTED BY PELVIC ORGAN PROLAPSE

Uterine prolapse and its various treatment options

Surgery for recurrent prolapse

Identifying risk factors for recurrent prolapse

Re-evaluation of prolapse quality of life questionnaires to ensure they are sensitive to change

The utilisation and incorporation of tissue engineering in pelvic organ prolapse surgery

Impact of POP surgery on bladder overactivity.

Impact of POP surgery on urinary voiding dysfunction

Impact of rectocele repair on symptoms of obstructed defaecation and faecal incontinence

Impact of various types of POP surgery on OAB.

Impact of various types of POP surgery on SUI.

Impact of various types of POP surgery on urinary voiding dysfunction.

Impact of rectocele repair on obstructed defaecation and faecal incontinence.

Long-term follow-up of LUTs and other adverse events (including chronic pain and mesh extrusions) in cases treated with transvaginal mesh surgery.

Re-evaluate prolapse quality of life (P-QOL) questionnaires to ensure they are sensitive to changes after treatment.

Identifying risk factors and predictors for persistent/de-novo incontinence after POP surgery.

6. RESEARCH PRIORITIES IN FAECAL INCONTINENCE

Develop and test interventions for promoting care seeking and self-management of faecal incontinence (and associated odour and urgency)

Develop and test interventions for increasing coping skills and health literacy related to faecal incontinence for patients and family caregivers

Evaluate tailoring the management of faecal incontinence based on patients' goals, peer support, and the use of current technologies such as mobile devices for delivering management and support interventions to patients and family caregivers

Collect data on faecal incontinence, whenever practical, as part of research on urinary incontinence

Develop techniques for diagnosing faecal incontinence and its aetiologies using new and available diagnostic technologies

Develop user-friendly measures and instruments for quantifying the severity of faecal incontinence and other components of anal incontinence separately and in total

Investigate the epidemiology of the different types and subtypes of bowel and anal incontinence

Well-designed and adequately powered studies are needed to evaluate faecal incontinence treatment modalities currently available including:

- Effectiveness of lifestyle modifications including weight loss, exercise, diet and eating pattern modifications, and supplementing dietary fibre as an adjuvant or combined strategy

- Comparative effectiveness trials of instrumented biofeedback training versus neuromodulation

7. RESEARCH PRIORITIES IN ECONOMIC ANALYSIS

Cost analysis should be incorporated into clinical studies whenever possible.